NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: FDA review was conducted in conjunction with other regulatory authorities under project Orbis. FDA collaborated with Israel's Ministry of Health (IMoH) and Switzerland's Swissmedic (SMC). While the conclusions and recommendations expressed herein reflect FDA's completed review of the application, the applications may still be under review at the other regulatory agencies. In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	New Drug Application
Application Number(s)	217513/217514
Priority or Standard	Standard
Submit Date(s)	August 17, 2022
Received Date(s)	August 17, 2022
PDUFA Goal Date	May 16, 2023
Division/Office	DO2/OND
Review Completion Date	See electronic stamp date
Established Name	Dabrafenib/Trametinib
(Proposed) Trade Name	Tafinlar/Mekinist
Pharmacologic Class	Dabrafenib is a kinase inhibitor Trametinib is a kinase inhibitor
Code name	Dabrafenib (GSK2118436) Trametinib (GSK1120212)
Applicant	Novartis Pharmaceuticals Corporation
Formulation(s)	TAFINLAR Capsules: 50 mg, 75 mg TAFINLAR Tablets for Oral Suspension: 10 mg MEKINIST Tablets: 0.5 mg, 2 mg MEKINIST for Oral Solution: 4.7 mg
Dosing Regimen	The dosage for dabrafenib tablets for oral suspension is based on weight and administered orally twice daily. The dosage for trametinib powder for oral solution is based on weight and administered orally once daily. Refer to the US Product Information for specific dosage information.

Applicant Proposed Indication(s)/Population(s)	The treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	The treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

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1 Reviewers of Multi-Disciplinary Review and Evaluation

[FDA will complete this section.]

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Abbreviations: DHOT, Division of Hematology Oncology Toxicology; OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology; OOD, Office of Oncologic Diseases

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	(b) (4)

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

3 Glossary

ADME	Absorption, distribution, metabolism, elimination
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anaplastic thyroid cancer
BLA	Biologics license application
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BOR	Best overall response
CBR	Clinical benefit rate
CFR	Code of Federal Regulations
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CSR	Clinical study report
DOR	Duration of response
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
FAS	Full analysis set
HGG	High-grade glioma
ICH	International Conference on Harmonization
ITT	Intent to treat
LCH	Langerhans cell histiocytosis
LGG	Low-grade glioma
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New drug application
NSCLC	Non-small cell lung cancer
ORR	overall response rate
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetics
PopPK	Population PK
PR	Partial response

PRO	Patient reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PSUR	Periodic Safety Update report
RANO	Response assessment in neuro oncology
REMS	Risk evaluation and mitigation strategy
RMP	Risk Management Plan
RP2D	Recommended Phase II dose
RSD	Rolling 6 design
SAE	Serious adverse event
SAP	Statistical analysis plan
TTR	Time to response
WHO	World Health Organization

4 Executive Summary

4.1 Product Introduction

Dabrafenib (TAFINLAR) is a BRAF kinase inhibitor. It is FDA approved as a single agent for the treatment of patients with metastatic or unresectable melanoma with BRAF V600E mutation. Dabrafenib in combination with trametinib (MEKINIST) is FDA approved for the treatment of:

- Patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations;
- Patients with melanoma with BRAF V600E or V600K mutations and lymph node involvement post complete resection;
- Patients with metastatic non-small cell lung cancer with BRAF V600E mutation;
- Patients with locally advanced or metastatic anaplastic thyroid cancer with BRAF V600E mutation without the option for satisfactory locoregional treatment;
- Adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.

Trametinib (MEKINIST) is a MEK1/MEK2 kinase inhibitor. It is FDA approved as a single agent for the treatment of BRAF-inhibitor naïve patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. Trametinib in combination with dabrafenib is FDA approved for the treatment of:

- Patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations;
- Patients with melanoma with BRAF V600E or V600K mutations and lymph node involvement post complete resection;
- Patients with metastatic non-small cell lung cancer with BRAF V600E mutation;
- Patients with locally advanced or metastatic anaplastic thyroid cancer with BRAF V600E mutation without satisfactory locoregional treatment options;
- Adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment without alternative treatment options.

The Applicant's proposed indication is for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. Dabrafenib is administered orally, twice daily, and trametinib is administered orally, once daily; the recommended dosages for trametinib and dabrafenib are based on body weight.

4.2 Conclusions on the Substantial Evidence of Effectiveness

The data submitted by the Applicant provides substantial evidence of effectiveness to support the regular approval of dabrafenib in combination with trametinib for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

The recommendation for traditional approval is based on the results of the low-grade glioma cohort from Study CDRB436G2201 (G2201), which demonstrated that treatment with dabrafenib in combination with trametinib resulted in a statistically significant and clinically meaningful improvement in overall response rate (ORR) and progression-free survival (PFS) compared to treatment with carboplatin and vincristine in pediatric patients aged 1 year and older with LGG with a BRAF V600E mutation.

G2201 is an open-label, global study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive LGG or relapsed or refractory high-grade glioma (HGG). The LGG cohort is a multi-center, randomized, open-label study conducted in pediatric patients ages 1 to < 18 years old with BRAF V600E mutation-positive, progressing LGG who required systemic treatment. Patients (n=110) were randomized in a 2:1 ratio to targeted therapy with dabrafenib plus trametinib (D+T) (n=73) or chemotherapy with carboplatin plus vincristine (C+V) (n=37). The primary endpoint was ORR by RANO-LGG criteria as determined by blinded independent central review (BICR); only complete and partial confirmed responses were considered in the calculation of ORR. In the LGG cohort, median age was 9.5 years (range 1 to 17 years); 60% were female. There was a statistically significant improvement in ORR and PFS in patients with LGG randomized to D+T over those randomized to C+V. The D+T arm demonstrated an ORR of 47% (95% CI: 35, 59) compared to the C+V arm which demonstrated an ORR of 11% (95% CI: 3.0, 25), with a p-value <0.001. The median duration of response (DOR) for the 34 responders in the D+T arm was 23.7 months (95% CI: 14.5, NE). The median DOR was not estimable in the chemotherapy arm due to the limited number of responders (n=4, DOR range: 6.6, 24.6+). The median progression free survival (PFS) was 20.1 months (95% CI: 12.8, NE) in the D+T arm and 7.4 months (95% CI: 3.6, 11.8) in the C+V arm, with a hazard ratio (HR) of 0.31 (95% CI: 0.18, 0.55; p< 0.001). At the time of the interim analysis of overall survival (OS), conducted when all patients had completed at least 32 weeks of treatment or had discontinued earlier, there was only one death on the C+V arm.

Additional supportive data for the combination therapy and to demonstrate the contribution of each component to the treatment regimen was provided from children and adolescents with cancers harboring V600E mutation enrolled in Study CTMT212X2101, a dose-finding and activity-estimating trial of trametinib as a single agent or in combination with dabrafenib, and from Study CDRB436A2102, a study of dabrafenib as a single agent in pediatric patients with BRAF V600-positive tumors, including gliomas. Further strong mechanistic support for dual BRAF/MEK inhibition is derived from a substantial amount of prior scientific evidence in

patients with BRAF V600E-driven tumors, including clinical trials leading to multiple FDA approvals, notably in children 6 years and older and adults with BRAF V600E mutant advanced solid tumors (tissue agnostic indication).

The submitted evidence meets the statutory evidentiary standard for regular approval. Treatment with dabrafenib and trametinib demonstrated a statistically significant and clinically meaningful improvement in ORR and PFS over carboplatin and vincristine in patients 1 year of age and older with LGG with BRAF V600E mutation. Therefore, the review team recommends granting approval to dabrafenib in combination with trametinib for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

4.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Pediatric LGGs represent 30% of all childhood brain tumors with approximately 1,600 new cases per year in the United States (Diwanji, 2017). BRAF V600E mutations are present in 5-17% of LGGs occurring in ~ 240 patients per year (Lassaletta, 2017). For pediatric patients with LGG, overall survival is generally > 90%; there is some variation in outcomes based on molecular subtype, especially with the BRAF V600E mutation which is associated with a poorer survival (de Blank, 2019; Nobre, 2020). In addition, many patients receiving therapy for pLGG experience sequelae of their disease or treatment, which can include cognitive impairment or delay, endocrine deficiencies, secondary malignancies, cardiovascular toxicity, and growth abnormalities. Due to the location of some tumors in the optic pathway, visual impairment is a significant concern, and threatened vision is an indication for systemic treatment. In pediatric patients with inoperable or progressive pediatric low-grade glioma (pLGG), there are several chemotherapeutic regimens in use in clinical practice (although not FDA-approved), including vincristine plus carboplatin, TPCV (thioguanine, procarbazine, lomustine, and vincristine), and vinblastine. In pediatric patients with pLGG receiving conventional chemotherapy irrespective of BRAF V600E mutation status, ORRs reported in the literature range from 26 to 35%. In pediatric patients receiving conventional chemotherapy for pLGG with BRAF V600E mutation, reported ORRs range from 10 to <23%.

Dabrafenib, a BRAF kinase inhibitor, in combination with trametinib, a MEK1/MEK2 kinase inhibitor, is approved for patients 6 years and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. This tissue agnostic indication includes patients with relapsed/refractory gliomas, but does not include patients with LGG who have not previously received systemic therapy; there are no therapies specifically targeting BRAF V600E currently approved in this population.

Support for this application is based on safety and efficacy data from Study G2201, an open-label, global study which evaluated the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive LGG or relapsed or refractory high-grade glioma (HGG) in two separate cohorts. Patients with LGG were enrolled in a multi-center, randomized, open-label study conducted in pediatric patients ages 1 to < 18 years old with BRAF V600E mutation-positive, progressing LGG who required systemic treatment. Patients (n=110) were randomized in a 2:1 ratio to targeted therapy with dabrafenib plus trametinib (D+T) (n=73) or chemotherapy with carboplatin plus vincristine (C+V) (n=37). The primary endpoint was ORR by RANO-LGG criteria as determined by blinded independent central review; only complete and partial confirmed responses were considered in the calculation of ORR. Secondary endpoints included DOR, PFS, OS and ORR as determined by investigator. The D+T arm demonstrated an ORR of 47% (95% CI: 35, 59) compared to the C+V arm which demonstrated an ORR of 11% (95% CI: 3.0, 25), with a p-value <0.001. The median duration of response (DOR) for the 34 responders in the D+T arm was 23.7 months

(95% CI: 14.5, NE). The median DOR for the 4 responders in the chemotherapy arm was not estimable due to limited number of responders (range: 6.6, 24.6+). The median progression free survival (PFS) was 20.1 months (95% CI: 12.8, NE) in the D+T arm and 7.4 months (95% CI: 3.6, 11.8) in the C+V arm, with a hazard ratio (HR) of 0.31 (95% CI: 0.18, 0.55; p< 0.001). At the time of the interim analysis of overall survival (OS), conducted when all patients had completed at least 32 weeks of treatment or had discontinued earlier, there was only one death on the C+V arm.

Change in visual acuity for patients with impaired or threatened vision was not included as an efficacy measure in the LGG cohort of the G2201 study; however visual acuity (VA) was assessed throughout the study for these patients. Review of VA data among responding patients in the D+T (n=19) arm and C+V (n=8) arm indicated that the majority of patients' symptoms in both groups were stable or improved while receiving therapy. Given the small number of patients with VA assessments and response data, conclusions on the effect of D+T on visual outcomes are limited.

In addition to data from the LGG cohort of Study G2201, supportive data for the combination therapy in pediatric patients with LGG, and to demonstrate the contribution of each component to the treatment regimen was provided from children and adolescents with cancers harboring V600E mutation enrolled in Study CTMT212X2101, a dose-finding and activity-estimating trial of trametinib as a single agent or in combination with dabrafenib, and from Study CDRB436A2102, a study of dabrafenib as a single agent in pediatric patients with BRAF V600-positive tumors, including gliomas. Further strong mechanistic support for dual BRAF/MEK inhibition is derived from a substantial amount of prior scientific evidence in patients with BRAF V600E-driven tumors, including clinical trials leading to multiple FDA approvals, notably in children 6 years and older and adults with BRAF V600E mutant advanced solid tumors (tissue agnostic indication).

Dabrafenib in combination with trametinib appears to have an acceptable safety profile when assessed in the context of a life-threatening disease. The pooled pediatric safety population included 166 pediatric patients with advanced solid tumors harboring BRAF V600E mutations who received at least one dose of dabrafenib and trametinib at the respective recommended phase 2 doses (RP2Ds). The G2201 LGG cohort safety population included 73 patients who received dabrafenib and trametinib and 33 patients who received carboplatin with vincristine.

Warnings and Precautions for dabrafenib and trametinib include new primary malignancies (cutaneous and non-cutaneous), tumor promotion in BRAF wild-type tumors, hemorrhage, cardiomyopathy, uveitis, serious febrile reactions, serious skin toxicities, hyperglycemia, risk of anemia in patients with glucose-6-phosphate dehydrogenase deficiency (G6PD), colitis and gastrointestinal perforation, venous thromboembolism, ocular toxicities, interstitial lung disease, and embryo-fetal toxicity. No additional Warnings and Precautions were proposed based on this application. Based on review of the data in these applications, a new safety signal of weight gain was identified in pediatric patients.

In the pooled safety population, serious adverse reactions occurred in 47% of pediatric patients who received dabrafenib in combination with trametinib. The most common (> 20%) adverse reactions in the pooled safety population were pyrexia (66%), rash (54%), headache (40%), vomiting (38%), musculoskeletal pain (36%), fatigue (31%), dry skin (31%), diarrhea (30%), nausea (26%), epistaxis and other bleeding events (25%), abdominal pain (24%) and dermatitis acneiform (23%). The most common (> 2%) Grade 3 or 4 laboratory abnormalities were decreased neutrophil count (20%), increased alanine aminotransferase (3.1%), and increased aspartate aminotransferase (3.1%). Significant safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling.

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). Dabrafenib and trametinib will be prescribed by pediatric oncologists and neuro-oncologists who are familiar with monitoring, identifying, and managing the toxicities described in the USPI. Two post-marketing requirements (PMRs) to address safety in the pediatric population will be issued to assess 1) the potential for growth plate abnormalities and other effects on growth and development and 2) the incidence of known serious risks associated with dabrafenib in combination with trametinib, including new primary malignancies, cardiomyopathy, and ocular toxicities.

The submitted evidence meets the statutory evidentiary standard for regular approval. The substantial improvement in ORR and PFS, with demonstration of durable responses, provides evidence of a statistically significant and clinically meaningful benefit with dabrafenib and trametinib in pediatric patients with LGG with BRAF V600E mutation. A post-marketing commitment (PMC) will be issued to obtain the final analysis for overall survival and progression-free survival once all patients with LGG have been followed for at least 2 years. As part of this PMC, the Applicant will include an analysis of change in visual acuity over the course of treatment with dabrafenib and trametinib for patients who enrolled on the study due to impaired vision.

Based on the favorable risk-benefit assessment for this pediatric population with a serious, life-threatening disease, regular approval is recommended for the following indication:

> Dabrafenib is indicated, in combination with trametinib, for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Approximately 1600 pediatric patients are diagnosed with low grade glioma each year in the US (Diwanji, 2017). • The majority of pediatric LGG are driven by activation of the MAPK pathway, including BRAF mutations and fusions; 17% of pediatric patients with LGG have BRAF V600E mutations (Lassaletta, 2017). • For pediatric patients with LGG, overall survival is generally > 90%; there is some variation based on molecular subtype, especially BRAFV 600E mutation which is associated with a poorer outcome (de Blank, 2019; Nobre, 2020). Although long-term survival is excellent in this population, disease and treatment sequelae are common and include functional, neurologic/neurocognitive, and endocrine complications.	There is an unmet medical need for pediatric patients with BRAFV600E mutant LGG. LGG with BRAF V600E mutation may be life-threatening. In addition, significant morbidity, including but not limited to vision loss and other neurologic complications, may result from the location of the tumor.
Current Treatment Options	• For patients who require therapy beyond surgical resection, the standard of care consists of several chemotherapeutic regimen options, including carboplatin and vincristine; thioguanine, procarbazine, lomustine, and vincristine (TCPV); and single agent vinblastine. There are no therapies approved specifically for patients with BRAF V600E mutation in the first-line setting. • ORRs for these therapies in pediatric patients with LGG range from 26 – 35%; however, for patients with BRAF V600E mutation, the reported ORR with traditional chemotherapy regimens is lower (10 - < 23%) (Lassaletta, 2017; Nobre, 2020). • Current standard of care chemotherapeutic regimens are associated with the potential for long term side effects that include hearing loss, risk for additional cancer, and neuropathy. • Dabrafenib, in combination with trametinib, is approved for patients 6	There are no FDA approved treatment options for pediatric patients with LGG with BRAF V600E mutations who require first-line systemic therapy after surgical resection. Chemotherapy treatment regimens used for these patients are associated with significant short- and long-term toxicities.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	years and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. This tissue agnostic indication includes patients with relapsed/refractory gliomas, but does not include patients with LGG who have not previously received systemic therapy.	
Benefit	• The primary efficacy data supporting these NDAs are derived from a Study G2201, a global, multi-center, randomized, open-label study conducted in pediatric patients ages 1 to < 18 years with BRAF V600E mutation-positive, progressing LGG who required systemic treatment. • The D+T arm demonstrated an ORR of 47% (95% CI: 35, 59) compared to the C+V arm which demonstrated an ORR of 11% (95% CI: 3.0, 25), with a p-value <0.001. The median DOR for the D+T arm was 23.7 months (95% CI: 14.5, NE). The median DOR was not estimable in the chemotherapy arm due to limited number of responders (n=4, range: 6.6, 24.6+). • The median PFS was 20.1 months (95% CI: 12.8, NE) in the D+T arm and 7.4 months (95% CI: 3.6, 11.8) in the C+V arm, with a HR of 0.31 (95% CI, 0.18, 0.55; p<0.001). At the time of the interim analysis of overall survival (OS), conducted when all patients had completed at least 32 weeks of treatment or had discontinued earlier, there was only one death on the C+V arm. • Review of VA data among responding patients with impaired or threatened vision in the D+T (n=19) arm and C+V (n=8) arm indicated that the majority of patients' symptoms in both groups were stable or improved while receiving therapy. Given the small number of patients	The submitted evidence meets the statutory evidentiary standard for regular approval. The substantial improvement in ORR and PFS, with demonstration of durable responses, provides evidence of a statistically significant and clinically meaningful benefit of dabrafenib and trametinib in pediatric patients with LGG with BRAF V600E mutation. A post-marketing commitment will be issued to obtain the final analysis for overall survival and progression-free survival once all patients with LGG have been followed for at least 2 years. The Applicant will include an analysis of change in visual acuity over the course of treatment with dabrafenib and trametinib for patients who enrolled on the study due to impaired vision.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with VA assessments and response data, conclusions on the effect of D+T on visual outcomes are limited.	
Risk and Risk Management	• The pooled safety database for these NDAs includes 166 pediatric patients with advanced solid tumors harboring BRAFV600E mutations who received at least one dose of dabrafenib and trametinib at the respective RP2Ds. The G2201 LGG cohort safety population included 73 patients who received dabrafenib and trametinib and 33 patients who received carboplatin with vincristine. • Warnings and Precautions for dabrafenib and trametinib include new primary malignancies (cutaneous, and non-cutaneous), tumor promotion in BRAF wild-type tumors, hemorrhage, cardiomyopathy, uveitis, serious febrile reactions, serious skin toxicities, hyperglycemia, risk of anemia in patients with G6PD deficiency, and embryo-fetal toxicity. No additional Warnings and Precautions were proposed based on this application. A new safety signal of weight gain was identified in pediatric patients. • In the pooled safety population, serious adverse reactions occurred in 47% of pediatric patients who received dabrafenib in combination with trametinib. • The most common (> 20%) adverse reactions in the pooled pediatric population were pyrexia (66%), rash (54%), headache (40%), vomiting (38%), musculoskeletal pain (36%), fatigue (31%), dry skin (31%), diarrhea (30%), nausea (26%), epistaxis and other bleeding events (25%), abdominal pain (24%) and dermatitis acneiform (23%).	Although dabrafenib and trametinib can cause serious adverse reactions, these safety concerns are adequately addressed by information in the Warnings and Precautions and Dosage and Administration sections of product labeling. 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). Two post-marketing requirements to address safety in the pediatric population will be issued to assess 1) the potential for growth plate abnormalities and other effects on growth and development and 2) the incidence of known serious risks associated with dabrafenib in combination with trametinib, including new primary malignancies, cardiomyopathy, and ocular toxicities.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The most common (> 2%) Grade 3 or 4 laboratory abnormalities were decreased neutrophil count (20%), increased alanine aminotransferase (3.1%), and increased aspartate aminotransferase (3.1%).	

4.4 Patient Experience Data

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

☐	The patient experience data that was submitted as part of the application, include: Data on PROMIS Parent Proxy Global Health 7+2 collected in Study G2201							Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as						[e.g., Section 6.1 Study endpoints]
			X	Patient reported outcome (PRO)				Section 11.1.2
			☐	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						[e.g., Section 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data						
	☐	Natural history studies						
	☐	Patient preference studies (e.g., submitted studies or scientific publications)						
	☐	Other: (Please specify)						
☐	Patient experience data that was not submitted in the application, but was considered in this review.							

X _____

Cross-Disciplinary Team Leader

Diana Bradford, MD

5 Therapeutic Context

5.1 Analysis of Condition

The Applicant's Position

Pediatric gliomas constitute approximately 46% of primary brain and other central nervous system (CNS) tumors in patients aged < 0-19 years (Ostrom et al 2020). These tumors are often categorized into World Health Organization (WHO) Grades (I, II, III, and IV), and further into low-grade glioma (LGG; WHO grade I and II) and high-grade glioma (HGG; WHO grade III and IV). Pediatric LGG and pediatric HGG are debilitating and rare (age-adjusted incidence 1.71 and 1.11 cases per 100,000, respectively) but represent one of the most common pediatric solid tumors harboring BRAF V600E mutations. BRAF V600E mutations have been positively identified in 6% of pediatric HGGs (Mackay et al 2017, Ostrom et al 2020) and in about 17% of pediatric LGG tumors, across many histologic subtypes and in tumors arising in various anatomic areas of the brain (Lassaletta et al 2017, Ryall et al 2020).

BRAF V600-activating mutations have been identified in pediatric tumors, including gliomas, while dabrafenib, trametinib and their combination have proven beneficial in adults with tumors harboring BRAF V600 activating mutations. This led to the investigations of this targeted therapy in this molecularly defined subset of pediatric patients with BRAFV600 mutant gliomas.

In addition to the key benefits of D+T for the treatment of pediatric patients with BRAF V600 mutation-positive glioma, the novel age-appropriate liquid formulations of dabrafenib (10 mg DT for oral suspension) and trametinib (4.7 mg PfOS) that can be conveniently dosed and administered in patients 1 year of age and older who are unable to swallow the solid dosage forms, also contributes to the intended benefits of this combination therapy.

The FDA's Assessment

FDA agrees with the Applicant's summary. In a comprehensive study, genomic profiling on 3,633 pediatric cancer samples identified a cohort of 221 (6.1%) cases with known or novel alterations in BRAF or RAF1 detected in extracranial solid tumors, brain tumors, or hematological malignancies. Eighty percent (176/221) of these tumors had a known-activating short variant (98, 55.7%), fusion (72, 40.9%), or insertion/deletion (6, 3.4%). Among BRAF altered cancers, the most common tumor types were brain tumors (74.4%), solid tumors (10.8%), hematological malignancies (9.1%), sarcomas (3.4%), and extracranial embryonal tumors (2.3%). Specifically, V600E accounts for approximately 50% of BRAF known-activating variants in pediatric cancers (Rankin 2021). BRAF V600E mutation is present in 3-6% of pediatric and young adult HGGs (Wen 2022, Mackay 2017) and in about 5-17% of pediatric LGGs (pLGGs) (Wen 2022, Lassaletta 2017). The most common histologies observed in pediatric patients with LGG are pilocytic astrocytoma Grade I/II, ganglioglioma, and pleomorphic xanthoastrocytoma

(PXA); ganglioglioma and PXA are associated with particularly high incidence of BRAF V600E mutation (Bouffett 2011, Packer 2017).

5.2 Analysis of Current Treatment Options

The Applicant's Position

The current treatment options for pediatric glioma are limited. The best choice of available treatment is chemotherapy, which requires specialized care to manage potential significant allergic reactions that may be very severe. Retrospective data in pediatric patients with LGG harboring the BRAF V600E mutation suggests that chemotherapy results in unfavorable progression-free survival (PFS) and overall survival (OS) outcomes (Lassaletta et al 2017, Ryall et al 2020). For HGG, the treatments are limited, with a common strategy of gross total surgical resection followed by focal irradiation to the tumor bed plus additional chemotherapy (MacDonald et al 2011). In addition, supportive care needed by patients receiving repeated infusions is a cumbersome challenge for caregivers (Sturm et al 2017).

The FDA's Assessment

Pediatric low-grade gliomas have historically been treated with surgery, radiation, and chemotherapy. Surgical resection is the treatment of choice for the majority of low-grade gliomas with a >87% 10-year OS observed in patients eligible for a complete, subtotal, or partial resection (Gnekow 2012). Although radiation may be used for patients with pLGG and may induce responses, it is associated with comorbidities such as neurocognitive, endocrine, and other long-term toxicities and secondary malignancy (Sievert 2009, Krishnatry 2016, Bandopadhayay 2014), and is generally avoided in younger pediatric patients.

Trials evaluating the efficacy of combination and single agent chemotherapy for children with pLGG have been performed by the Children's Oncology Group (COG). In these studies, ORR ranged from 4 to 35% and 5-year OS rates ranged from 86 to 94% as described in Table 5-1.

Table 5-1. The Efficacy of Combination and Single Agent Chemotherapy for Children With Pediatric Low-Grade Glioma

Study	Therapy	ORR	5-year OS Rate	PFS Rate
ACNS0223 n=65 Chintagumpala 2015	Temozolomide, carboplatin, and vincristine (TCV)	26%	87% (95% CI: 75,93)	-
Bouffett 2011 n=51	Vinblastine	4%	93% (± 3.8%)	-
Lassaletta 2016 n=54	Vinblastine	26%	94% (95% CI: 89,100)	53% (95% CI: 41, 695)
A9952 n=137 Ater 2012	Carboplatin and vincristine (CV)	35% (95% CI:27, 46)	86% (± 3%)	-
A9952 n=137 Ater 2012	Thioguanine, procarbazine, lomustine, and vincristine (TPCV)	30% (95% CI: 22, 40])	87% (± 7%)	-

Abbreviations: CI, confidence interval; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

Studies of BRAF V600E selected pLGG populations receiving chemotherapy with or without radiation have demonstrated lower response rates compared to an unselected population. In a study of 69 pediatric patients with BRAF V600E mutant LGGs receiving chemotherapy and radiation, the 10-year PFS rate was 27% in the BRAF V600E group while in pediatric patients with LGG unselected for BRAF V600E, the 10-year PFS rate was 60% (Lassaletta 2017). In a small, retrospective analysis of patients who received either BRAF inhibition (dabrafenib or vemurafenib) or chemotherapy (including carboplatin with vincristine, vinblastine, and temozolomide) the ORR for BRAF inhibitors was 53% compared to 10% for chemotherapy (Nobre 2020). In another study, clinical and treatment data from pediatric patients with LGGs with BRAF V600E mutation were analyzed revealing an ORR of 23% after conventional chemotherapy (Lassaletta 2017). In these studies, it was noted that some patients who received BRAF inhibition therapy experienced rapid disease progression and clinical deterioration upon cessation of these drugs, and required re-initiation of BRAF inhibition (Lassaletta 2017, Nobre 2020).

6 Regulatory Background

6.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position

Tafinlar (dabrafenib; new drug application [NDA] 202806) was first approved by FDA in 2013 as monotherapy for the treatment of subjects with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Mekinist (trametinib; NDA 204114) was first approved by FDA in 2013 as monotherapy for the treatment of BRAF-inhibitor

treatment-naïve subjects with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA approved test. Since the initial approvals, Tafinlar in combination with Mekinist has been FDA-approved for:

- Treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test (January 2014).
- Adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph nodes, following complete resection (April 2018).
- Treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test (June 2017).
- Treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options (May 2018).
- Treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed on prior therapy and have no satisfactory alternative treatment options (June 2022).

The FDA's Assessment

We agree with the Applicant's summary of regulatory actions and marketing history.

6.2 Summary of Presubmission/Submission Regulatory Activity The Applicant's Position

The key FDA interactions related to this application are summarized in Table 6-1.

Table 6-1. Applicant - Key FDA Interactions

Meeting Type	Date	Meeting Purpose
C	November 29, 2021	To discuss the final results of your retrospective central BRAF assessment for the high-grade glioma (HGG) cohort of Study CDRB436G2201 and propose amended language for the number of patients with BRAF V600 mutation to be studied in Study CDRB436G2201 of the Tafinlar (dabrafenib) and Mekinist (trametinib) Written Requests.
B	March 16, 2022	To obtain FDA's feedback on whether the data from Study G2201 supports the use of dabrafenib in combination with trametinib for the treatment of pediatric patients 1 year of age and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy and to obtain feedback on the content and format of the proposed sNDA/NDA submission package and overall regulatory submission strategy.

Meeting Type	Date	Meeting Purpose
C - Written Response Only	August 9, 2021	To seek the FDA's agreement on whether Betadex Sulfobutyl Ether Sodium (USP, Ph. Eur.) can be considered a non-novel excipient when used in the trametinib PfOS formulation. FDA did not have concerns with calling (b) (4) a non-novel excipient.

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine kinase; NDA, new drug application; PfOS, powder for oral solution; (b) (4) ; sNDA, supplemental NDA

On March 28, 2022, FDA granted Breakthrough Therapy designation for dabrafenib in combination with trametinib for the treatment of pediatric patients one year of age and older with LGG with a BRAF V600E mutation who require systemic therapy.

On June 24, 2022, FDA granted orphan drug designation for trametinib for the treatment of malignant glioma with BRAF V600 mutation (ODA 22-8827). Dabrafenib was granted orphan drug designation for the treatment of malignant glioma with BRAF V600 mutation on February 8, 2016 (ODA 15-5064).

The FDA's Assessment

We agree with the Applicant's timeline stated above and have several additions as noted below.

On March 7, 2013, the Applicant submitted IND 117898 to FDA.

On March 1, 2016, FDA issued Written Requests for dabrafenib and trametinib. The clinical study submitted to support the proposed sNDA is included in the Written Request.

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

7.1 Office of Scientific Investigations (OSI)

Clinical data from Study CDRB436G2201 LGG Cohort were submitted to the Agency in support of NDA 217513 and NDA 217514 for dabrafenib in combination with trametinib in children and adolescents with BRAF V600 mutation positive LGG. Three clinical investigators (Drs. Ashley Plant [site # 5008], Jordan Hansford [site # 4001], and Maria Luisa Garrè [site # 3801]), as well as the imaging contract research organization (CRO), (b) (4) were inspected.

At Dr Plant's site, the tumor assessment for a key secondary endpoint of investigator assessed overall response rate (ORR) per response assessment in neuro-oncology (RANO) criteria was not performed according to the protocol. At the time of the inspection, the site had screened 4 patients and enrolled 3 patients in the LGG cohort of the study. Of the 3 patients enrolled, 1

patient discontinued the study due to progression of disease and 2 have completed treatment in the control arm and are currently in follow-up. All 3 patients had imaging scans performed at protocol specified timepoints and all scans were submitted to the imaging CRO for central review for assessment and determination of primary efficacy endpoint. During the inspection, it was noted that for the overall evaluation of the imaging scans for tumor response/progression, the investigator did not follow the protocol. Generally, the investigator did not compare the findings of newly acquired scans to that of the baseline or best response scans as required by the protocol, but rather to the immediately previous scan.

The tumor assessments for the secondary endpoint were performed according to the protocol at the other inspected sites. At Dr. Hansford's, Dr. Garrè's, and (b) (4) sites, the inspection found no regulatory violations.

Except for the tumor assessment methodology used to determine one of the key secondary endpoints at Dr. Plant's site, Study CDRB436G2201 appears overall to have been conducted adequately. The review team concluded that, since response assessment for the primary endpoint was determined by central review, the incorrect method of determination of investigator-assessed response did not affect the primary evidence of effectiveness presented in the application. The data generated by the inspected clinical investigators and the imaging CRO appear acceptable in support of the respective indication in these NDAs.

For the full report see OSI's January 13, 2023, site inspection submission.

7.2 Product Quality

For a full discussion of product quality review issues, refer to the OPQ Integrated Quality Assessment uploaded in DARRTs on February 1, 2023. The summary below has been adapted from the executive summary of this review.

The below summary is for the following product combination: trametinib 4.7 mg powder for oral solution in combination with dabrafenib 10 mg dispersible tablets for the treatment of BRAF V600E mutation-positive low-grade glioma in pediatric patients 1 year of age and older.

The Applicant provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities were deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends approval of NDA 217514 for TAFINLAR® (dabrafenib) tablets for oral suspension.

During review of NDA 217513, the CMC drug product reviewer requested feedback from the nonclinical discipline regarding the levels of excipients in trametinib powder for oral solution. The levels of excipients, betadex sulfobutyl ether sodium, dibasic sodium phosphate, and potassium sorbate in trametinib powder for oral solution were reviewed by the nonclinical

team. The Applicant provided a safety toxicology assessment of (b) (4), also known as betadex sulfobutyl ether sodium or (b) (4) to support its use for oral administration to pediatric (≥ 1 year of age) and adult patients. Also, the Applicant provided a letter of authorization to cross-reference DMF (b) (4) for (b) (4) The assessment included discussion of 90-day repeat dose toxicity studies with (b) (4) given by oral gavage to rats and dogs, to justify the level and oral route of administration of (b) (4) Toxicology study reports were also accessed by DMF for (b) (4) In the rat study, clinical observations included liquid or non-formed feces at 3750 mg/kg in males and females. There were remarkable increases in ALT and AST in males at the dose of 3750 mg/kg correlating to histopathology findings of minimal necrosis and acute inflammation in the liver. Histopathology findings included cecal hyperplasia in males and females, cardiomyopathy in males and minimal vacuolation of tubular epithelia in the kidneys, all at the dose of 3570 mg/kg. Clinical observations in dogs included liquid or non-formed feces between 2 and 6 hours post dose at ≥600 mg/kg in males and females. By week 12, urinalysis showed that the urine from animals given 3600 mg/kg was darker and more turbid than that from control animals, with higher pH and urobilinogen. There were no remarkable histopathology findings. The no observed adverse effect level (NOAEL) for (b) (4) in rats was (b) (4) mg/kg/day ((b) (4) mg/m^2) and in dogs was (b) (4) mg/kg/day (b) (4) mg/m^2/day). These results provide a (b) (4) and (b) (4) safety margin from the NOAEL for dogs and rats, respectively, compared to the amount of (b) (4)) (b) (4) administered to pediatric patients with the maximum recommended daily dose of 2 mg trametinib.

For pediatric patients receiving 2 mg of trametinib, the maximum daily exposure of potassium sorbate and dibasic sodium phosphate is (b) (4) mg and (b) (4) mg, respectively. Given previous clinical experience with a maximum daily exposure of 400 mg of potassium sorbate in pediatric patients and the GRAS designation of phosphates, including dibasic sodium phosphate, the levels of the excipients are acceptable. In addition, the MEKINIST® powder for oral solution formulation is already in use in pediatric patients.

Overall, based on available data, previous clinical experience and the proposed clinical indication, there are no nonclinical safety concerns with the proposed levels of excipients in the drug product.

Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends approval of NDA 217513 for MEKINIST® (trametinib) for oral solution.

7.3 Clinical Microbiology

Refer to OPQ Integrated Quality Review referenced in Section 7.2.

7.4 Devices and Companion Diagnostic Issues

In Study G2201, local assessment of BRAF V600E mutation status was required for enrollment and central confirmation was performed retrospectively. BRAF V600 mutation in the tumor was assessed locally or at a Novartis designated central reference laboratory, if local BRAF V600 testing was unavailable. A companion diagnostic (CDx) for the detection of BRAF V600E is (b) (4) part of the PMC issued on June 22, 2022, in the approval letter for the tissue agnostic indication. (b) (4) A post-marketing commitment for submission of a companion diagnostic for the selection of pediatric patients with BRAF V600E mutant LGG will be included in the approval letter.

8 Nonclinical Pharmacology/Toxicology

8.1 Executive Summary

Dabrafenib is an orally administered, RAF kinase inhibitor of the mutated forms BRAF V600E, BRAF V600K, and BRAF V600D as well as wild-type BRAF and CRAF kinases. Other kinases inhibited at clinically achievable concentrations include CK1, SIK1, NEK11, ALK5, and LIMK1.

Trametinib is a reversible inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity.

The combination of dabrafenib (capsule formulation) and trametinib (tablet formulation) has been approved for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutations, among other indications.

On August 17, 2022, Novartis Pharmaceuticals Corporation (Novartis) submitted NDA 217513 for a new liquid formulation of MEKINIST® (trametinib) powder for oral solution and NDA 217514 for a new liquid formulation of TAFINLAR® (dabrafenib) tablet for oral suspension. The Applicant states that the development of the age-appropriate pediatric formulations of dabrafenib and trametinib was in fulfillment of PMR 4298-2 for TAFINLAR (NDA 202806) and PMR 4297-2 for MEKINIST (NDA 204114). The proposed indication is for the combination of trametinib and dabrafenib for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) harboring a BRAF V600E mutation. Based on advice from the FDA, the Applicant submitted supplemental applications to NDA 202806 for TAFINALR capsules and NDA 204114 for MEKINIST tablet to use their solid formulations to treat pediatric patents 1 year of age and older with low-grade glioma (LGG) harboring BRAF V600E mutation who require systemic therapy.

No new nonclinical data were included in the current submission. The Applicant cross-referenced the original NDA 202806 for TAFINLAR (dabrafenib) as well as the original NDA 204114 for MEKINIST (trametinib), both of which were approved on May 29, 2013, and their subsequent respective efficacy supplements for nonclinical data to support the current NDAs. The nonclinical data under NDAs 202806 and 204114 are relevant for the current NDAs since the active pharmaceutical ingredients for the new liquid pediatric formulation are the same as the previously approved tablets or capsules.

During review of NDA 217513, the CMC drug product reviewer requested feedback from the nonclinical discipline regarding the levels of excipients in trametinib powder for oral solution. See the Section 7.2 for the pharmacology/toxicology assessment.

There were no major labeling revisions to the nonclinical sections. Minor edits were made to Sections 5.12, 8.1, 8.2, 8.3, 13.1 and 17 for MEKINIST (NDA 271513, NDA 204114) and Sections 5.11, 8.1, 8.2, 8.3, 13.1, 13.2 and 17 for TAFINLAR (NDA 217514, NDA 202806) to clarify that animal to human exposure multiples referred to in the label were based on the adult clinical dose or to conform with current labeling practices.

From a nonclinical perspective, there are no outstanding issues, and the cross-referenced data from NDAs 202806 and 204114 for dabrafenib and trametinib, respectively, are adequate to support approval of the NDAs 217513 and 217514 for the proposed indication.

8.2 Referenced NDAs, BLAs, DMFs

The Applicant's Position

Reference is made to the original NDA for Tafinlar (dabrafenib) NDA 202806 submitted 29-Jul-2012 and approved on 29-May-2013, and subsequent efficacy supplements S-002, S-006, S-008, S-010, and S-022. Additional reference is made to the original NDA for Mekinist (trametinib) NDA 204114 submitted 02-Aug 2012 and approved on 29-May-2013, and subsequent efficacy supplements S-001, S-005, S-007, S-009, and S-024. The nonclinical pharmacology/toxicology profile for dabrafenib and trametinib has not changed and results support the treatment of pediatric patients with LGG with BRAF V600E mutation.

8.3 Pharmacology

The Applicant's Position

No new information is provided in the current submission.

The FDA's Assessment

FDA agrees that the Applicant did not provide new pharmacology data in the current application. Pharmacology data previously submitted and reviewed under NDA 202806 (dabrafenib) and NDA 204114 (trametinib) and their respective supplements are relevant for the proposed indication of pediatric patients with LGG with BRAF V600 mutation.

8.4 ADME/PK

The Applicant's Position

No new information is provided in the current submission.

The FDA's Assessment

FDA agrees that the Applicant did not provide new ADME/PK data in the current application.

8.5 Toxicology

The Applicant's Position

No new information is provided in the current submission.

The FDA's Assessment

FDA agrees that the Applicant did not provide new toxicology data in the current submission, but rather cross-referenced toxicology data submitted to previously approved NDA 202806 for dabrafenib (TAFINLAR) and NDA 204114 for trametinib (MEKINIST).

X X

G. Sachia Khasar, PhD.
Primary Reviewer

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Acting Supervisor

9 Clinical Pharmacology

9.1 Executive Summary

The FDA's Assessment

The Applicant is seeking approval of MEKINIST (trametinib) and TAFINLAR (dabrafenib) in combination for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation. The Applicant is also seeking approval of two new pediatric liquid oral dosage forms: trametinib oral solution and dabrafenib tablets for oral suspension.

Three pediatric studies (Study G2201, Study A2102 and Study X2101) provided pharmacokinetic (PK) data to support the proposed recommended dosages of the approved oral solid dosage forms and the proposed pediatric oral liquid dosage forms. The population PK (PopPK) analyses support weight-based dosing for both trametinib and dabrafenib in patients 1 to <18 years of age given age is not a significant covariate of the exposures after accounting for weight. Simulations based on pediatric PopPK model predicted that steady state exposures of dabrafenib and trametinib in combination in pediatric patients with weight-based dosing are generally comparable to those in the adult population at the approved recommended dosages. The exposure-response (E-R) analyses also support the proposed pediatric dosages as no clear E-R relationships for overall response rate (ORR) or progression-free survival (PFS) were observed in pediatric patients with LGG and HGG or LGG alone. In addition, the E-R relationships for safety in pediatric patients were broadly consistent with previous E-R analyses in adults with melanoma. Overall, the proposed weight-based dosing for pediatric patients is acceptable based on the PopPK and E-R analyses.

FDA guidance recommends that a food-effect study should be conducted when a new age-appropriate formulation is developed; however, the effects of food on the two new pediatric liquid formulations have not been studied. Therefore, a postmarketing commitment (PMC) will be issued for each of the NDAs to evaluate the effects of food on the exposure of trametinib and dabrafenib pediatric formulations.

9.1.1 Recommendation

The Office of Clinical Pharmacology reviewed the information contained in NDA 217513 and NDA 217514. These NDAs are approvable from a clinical pharmacology perspective, provided the Applicant and the FDA reach an agreement regarding the labeling language. The key review issues with specific recommendations/comments are summarized below**.**

Table 9-1. Key Clinical Pharmacology Review Issues

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The PopPK and E-R analyses support the proposed weight-based dosing for both trametinib and dabrafenib solid and liquid dosage forms. The PopPK analysis predicted that steady state exposures of dabrafenib and trametinib in combination in pediatric patients with weight-based dosing are generally comparable to those in adult population at the approved recommended dosages. No clear E-R relationships for ORR or PFS were observed in pediatric patients with LGG and HGG or LGG alone, and the E-R relationships for safety in pediatric patients were broadly consistent with previous E-R analyses in adults with melanoma (refer to Section 23.4 for the detailed analysis).
General dosing instructions	The recommended dosages for trametinib and dabrafenib solid and liquid oral dosage forms are based on body weight for pediatrics. See Applicant's Table 9-3 and Table 9-4.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Age, sex, body weight, renal impairment and hepatic impairment had no clinically significant effect on the exposure of trametinib or dabrafenib in adults. Insufficient data were available to evaluate the potential differences in the exposure of trametinib or dabrafenib by race or ethnicity. The impact of these covariates would not be expected to be different in the pediatric population, with exception of weight as weight had a clinically significant effect on exposure of trametinib and dabrafenib in pediatric patients. Insufficient data were available to evaluate the potential differences in the exposure of trametinib or dabrafenib by race or ethnicity in adult and pediatric populations.
Labeling	The labeling was updated to be consistent with regulations, current guidances and best practices. The following key modifications were made to the approved labeling documents: Subsection 12.3 Pharmacokinetics: FDA removed (b) (4) Refer to Section 9.2.2.2 of this review for additional information. FDA recommended the following statement regarding pediatric exposure relative to adult exposure: Pharmacokinetic parameters in patients aged 1 to 18 years of age are within range of values previously observed in adults give the same dose based on weight.
Other (specify)	None.

Abbreviations: E-R, exposure-response; HGG, high-grade glioma; LGG, low-grade glioma; ORR, overall response rate; PFS, progression-free survival; popPK, population pharmacokinetics

9.1.2 Post-Marketing Requirements and Commitments

The rationale and descriptions of post-marketing commitments (PMCs) are summarized in the table below. The PMCs are issued to address the food effect study for new pediatric dosage formulations of trametinib and dabrafenib.

Table 9-2. Summary of Postmarketing Commitments

Postmarketing commitments for NDA 217513	
PMC rationale	The food effect on the trametinib for oral solution is unknown. Therefore, a food effect study should be conducted to evaluate the effect of food on the absorption and systemic exposure of trametinib for pediatric oral solution formulation.
PMC description	Conduct a food effect study to evaluate the impact of food on exposure of trametinib for oral solution per FDA food effect guidance titled "Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry."
Postmarketing commitments for NDA 217514	
PMC rationale	The food effect on dabrafenib tablets for oral suspension is unknown. Therefore, a food effect study should be conducted to evaluate the effect of food on the absorption and systemic exposure of dabrafenib tablets for oral suspension.
PMC description	Conduct a food effect study to evaluate the impact of food on exposure of dabrafenib tablets for oral suspension per FDA food effect guidance titled "Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry."

Abbreviations: IND, investigational new drug; NDA, new drug application; PMC, postmarketing commitment

9.2 Summary of Clinical Pharmacology Assessment

All relevant information to support the clinical pharmacology profile of dabrafenib plus trametinib was submitted within the DRB436 (dabrafenib) NDA.

9.2.1 Pharmacology and Clinical Pharmacokinetics

The Applicant's Position

Pharmacokinetics and ADME characteristics of dabrafenib and trametinib have been well characterized in adult patients for the currently approved solid formulations. The clinical pharmacology assessment in this application focused on dabrafenib plus trametinib (D+T) combination as an oral liquid formulation in the pediatric population with BRAF V600E mutation-positive glioma. Three pediatric studies (Study G2201, Study A2102 and Study X2101) contributed PK data in the pediatric population and used both oral solid and the proposed oral liquid formulations as follow:

- The supportive study [Study A2102] investigating dabrafenib monotherapy for the treatment of advanced BRAF V600-mutation positive solid tumors in 85 pediatric patients aged 12 months to < 18 years. This study was completed on 04-Dec-2020.
- The supportive study [Study X2101] investigating trametinib monotherapy and D+T combination therapy for the treatment of advanced solid tumors in 139 pediatric patients aged 1 month to < 18 years. This study was completed on 29-Dec-2020.
- The pivotal study [Study G2201] in 151 children and adolescents (≥ 12 months to < 18 years) with BRAF V600 mutation positive, refractory or relapsed HGG tumors after

having received at least one previous standard therapy (single arm HGG cohort, n=41) or with BRAF V600 mutant LGG tumors with progressive disease following surgical excision, or non-surgical candidates with necessity to begin first systemic treatment because of a risk of neurological impairment with progression compared to chemotherapy (carboplatin with vincristine) (randomized LGG cohort, n=110). This study is currently ongoing; enrolment is completed and the data cut-off for the primary analysis occurred on 23-Aug-2021.

A Population PK (PopPK) analysis of the integrated pediatric pharmacokinetics (PK) data, guided by the previously established exposure-response relationships in adults, was used to guide the pediatric dosing for the liquid formulations for patients 1 year of age and older.

Initial trials of dabrafenib (Study A2102) and trametinib (Study X2101) in the pediatric population sought to identify doses of single agents, followed by combination, that matched exposures associated with efficacy in the adult population.

Rapid absorption of both dabrafenib and trametinib was observed for the liquid formulations and Tmax values were largely comparable with solid formulations. Following single oral administration of dabrafenib in Study G2101, rapid absorption was observed with median Tmax of 1.4 h and 1.5 h for solid and liquid formulations, respectively. Following single oral administration of trametinib in Study MEK115892, rapid absorption was observed with median Tmax of 1.8 h and 1.0 h for solid and liquid formulations, respectively. Administration of dabrafenib and trametinib as combination in Study G2201 showed similar rapid absorption of individual agents. Median Tmax for dabrafenib and trametinib at steady state was 1.4 h and 1.3 h, respectively, in the LGG cohort, and 2.0 h in the HGG cohort.

In Study G2201, the observed plasma exposure of dabrafenib and trametinib in pediatric patients with BRAF V600 mutation-positive glioma was comparable to exposures in adult patients in previously approved indications. The steady-state Cavg was 409 ng/mL (LGG) and 359 ng/mL (HGG) for dabrafenib and 14.1 ng/mL (LGG) and 12.8 ng/mL (HGG) for trametinib. These exposures met the target plasma exposure levels for dabrafenib (~300 ng/mL) and trametinib (~10 ng/mL) that have been established in adult patients based on previous preclinical and clinical exposure-response analyses. For both LGG and HGG pediatric patient populations, the geometric mean dabrafenib metabolite to parent AUC0-τ ratios for hydroxy-dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib were also consistent with historical dabrafenib metabolite ratios in adult patients.

In the pediatric popPK modeling, rapid oral absorption rate constants (mean Ka) were observed for both dabrafenib and trametinib in adults (1.2 h^{-1} and 1.6 h^{-1}) and pediatrics (1.3 h^{-1} and 1.4 h^{-1}), indicating rapid and similar absorption of dabrafenib and trametinib from both formulations in adults and pediatric patients. Similar steady state exposure was observed for dabrafenib liquid and solid formulations with AUCtau and Cmax ratios of 1.0 and 1.0, respectively. The steady state trametinib exposure for liquid and solid formulations was close with AUCtau and Cmax ratios of 1.2 and 1.3, respectively. These results supported comparable

PK of dabrafenib and trametinib between liquid and solid formulations. In addition, the population PK analysis determined that apparent clearance depended on weight and gender. For a typical male pediatric patient who weighs 38.7 kg (median in the pooled pediatric studies), the apparent maximum inducible dabrafenib clearance at steady state was 20.94 L/h (18.6 L/h for the adults) and the estimated dabrafenib apparent base clearance was 8.82 L/h, (16.7 L/h in adults). For a typical male pediatric patient who weighs 32.85 kg (median in the pooled pediatric studies) the estimated population apparent trametinib clearance was 3.44 L/h (5.07 L/h in adults). Differences in PK based on gender were not considered clinically relevant in pediatric glioma population.

The FDA's Assessment

FDA agrees with the Applicant's position on the summary PK and ADME characteristics of the new oral liquid dosage forms of dabrafenib and trametinib.

Body weight had no clinically significant effect on the exposure of trametinib or dabrafenib in adults. However, in the PopPK analysis for patients 1 to 17 years of age, body weight (8 to 156 kg for trametinib; 6 to 156 kg for dabrafenib) was identified as a significant covariate for clearance and volume of distribution. Patients with higher body weights tended to have higher clearance for dabrafenib and trametinib. PopPK simulation predicted that steady state exposures of dabrafenib and trametinib in pediatric patients given weight-based dosing are within the range of values previously observed in adults given the approved recommended flat dosage.

9.2.2 General Dosing and Therapeutic Individualization

9.2.2.1 General Dosing

The Applicant's Position

The recommended posology for the dabrafenib and trametinib combination therapy was established using the learnings from the pivotal study that used an age-specific weight-based dose regimen and further dose optimization with additional pediatric PK data and population PK analyses.

Dabrafenib dispersible tablet is available as single strength of 10 mg only, and calculation of weight-based dosing may be cumbersome for patients and caregivers. Table 9-3 displays the proposed weight-based dosage for dabrafenib dispersible tablets in patients 1 year of age and older. The dose reductions follow the established algorithm for the solid formulation in adult patients, with up to three dose reduction levels and reductions by 33% (from 150 mg BID to 100 mg BID in adults), 50% (to 75 mg BID in adults) and 66% (to 50 mg BID in adults) from the starting dose.

Table 9-3. Applicant - Recommended Weight-Based Dosing and Dosage Reductions for Dabrafenib Dispersible Tablets in Pediatric Patients

	Starting Dosage			Recommended Dosage Reductions (Number of Dispersible Tablets)		
Body Weight (kg)	Dose	Number of 10-mg Dispersible Tablets BID	Dose in mg/kg BID	First Reduction	Second Reduction	Third Reduction
8 to 9 kg	20 mg BID	2	2.2-2.5	1	-	-
10 to 13 kg	30 mg BID	3	2.3-3.0	2	1	-
14 to 17 kg	40 mg BID	4	2.4-2.9	3	2	1
18 to 21 kg	50 mg BID	5	2.4-2.8	3	2	1
22 to 25 kg	60 mg BID	6	2.4-2.7	4	3	2
26 to 29 kg	70 mg BID	7	2.4-2.7	5	4	2
30 to 33 kg	80 mg BID	8	2.4-2.7	5	4	3
34 to 37 kg	90 mg BID	9	2.4-2.6	6	5	3
38 to 41 kg	100 mg BID	10	2.4-2.6	7	5	3
42 to 45 kg	110 mg BID	11	2.4-2.6	7	6	4
46 to 50 kg	130 mg BID	13	2.6-2.8	9	7	4
≥51 kg	150 mg BID	15	≤ 2.9	10	8	5

Abbreviations: BID, twice a day

The trametinib oral solution is prepared at a concentration of 0.05 mg/mL, and calculation of weight-based dosing may again be cumbersome for patients and caregivers. The recommended weight-based doses in Table 9-4 are therefore expressed in mL of solution that can be measured with the graduated syringe which is co-packaged with the drug product. The dose reductions also follow the established algorithm for the solid formulation in adult patients, with up to two dose reduction levels and reductions by 25% (from 2 mg/day to 1.5 mg/day in adults) and by 50% (to 1 mg/day in adults).

Table 9-4. Applicant - Recommended Weight-Based Dosing and Dosage Reductions for Trametinib Oral Solution in Pediatric Patients

	Starting Dosage		Recommended Dosage Reductions	
Body Weight (kg)	Volume of Oral Solution in mL, Once Daily (Equal to mg of Trametinib)	Dose in mg/kg Once Daily	First Reduction (mL)	Second Reduction (mL)
8 kg	6 mL (0.3 mg)	0.038	5	3
9 kg	7 mL (0.35 mg)	0.039	5	4
10 kg	7 mL (0.35 mg)	0.035	5	4
11 kg	8 mL (0.4 mg)	0.036	6	4
12 to 13 kg	9 mL (0.45 mg)	0.035-0.038	7	5
14 to 17 kg	11 mL (0.55 mg)	0.032-0.039	8	6
18 to 21 kg	14 mL (0.7 mg)	0.033-0.039	11	7
22 to 25 kg	17 mL (0.85 mg)	0.034-0.039	13	9
26 to 29 kg	18 mL (0.9 mg)	0.031-0.035	14	9
30 to 33 kg	20 mL (1 mg)	0.030-0.033	15	10
34 to 37 kg	23 mL (1.15 mg)	0.031-0.034	17	12
38 to 41 kg	25 mL (1.25 mg)	0.030-0.033	19	13
42 to 45 kg	28 mL (1.4 mg)	0.031-0.033	21	14
46 to 50 kg	32 mL (1.6 mg)	0.032-0.035	24	16
≥51 kg	40 mL (2 mg)	≤ 0.039	30	20

The FDA's Assessment

FDA agrees with the Applicant's position on weight-based dosing for the pediatric population. PopPK models for dabrafenib and trametinib were developed based on the previous adult model with dabrafenib PK data from 243 patients (n=105 for 12 years of age and older; n=77 for 6-11 years of age; n=61 for <1 to 5 years of age) and trametinib PK data from 244 patients (n=91 for 12 years of age and older; n=77 for 6-11 years of age; n=76 for <1 to 5 years of age). Body weight (7-156 kg) was found to be a significant covariate for clearance and volume of distribution supporting weight-based dosing. Age (1-17 years) was not found to be a statistically significant covariate after accounting for body weight. Simulation based on pediatric PopPK models predicted that the steady state exposures of dabrafenib and trametinib at the proposed weight-based dosages are within the range of values previously observed in the adult population at the approved recommended flat dosages.

9.2.2.2 Therapeutic Individualization

Data

The doses in pediatric details are provided in Section 9.2.2.1.

The Applicant's Position

The drug-drug interaction potential of liquid formulations of dabrafenib and trametinib are expected to be similar to that of the currently marketed solid formulations, as described in the label. Administration of dabrafenib and trametinib in combination had no clinically relevant effect on the exposure of either agent relative to administration of either agent alone in previous clinical studies. No additional clinically relevant drug-drug interactions specific to the liquid formulations are expected.

The liquid oral dosage forms (dabrafenib DT and trametinib PfOS) were used under fasting conditions (defined as at least 1 h before or 2 h after a meal) in the pivotal Study G2201. Based on similar relative bioavailability of solid and liquid formulations, the liquid formulations are expected to be similar to the immediate release solid formulation with respect to the effect of food and are proposed to be administered under fasting conditions in the marketed setting, similar to the solid formulations.

No additional therapeutic individualization is proposed. Further evaluation of other intrinsic factors (such as organ impairment) was not evaluated as part of this application.

The FDA's Assessment

FDA agrees with the Applicant's position that the drug-drug interaction potential of the proposed oral liquid dosage forms of dabrafenib and trametinib are expected to be similar to that of the approved oral solid dosage forms.

FDA, however, disagrees with the Applicant's position that food effects on the absorption and systemic exposure of the oral liquid dosage forms of dabrafenib and trametinib are expected to be similar to the oral solid dosage forms, as there are no available data to support this position. Therefore, FDA issued postmarketing commitments (PMCs) to conduct food effect studies for both oral liquid dosage forms. Refer to Section 17.

9.2.2.3 Outstanding Issues

The Applicant's Position

None.

The FDA's Assessment

Two PMCs will be issued to conduct food effects studies for both liquid formulations.

9.3 Comprehensive Clinical Pharmacology Review

9.3.1 General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position

A comprehensive overview of the pharmacokinetics and Absorption, distribution, metabolism, elimination (ADME) characteristics of dabrafenib and trametinib have been well characterized in adult patients for the currently approved solid formulations.

PopPK modeling of dabrafenib plus trametinib characterized the PK of the solid and liquid formulations in the pediatric population and demonstrated comparability with the adult population. Similar rates of absorption were estimated for the solid and liquid formulations. The apparent steady state clearances of dabrafenib and trametinib were determined to depend on weight and gender in pediatric patients.

The steady state exposure levels in pediatric patients with BRAF V600 mutation-positive glioma met the target plasma exposure levels that had been established in adult patients based on the exposure-response analyses in the approved indications.

For both compounds, body weight was a significant population PK covariate and was an important factor affecting dabrafenib and trametinib exposures in pediatric patients. Thus, body weight was used to guide development of the pediatric posology in order to achieve the target exposure for both agents, while not exceeding the upper end of the recommended dose for trametinib. The dose recommendations for dabrafenib and trametinib are further explained in Section 9.2.2.1.

The FDA's Assessment

FDA agrees with the Applicant's position that body weight is a statistically significant covariate for clearance and volume of distribution in patients aged 1 to 17 years. Patients with higher body weights tend to have higher clearance for dabrafenib and trametinib. Simulation-based pediatric PopPK models predicted that steady state exposures of dabrafenib and trametinib administered using weight-based dosing are within the range of those observed in adult population administered the approved recommended flat dosage (Table 9-5). Although sex was identified as a significant covariate for the apparent steady state clearances of dabrafenib and trametinib in pediatric patients in the PopPK analysis, this effect is not considered clinically significant.

Table 9-5. Summary of Simulated $C_{avg,ss}$ of Dabrafenib and Trametinib in Adult and Pediatric Subjects

Drug	Population	Weight	Dose	$C_{avg,ss}$ (ng/mL) Median (5^{th}, 95^{th} Percentile)
Dabrafenib	Adult		150 mg BID	464.7 (233.1, 756.4)
	Pediatric	<17 kg	Recommended Weight-based	308.6 (127.6, 580.1)
		17-25 kg		367.4 (168.5, 604.8)
		26-37 kg		397.6 (196.2, 599.4)
		38-50 kg		414.3 (223.4, 579.4)
		≥51 kg		408.1 (234.3, 549.6)
Trametinib	Adult		2 mg QD	14.9 (9.2, 22.7)
	Pediatric	<17 kg	Recommended Weight-based	9 (6.4, 12.6)
		17-25 kg		11.4 (8.2, 16.1)
		26-37 kg		12.1 (8.8, 16.9)
		38-50 kg		14.5 (10.5, 19.9)
		≥51 kg		16.7 (11.7, 23.6)

Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 23, Table 6-3, 6-4, Page 181, Table 11-14, Page 186, Table 11-15.
Abbreviations: BID, twice a day; QD, once a day

9.3.2 Clinical Pharmacology Questions

9.3.2.1 Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

Applicant's Position

The observed plasma exposure of dabrafenib and trametinib in pediatric patients with BRAF V600 mutation-positive glioma in Study G2201 was comparable to exposures in adult patients in previously approved indications. The steady-state Cavg was 409 ng/mL (LGG) and 359 ng/mL (HGG) for dabrafenib and 14.1 ng/mL (LGG) and 12.8 ng/mL (HGG) for trametinib. These exposures met the target plasma exposure levels for dabrafenib (~300 ng/mL) and trametinib (~10 ng/mL) that have been established in adult patients based on previous preclinical and clinical exposure-response analyses. For both LGG and HGG pediatric patient populations, the geometric mean dabrafenib metabolite to parent AUC0-τ ratios for hydroxy dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib were also consistent with historical dabrafenib metabolite ratios in adult patients.

The FDA's Assessment

FDA agrees with the Applicant's position. See Table 9-6 and Table 9-7 for the supporting data.

Table 9-6. Summary of Dabrafenib and Trametinib C_{avg} for LGG and HGG Cohorts at Week 3, Day 1

	Geo-mean Cavg in ng/mL (Geo-mean CV%)	
	LGG	HGG
Dabrafenib	409 (54.0)	359 (44.7)
Trametinib	14.1 (22.2)	12.8 (22.8)

Source: [Study G2201-Table 14.2-4.1H, Table 14.2-4.2H, Table 14.2-4.1L and Table 14.2-4.2L]

Abbreviations: CV, coefficient of variation; HGG, high-grade glioma; LGG, low-grade glioma

Table 9-7. Dabrafenib Metabolite to Parent $AUC_{0-\tau}$ Ratio in LGG and HGG Cohorts

	Geometric mean (% CV) dabrafenib metabolite to parent AUC0-τ ratio in pediatric patients	
	LGG	HGG
Hydroxy-dabrafenib	0.62 (26.6)	0.67 (27.7)
Desmethyl-dabrafenib	0.73 (63.6)	0.74 (63.6)

Source: [Study G2201-Table 14.2-4.3L and Table 14.2-4.3H]

Abbreviations: CV, coefficient of variation; HGG, high-grade glioma; LGG, low-grade glioma

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

The Applicant's Position

A PopPK analysis of the integrated pediatric PK data, guided by the previously established exposure-response relationships in adults, was used to guide the pediatric dosing for the liquid formulations for patients 1 year of age and older. The age of patients was not found to be a significant covariate on PK parameters in neither dabrafenib nor trametinib model. However, body weight was an important covariate in PopPK analysis for both dabrafenib and trametinib and was identified as the main patient-related factor affecting exposure in this population.

The proposed dosing schedule for dabrafenib and trametinib combination in pediatric patients from 1 to 17 years old (weight-adjusted dose and dose reduction) is detailed in Section 9.2.2.1, Table 9-3 and Table 9-4.

The FDA's Assessment

FDA agrees with the Applicant's position. Refer to Section 23.4 for detailed data analysis.

9.3.2.3 Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

The Applicant's Position

No. The effect of ethnic origin, hepatic impairment and renal impairment in adults were evaluated previously for both dabrafenib and trametinib and were not statistically significant. As a result, they were not included in the adult popPK model. It was assumed that, similar with the adults, these covariates would not impact pediatric PK. Therefore, these covariates were not specifically evaluated again in the pediatric population.

The FDA's Assessment

FDA generally agrees with Applicant's position. Age, sex, body weight, renal impairment and hepatic impairment had no clinically significant effect on the exposure of trametinib or dabrafenib in adults, but insufficient data were available to evaluate the potential differences in the exposure of trametinib or dabrafenib by race or ethnicity. The impact of these covariates would not be expected to be different in the pediatric population, with the exception of weight as weight had a clinically significant effect on exposures of trametinib and dabrafenib in pediatric patients. Potential differences in the exposure by race or ethnicity has not been evaluated in either adult or pediatric populations.

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

The Applicant's Position

The food-drug or drug-drug interaction data of liquid formulations of dabrafenib and trametinib are expected to be similar to that of the currently marketed solid formulations.

The FDA's Assessment

FDA agrees with Applicant's position that potential drug-drug interaction is expected to be similar to that of approved solid dosage forms. However, FDA disagrees that food effect is expected to be similar for these new oral liquid formulations to that of the marketed solid oral formulations. A food effect study with each of the new oral liquid dosage forms has been requested as a PMC.

X _____ X _____

Primary Reviewer: Banu Zolnik, Ph.D. Team Leader: Hong Zhao, PhD

X _____ X _____

PM Reviewer: Yanbing, Li Ph.D. PM Team Leader: Youwei Bi, PhD

10 Sources of Clinical Data

10.1 Table of Clinical Studies

The Applicant's Position

Table 10-1. Applicant - Listing of Clinical Trials in Pediatrics Relevant to This sNDA

Trial Identity/ NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
Pivotal pediatric study							
CDRB436G2201 NCT02684058	D+T targeted therapy: Phase II, open-label	**LGG:** D+T vs. C+V **HGG:** D+T dabrafenib 5.25 mg/kg/day (< 12 years old) and 4.5 mg/kg/day (≥ 12 years old) BID plus trametinib 0.032 mg/kg/day (< 6 years old) and 0.025 mg/kg/day (≥ 6 years old) QD, oral	ORR by independent assessment per RANO 2017 criteria for LGG and RANO 2010 for HGG ORR, DoR, PFS, TTR, CBR, OS, PRO (LGG only)	**LGG**: For the prescribed number of cycles as tolerated, or until unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient/legal guardian, lost to follow-up, death, study termination by the sponsor, or until disease progression. **HGG:** until disease progression by RANO criteria or loss of clinical benefit as determined by the investigator,	Total: 151, LGG: 110 HGG: 41	Pediatric patients (≥ 12 months to < 18 years) with BRAF V600 mutation positive LGG or relapsed or refractory HGG	Centers: 58 Countries: 20

Trial Identity/ NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
				unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient/legal guardian, loss to follow-up, death, or study termination by the Sponsor. **Follow-up:** for at least 2 y after the last patient first study treatment			
Supportive studies							
CDRB436A2102 NCT01677741	Phase I/IIa, 2-part, single arm, open-label	Dabrafenib 1.5 to 2.625 mg/kg (max 150 mg) BID, oral	Safety, PK	Until disease progression, death, lack of clinical benefit, or unacceptable toxicity **Follow-up** every 3 mth for 2 y	85	Pediatric subjects (12 months to < 18 years) with advanced BRAF V600-mutation positive solid tumors	19 centers in 8 countries

Trial Identity/ NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
CTMT212X2101 NCT02124772	4-part, Phase I/IIa, multi-center, open-label	Trametinib 0.0125 to 0.04 mg/kg (max 2 mg) QD with (Parts C+D) or without (Parts A+B) dabrafenib 1.5 to 2.625 mg/kg (max 150 mg) BID, oral	Safety, PK, tumor response as assessed by investigator, palatability, biomarker	Until disease progression, death, or unacceptable toxicity **Follow-up** every 3 mth for 2 y	139	Pediatric subjects (1 month to < 18 years) with refractory or recurrent solid tumors. For Parts C and D (BRAF V600 mutation-positive tumors), 12 months to < 18 years.	16 centers in 5 countries

Abbreviations: BID, twice a day; BRAF, B-Raf proto-oncogene, serine/threonine kinase; C+V, carboplatin plus vincristine; CBR, clinical benefit rate; D+T, dabrafenib plus trametinib; DOR, duration of response; HGG, high-grade glioma; LGG, low-grade glioma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient reported outcome; RANO, Response Assessment in Neuro-Oncology; TTR, time to response

The FDA's Assessment

FDA agrees with the Applicant's summary of clinical trials relevant to the application. For these NDAs, the primary clinical data for FDA's analysis of efficacy were based on data from 110 pediatric patients (age 12 months to <18 years) in the LGG cohort of Study G2201.

11 Statistical and Clinical Evaluation

11.1 Review of Relevant Individual Trials Used to Support Efficacy

The Applicant's Description

This submission is based mainly on the results from 3 clinical studies: primary evidence for the efficacy of D+T in the treatment of pediatric patients with BRAF V600 mutation-positive glioma was obtained in Study CDRB436G2201. Additionally, efficacy evaluations were supported with clinical activity data from: Study CDRB436A2102 in pediatric patients with BRAF V600 mutant LGG or r/r HGG treated with dabrafenib monotherapy and Study CTMT212X2101 in pediatric patients with BRAF V600 mutant LGG treated with trametinib monotherapy or combination therapy with D+T. In the following text, these studies are referred to by their abbreviated Novartis study codes G2201, A2102 and X2101, respectively. Study G2201 is ongoing, and studies A2102 and X2101 are completed.

11.1.1 Study G2201

Trial Design

The G2201 study combines two pediatric glioma cohorts (LGG and HGG cohorts) into a single multi-center, open-label, Phase II study.

The LGG cohort is a multi-center, randomized, open-label part of this Phase II study conducted in children and adolescent patients with BRAF V600 mutation-positive LGG whose tumor was unresectable and who required first systemic treatment. Patients randomized to the carboplatin with vincristine treatment arm were allowed to cross over to receive dabrafenib in combination with trametinib after centrally confirmed Response Assessment in Neuro-Oncology (RANO)-defined disease progression. Cross-over was allowed during the treatment period or the post-treatment period.

The HGG cohort is a multi-center, single-arm, open-label part of this Phase II study conducted in children and adolescent patients with BRAF V600 mutation-positive, refractory, or relapsed HGG tumors after having received at least one previous standard therapy.

LGG patients on dabrafenib with trametinib treatment and all patients in the HGG cohort continued to receive the assigned study treatment until disease progression by RANO criteria or loss of clinical benefit as determined by the investigator, unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient/legal guardian, loss to follow-up, death, or study termination by the Sponsor.

All patients were to be followed for survival for at least 2 years after the last patient first study treatment (except if consent was withdrawn, death, or the patient was lost to follow-up or discontinued study). The primary analysis was conducted as all treated patients had either completed at least 32 weeks of treatment or discontinued earlier.

The FDA's Assessment

FDA agrees with the Applicant's description of the G2201 study design. LGG responses were based on RANO 2017 (specifically, LGG criteria) and the HGG criteria was based on RANO 2010.

Drug dosing was carried out per standard of care in the carboplatin plus vincristine LGG cohort of G2201 and per RP2D in the dabrafenib and trematinib HGG and LGG cohorts. Therapy with C+V included 10 weeks of induction and 8 cycles of maintenance: Carboplatin was dosed at 175 mg/m^2 as weekly i.v. infusions over 60 minutes and vincristine was dosed at 1.5 mg/m^2 as weekly i.v. bolus infusions. In both the HGG and LGG cohorts, dabrafenib and trametinib were given: for ≤12-year-old patients 5.25 mg/kg/day dabrafenib administered orally, divided into two equal doses and for >12-year-old patients 4.5 mg/kg/day dabrafenib administered orally, divided into two equal doses; and trametinib was dosed at 0.032 mg/kg/day (< 6 years old) or 0.025 mg/kg/day (≥ 6 years old).

Study Population

Key Inclusion Criteria

- Male or female ≥ 12 months and < 18 years of age. Patients under 6 years old were to weigh at least 7 kg at the time of enrollment. Patients ≥ 6 years old were to weigh at least 10 kg at the time of enrollment.
- Locally determined LGG or HGG as defined by WHO histological classification system, revised 2016.
  - LGG cohort only:
    - Locally confirmed histologic diagnosis of LGG (Grade I or II).
    - Patients with progressive disease following surgical excision, or non-surgical candidates with necessity to begin systemic treatment because of a risk of neurological impairment with progression.
  - HGG cohort only:
    - Locally confirmed histologic diagnosis of HGG (Grade III or IV), including anaplastic pleomorphic xanthoastrocytoma (aPXA) and anaplastic ganglioglioma.
    - Relapsed, progressed, or failed to respond to frontline therapy.

- BRAF V600 mutation-positive tumor assessed locally, or at a Novartis designated central reference laboratory if local BRAF V600 testing was unavailable.
- Locally determined and centrally confirmed measurable disease with minimal bi-perpendicular diameter that was to be at least twice the imaging slice thickness to be used for efficacy assessments.
- Tumor tissue was to be provided for central confirmatory testing of BRAF mutational status (LGG and HGG cohorts), and for HGG histopathology (HGG cohort only).
- Karnofsky/Lansky performance score of ≥ 50%.

Key Exclusion Criteria

- Malignancy other than BRAF V600 mutant HGG or LGG.
- Previous treatment with dabrafenib or another RAF inhibitor, trametinib or another MEK inhibitor, or an ERK inhibitor.
- LGG patients
  - Any systemic anticancer therapy (chemotherapy, immunotherapy, biologic therapy, or vaccine therapy) or investigational drugs prior to enrollment.
  - Radiotherapy to CNS glioma lesions at any point prior to enrollment.
- HGG patients
  - Cancer therapy (chemotherapy with delayed toxicity, immunotherapy, biologic therapy, vaccine therapy) or investigational drugs within 3 weeks preceding the first dose of study treatment.
  - Radiotherapy to CNS glioma lesions within 3 months prior to first dose of study treatment unless there was clear evidence of radiologic progression outside of the field of radiation.
- History of malignancy with confirmed activating RAS mutation or with BRAF fusion such as BRF-KIAA1549 or with known diagnosis of NF1.
- Current use of a prohibited medication or herbal preparation or requiring any of these medications during the study.
- Unresolved toxicity greater than National Cancer Institute-Common Terminology Criteria for Adverse Event (NCI-CTCAE) v 4.03 grade 2 from previous anti-cancer therapy, including major surgery, except those that in the opinion of the investigator are not clinically relevant given the known safety/toxicity profile of the study treatment (e.g., alopecia and/or peripheral neuropathy related to platinum or vinca alkaloid-based chemotherapy).

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to dabrafenib, trametinib, and their excipients. For LGG patients only: history of allergic reactions or contraindications to the use of carboplatin or vincristine.
- Autologous or allogeneic stem cell transplant within 3 months prior to the first dose of study treatment. Patients with evidence of active graft versus host disease were excluded regardless of elapsed time.
- History or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the study such as uncontrolled or significant cardiac disease.
- Uncontrolled medical conditions (e.g., diabetes mellitus, hypertension, liver disease or uncontrolled infection), psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol; or unwillingness or inability to follow the procedures required in the protocol.
- Presence of active gastrointestinal disease or other condition (e.g., small bowel or large bowel resection) that could interfere significantly with the absorption of drugs.
- A history of hepatitis B virus or hepatitis C virus infection (patients with laboratory evidence of cleared hepatitis B virus and/or hepatitis C virus could be enrolled).
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant (e.g., are menstruating), unless they were using highly effective methods of contraception during dosing of study treatment and for 16 weeks after stopping study medication with trametinib monotherapy or dabrafenib in combination with trametinib, and 2 weeks after stopping treatment with dabrafenib monotherapy, whichever was longer. Note: Oral contraceptives methods were not permitted as a method of contraception due to potential drug-drug interactions with dabrafenib.
- Women who were pregnant or actively breast feeding.
- Sexually active males (including those that have had a vasectomy) unless they used a condom during intercourse while on study and for 16 weeks after stopping study treatment, and agreed not to father a child during this period.
- A history or current evidence RVO or central serous retinopathy.

Study Endpoints

The Applicant's Description

All the study objectives and their respective endpoints are presented in Table 11-1, Table 11-2, and Table 11-3.

Table 11-1. Applicant – Study G2201 Primary Objectives and Their Respective Endpoints

LGG Cohort		HGG Cohort	
Objective	**Endpoint**	**Objective**	**Endpoint**
Compare the anti-tumor activity of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by ORR by central independent assessment using the RANO criteria.	ORR, proportion of patients with a best overall confirmed CR or PR by blinded independent review per RANO criteria.	Evaluate the anti-tumor activity of dabrafenib in combination with trametinib, as measured by ORR by central independent assessment using the RANO criteria.	ORR, proportion of patients with a best overall confirmed CR or PR by independent assessment per RANO criteria.

Abbreviations: CR, complete response; HGG, high-grade glioma; LGG, low-grade glioma; ORR, overall response rate; PR, partial response; RANO, Response Assessment in Neuro-Oncology Criteria

Table 11-2. Applicant – Study G2201 Secondary Objectives and Their Respective Endpoints

LGG Cohort		HGG Cohort	
Objectives	**Endpoints**	**Objectives**	**Endpoints**
Evaluate ORR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by investigator assessment.	ORR by investigator assessment per RANO criteria.	Evaluate ORR by investigator assessment.	ORR by investigator assessment per RANO criteria.
Evaluate the DOR of dabrafenib in combination with trametinib versus carboplatin with vincristine by both investigator and central independent assessment.	DOR, calculated as the time from the date of the first documented confirmed response (CR or PR) to the first documented progression or death due to any cause, as assessed separately by investigator and central independent reviewer per RANO criteria.	Evaluate DOR by investigator and central independent assessment.	DOR, calculated as the time from the date of the first documented confirmed response (CR or PR) to the first documented progression or death due to any cause, as assessed separately by investigator and central independent reviewer per RANO criteria.
Evaluate PFS of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent assessment.	PFS, defined as time from date of randomization to progression or death due to any cause, as assessed separately by central independent reviewer and investigator per RANO criteria.	Evaluate PFS by investigator and central independent assessment.	PFS, defined as time from first dose of study treatment to progression or death due to any cause, as assessed separately by central independent reviewer and investigator per RANO criteria.

LGG Cohort		HGG Cohort	
Objectives	**Endpoints**	**Objectives**	**Endpoints**
Evaluate TTR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent assessment.	TTR, calculated as the time from the date of randomization to first documented confirmed response CR or PR (which must be confirmed subsequently) as assessed separately by investigator and independent central reviewer per RANO criteria.	Evaluate TTR by investigator and central independent assessment.	TTR, calculated as the time from the start date of study treatment to first documented confirmed response CR or PR (which must be confirmed subsequently) as assessed separately by investigator and independent central reviewer per RANO criteria.
Evaluate CBR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent assessment.	CBR is the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of at least 24 weeks, as assessed separately by investigator and central independent reviewer per RANO criteria.	Evaluate CBR by investigator and central independent assessment.	CBR is the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of at least 24 weeks, as assessed separately by investigator and central independent reviewer per RANO criteria.
Evaluate OS of dabrafenib in combination with trametinib versus carboplatin with vincristine.	OS, defined as the time from date of randomization to death due to any cause.	Evaluate OS.	OS, defined as the time from first dose of study treatment to death due to any cause.
Evaluate 2-year OS estimate of dabrafenib in combination with trametinib versus carboplatin with vincristine.	2-year OS estimate.	Evaluate the safety and tolerability profile of dabrafenib in combination with trametinib in children and adolescents.	Incidence of adverse events and serious adverse events, changes in laboratory results, vital signs, ECG and ECHO.
Evaluate the safety and tolerability of dabrafenib in combination with trametinib versus carboplatin with vincristine.	Incidence of adverse events and serious adverse events, changes in laboratory results, vital signs, ECG and ECHO.	Evaluate the palatability of dabrafenib oral suspension and trametinib oral solution.	Palatability questionnaire data.
Evaluate the palatability of dabrafenib and trametinib.	Palatability questionnaire data.	Characterize the PK of dabrafenib, its metabolites and trametinib in the study population.	Plasma concentration-time profiles of dabrafenib, its metabolites and trametinib and PK parameters.

LGG Cohort		HGG Cohort	
Objectives	**Endpoints**	**Objectives**	**Endpoints**
Characterize the pharmacokinetics of dabrafenib, its metabolites and trametinib in the study population.	Plasma concentration-time profiles of dabrafenib, its metabolites and trametinib and PK parameters.		
Assess patient reported outcomes of dabrafenib in combination with trametinib versus carboplatin with vincristine.	Change from baseline in PROMIS Parent Proxy scale - Global Health 7+2.		

Abbreviations: CBR, clinical benefit rate; CR, complete response; DOR, duration of response; ECG, electrocardiogram; ECHO, echocardiogram; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; RANO, Response Assessment in Neuro-Oncology Criteria; TTR, time to response

Table 11-3. Applicant – Study G2201 Exploratory Objectives and Their Respective Endpoints

Objectives	Endpoints
(b) (4)	

The FDA's Assessment

FDA agrees with the Applicant's description of the eligibility criteria and study endpoints. The primary endpoint was confirmed overall response rate (ORR) by blinded independent assessment per RANO criteria. Secondary endpoints were ORR by investigator assessment per RANO criteria, progression free survival (PFS), duration of response (DOR), and overall survival (OS). Patients in both the LGG and the HGG cohorts were assessed at screening, every 8 weeks for the first year, and every 16 weeks thereafter for efficacy using RANO criteria. All radiological scans were collected for independent central review.

FDA notes that CBR is not considered to be a clinically relevant endpoint for efficacy evaluation. Given that the HGG cohort was a single-arm cohort, time-to-event endpoints measured in this cohort, such as PFS and OS, are not interpretable in absence of an appropriate comparator arm and are considered descriptive only.

Statistical Analysis Plan and Amendments

The Applicant's Description

The statistical reporting and analysis plans for Study G2201 were amended and finalized on 30-Sep-2021 for both the LGG cohort and HGG cohort (Table 11-4).

LGG Cohort

The analysis sets for the LGG cohort are denoted with '- L' in this document.

Full analysis set (FAS-L) comprised of all patients to whom study treatment had been assigned by randomization regardless of whether or not treatment was administered. According to the intent to treat (ITT) principle, patients were analyzed according to the treatment they had been assigned to during the randomization procedure. This population was the primary population for efficacy analyses.

Safety set (Safety set-L) included all patients who received at least one dose of any component of the study treatment. Patients were analyzed according to the study treatment they actually received where treatment received was defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

Evaluable set (Evaluable set-L) consisted of all evaluable patients in the FAS who had centrally confirmed measurable disease, centrally confirmed positive BRAF V600 mutation, an adequate tumor assessment at baseline, and a follow-up tumor assessment at least 8 weeks after starting treatment (unless disease progression is observed before that time) or had discontinued for any reason. An adequate tumor assessment at baseline refers to baseline measurable disease

assessed by investigator and confirmed by central independent reviewer per RANO criteria. The evaluable set was used for sensitivity analyses.

Cross-over set (Cross-over set-L) comprised the subset of patients who were randomized to carboplatin with vincristine control arm and elected to cross-over to receive dabrafenib in combination with trametinib treatment after centrally confirmed and RANO-defined disease progression. Only patients who received at least one dose of cross-over treatment were included in the cross-over set.

Pharmacokinetic analysis set (PAS-L) consisted of all patients who received at least one (full or partial) dose of dabrafenib or trametinib in the randomized phase and provided at least one evaluable PK blood sample.

Analysis of the primary endpoint: ORR was defined as the proportion of patients with best overall response (BOR) of confirmed CR or PR according to RANO criteria. ORR was calculated based on the FAS using central independent review of tumor assessment data. Only tumor assessments performed before the start of any further antineoplastic therapy (i.e., any additional secondary antineoplastic therapy or surgery) was considered in the assessment of BOR.

Statistical hypotheses, model, and method of analysis: The primary efficacy analysis in the LGG cohort was the comparison of ORR based on independent review assessment between the two treatment arms. The following statistical hypothesis was tested:

$$\mathrm{H}_{01}: ORR_t \leq ORR_c \text{ vs. } \mathrm{H}_{\mathrm{A1}}: ORR_t > ORR_c$$

Where ORR_t was the ORR in the trametinib plus dabrafenib arm and ORR_c is the ORR in the control arm (carboplatin with vincristine). The analysis to test these hypotheses and compare the two treatment groups consisted of a Mantel Haenszel chi-square test at one-sided 2.5% level of significance. The primary efficacy analysis was performed on the FAS. ORR was summarized using descriptive statistics (N, %) by treatment arm along with two-sided exact binomial 95% CIs (Clopper and Pearson 1934). The odds ratio (dabrafenib + trametinib vs carboplatin + vincristine) and its 95% CI were determined by logistic regression.

Supportive analyses of primary endpoint: ORR was calculated and summarized for patients from the Evaluable set. The ORR analyses were also repeated including all response assessments irrespective of new antineoplastic therapy using FAS and based on radiographic response by independent review.

Analysis of secondary endpoints for the LGG cohort: A hierarchical approach was taken to control for the overall type-I error rate for testing of multiple endpoints: PFS was to be formally tested only if the primary endpoint ORR was statistically significant and then OS was to be formally tested if PFS was also significant. PFS and OS were to be formally tested at the time of primary analysis if ORR was significant. No other multiplicity adjustments were planned for secondary endpoints testing.

ORR by Investigator review: The evaluation of ORR was repeated by investigator review assessment as per RANO criteria based on the FAS and the Evaluable set separately. ORR assessed by investigator review per RANO criteria was summarized by treatment group using descriptive statistics (N, %) by treatment arm along with two-sided exact binomial 95% CIs. The odds ratio and 95% CIs were also presented.

Duration of response: DOR only applies to patients whose BOR was CR or PR according to RANO criteria. The start date was the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date was defined as the date of the first documented progression per RANO or death due to any cause. DOR was analyzed as per investigator and central independent reviewer assessments separately. The analyses of DOR were based on the FAS and was repeated based on the Evaluable set. DOR was analyzed according to the K-M method and the median DOR was presented along with 95% CI.

Progression-free survival: PFS is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS was calculated using RANO criteria based on investigator and central independent review of tumor assessments separately, and analyzed by the FAS and Evaluable set separately. The distribution of PFS was estimated using the K-M method. The results were plotted graphically by treatment group. The median and 25^{th} and 75^{th} percentiles of PFS along with 95% CIs were presented by treatment group. The hazard ratio for PFS was calculated, along with its 95% CI, using a Cox model. A log-rank test at the one-sided 2.5% level of significance was used to compare the two treatment groups. The PFS was formally tested at the time of primary analysis.

Time to response: TTR (CR or PR) is the time from date of randomization to first documented response of CR or PR (which must be confirmed subsequently) according to RANO criteria. All patients in the FAS were included. TTR was analyzed using investigator and independent reviewer assessments separately. TTR data was listed and summarized by treatment group. The distribution of TTR was estimated using the K-M method. In addition, a responders-only analysis was performed using descriptive summary statistics.

Clinical benefit rate: CBR is defined as the proportion of patients with a BOR of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of 24 weeks. CBR was analyzed using investigator and independent reviewer assessments separately, and presented by the FAS and Evaluable set separately. CBR was summarized by treatment group using descriptive statistics (N, %) by treatment arm along with two-sided exact binomial 95% CI. The odds ratio and 95% CI were also presented.

Overall survival: OS is defined as the time from date of randomization to date of death due to any cause. The survival distribution of OS was estimated using the K-M method. The median and 25^{th} and 75^{th} percentiles of OS along with 95% CIs were presented by treatment group. The hazard ratio for OS was calculated, along with its 95% CI, using a Cox model. In addition, K-M estimated probabilities with corresponding 95% CIs were summarized. A log-rank test at the

one-sided 2.5% level of significance was used to compare the two treatment groups. The OS was formally tested at the time of primary analysis.

Safety: Adverse events were coded using medical Dictionary for Regulatory Activities (MedDRA) terminology. AEs were assessed according to the CTCAE v4.03. AE summaries included all AEs occurring during on-treatment period. AEs with start dates outside of the on-treatment period were flagged in the listings. AEs were summarized by number and percentage of patients having at least one AE in each primary SOC and for each PT using MedDRA. The following AE summaries were produced: overview of AEs and deaths, AEs by SOC and PT, summarized by relationship to study treatment, seriousness, leading to treatment discontinuation, leading to dose interruption/adjustment, and leading to fatal outcome. Summaries of the adverse event(s) of special interest (AESI)s and time to first occurrence of AESIs were provided. Separate outputs for on-treatment and all deaths including on-treatment and post-treatment deaths were summarized by SOC and PT.

Laboratory data: For analysis, laboratory data from all sources (central and local) were combined. The summaries included all assessments available for the laboratory parameters collected no later than 30 days after the last study treatment administration date. Liver function parameters of interest were total bilirubin (TBIL), ALT, AST, and ALP. The number and percentages of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines were summarized.

Other safety data: The number and percentage of patients with notable electrocardiogram (ECG) values and heart rate were presented. For each ECG parameter, descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point were summarized. Descriptive statistics at worst post-baseline and changes from baseline to worst post-baseline were also summarized separately. ECHO data were analyzed based on locally reported results. The summaries included all ECHO assessments performed no later than 30 days after the last date of study drug. The absolute change from baseline in left ventricular ejection fraction (LVEF) was summarized for the worst case post-baseline. Vital signs (height, weight, body temperature, pulse rate, and systolic and diastolic BP) collected on treatment were summarized.

The number and percentage of patients with notable vital sign values (high/low) were presented. Vital sign shift tables based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline were produced for pulse rate, diastolic BP and systolic BP. Frequency counts and percentages of patients in the Karnofsky and Lansky performance status scale scores were provided by time point. A summary of change from baseline by scheduled visits was performed, as well as the worst case post-baseline and the best case post-baseline changes during the study.

Skin examination results were summarized by frequency counts and percentages of patients in each category (normal, abnormal) by scheduled time points. Sexual maturation was monitored by Tanner stages. Bone age SDS, height and BMI SDS, and changes in visual acuity, and number

of seizure events assessed were summarized. Data on palatability assessments for dabrafenib and trametinib oral solutions (bitterness, sweetness, texture, and overall taste) were also summarized.

Pharmacokinetics: All PK analyses were performed based on the PAS unless otherwise specified. The PK parameters were derived using non-compartmental methods using WinNonlin® software version 6.4. Descriptive statistics (n, mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) were presented for the PAS for all dabrafenib (and its metabolites) and trametinib PK parameters, except Tmax, where only n, median, minimum, and maximum were presented.

Patient-reported outcomes (LGG cohort only): The FAS was used for analyzing PRO data unless specified differently. One PRO questionnaire: the Patient-Reported Outcomes Measurement Information System (PROMIS) Parent Proxy Global Health 7+2 was used to evaluate the QoL of patients between treatment groups. The 7+2 item parent proxy pediatric global health measure included a one global health score plus a single score from pain and a score from fatigue interference item which were scored independently. Compliance to the schedule of administration of PRO assessments was summarized by treatment group, for baseline and post-baseline on treatment assessments and scheduled post-treatment time points. A summary of the number and percentage of patients with questionnaire completion of 'yes' or 'no' (where categories 1-3 are counted as 'yes' and categories 4-13 are counted as 'no') was summarized by treatment group and time point. Descriptive statistics were used to summarize the scored scales of PROMIS Parent Proxy Global Health 7+2 at each scheduled assessment time point for each treatment group. Change from baseline in the scale at the time of each assessment was summarized. In addition, a repeated measures model for longitudinal data was used to estimate differences in PROMIS Parent Proxy Global Health 7+2 scores between treatment groups.

HGG Cohort

The analysis sets for the HGG cohort are denoted with '- H' in this document.

Full analysis set (FAS-H) comprised all patients to whom study treatment had been assigned and who received at least one dose of study treatment.

Safety set (Safety set-H) included all patients who received at least one dose of any component of the study treatment.

Evaluable Set (Evaluable set–H) consisted of all evaluable patients in the FAS who had centrally confirmed HGG through histology, centrally confirmed positive BRAF V600 mutation, an adequate tumor assessment at baseline, a follow-up tumor assessment at least 8 weeks after starting treatment (unless disease progression was observed before that time) or had discontinued for any reason. An adequate tumor assessment at baseline refers to baseline

measurable disease assessed by the investigator and confirmed by central independent reviewer per RANO criteria. The Evaluable set was used for sensitivity analyses.

Pharmacokinetic analysis set (PAS-H) consisted of all patients who received at least one (full or partial) dose of dabrafenib or trametinib and provided at least one evaluable PK blood sample. A sample was considered evaluable if the following conditions were satisfied:

- Patient did not vomit within 4 hours after the dosing of dabrafenib/trametinib prior to sampling
- For pre-dose samples: had the sample collected before the next dose administration.

Analysis of the Primary Endpoint

Overall response rate (ORR) was defined as the proportion of patients with BOR of confirmed CR or PR according to RANO criteria. ORR was calculated based on the FAS using central independent review of tumor assessment data.

Statistical hypotheses, model, and method of analysis: The primary analysis was performed on the FAS. The point estimate and exact CIs of ORR were provided. The lower bound of the CIs was used to provide evidence that the true ORR is greater than a certain specific response rate. The 95% CI, via the lower limit, was used to establish the levels of response which were exceeded by taking the combination therapy according to a robust standard of evidence (i.e., one-sided alpha = 0.025).

The study also aimed to provide evidence that trametinib gives added value to the dabrafenib plus trametinib combination over and above dabrafenib monotherapy treatment. Since a lower standard of evidence is usually required to show such added value, the lower limit of an 80% CI was used to identify the response rates which was to be exceeded by taking the combination therapy based on a reduced level of evidence (one-sided alpha of 0.1).

Planned supportive analyses of primary endpoint in the HGG cohort were similar to the LGG cohort.

Analysis of Secondary Endpoints

ORR by investigator assessment: The evaluation of ORR was repeated by investigator assessment as per RANO criteria based on the FAS and the Evaluable set separately. ORR was summarized using descriptive statistics (N, %) along with 2-sided exact 95% and 80% CIs.

Duration of response: DOR was analyzed according to the Kaplan-Meier (K-M) method. The estimated median (in weeks) along with 95% CIs, as well as 25^{th} and 75^{th} percentiles were reported.

Progression-free survival: PFS is defined as the time from the start date of study treatment to the date of the first documented progression or death due to any cause. PFS was described in tabular and graphical format using K-M methods as described for DOR, including estimated median (in months) with 95% CI, 25th and 75th percentiles.

Time to response: TTR (CR or PR) is the time from start date of study treatment to first documented response of CR or PR (which must be confirmed subsequently) according to RANO criteria. All patients in the FAS were included in the TTR calculation. TTR was analyzed using investigator and independent reviewer assessments separately. TTR data were listed and summarized. The distribution of TTR was estimated using the K-M method. In addition, a responders-only analysis was performed using descriptive summary statistics.

Clinical benefit rate: CBR was analyzed using investigator and independent reviewer assessments separately. CBR was calculated using the FAS and Evaluable set separately. CBR was summarized using descriptive statistics (n, %) along with the two-sided exact binomial 95% CI.

Overall survival: OS is defined as the time from start date of study treatment to date of death due to any cause. OS was described in tabular and graphical format using K-M methods as described for DOR, including estimated median (in months) with 95% CI (Brookmeyer and Crowley 1982), 25th and 75th percentiles and K-M estimated probabilities with corresponding 95% CIs.

The safety and PK analyses for HGG cohort was similar to the LGG cohort.

SAP Amendments

The LGG statistical analysis plan (SAP) was amended once, and the HGG SAP was amended twice, and the key features of each amendment are presented below.

Table 11-4. Applicant – Study G2201 SAP Amendments

Version and Date	Summary of Key Changes
Amendment 01 dated 30-Sep-2021	**LGG cohort** Changes related to the analysis of the primary endpoint: • Clarification added that BOR is determined up to progression • Supportive analysis for randomized not treated subjects added, Odds ratio for ORR added • Estimand language added All other changes were minor updates and clarifications
Amendment 01 dated 26-Sep-2018	**HGG cohort** • Addition of IDMC for the study • Changes related to the analysis of the primary endpoint: – Primary endpoint updated to use central independent review, as per FDA feedback – Additional sensitivity analysis for ORR included All other changes were minor updates and clarifications

Version and Date	Summary of Key Changes
Amendment 02 dated 01-May-2021	**HGG cohort** Changes related to the analysis of the primary endpoint: • Clarification added that BOR is determined up to progression • Added number of days to clearly define 16-week SD requirement • Estimand language added • Details of RANO guidelines and identification of response from datasets defined All other changes were minor updates and clarifications

Abbreviations: BOR, best overall response; HGG, high-grade glioma; IDMC, independent data monitoring committee; LGG, low-grade glioma; ORR, overall response rate; RANO, response assessment in neuro-oncology; SAP, statistical analysis plan; SD, stable disease

The FDA's Assessment

In general, FDA agrees with the study objectives, safety, and efficacy plans as well as the statistical analysis plan with amendmants presented by the Applicant.

The sample size for the randomized comparison in the LGG cohort was calculated to adequately power the analysis of primary endpoint only (80% power to detect a difference in ORR of 30% while maintaining a one-sided Type I error probability of 0.025). Secondary endpoints of PFS and OS were tested in a hierarchical order; however, the trial was not designed to evaluate these endpoints with adequate power.

During the pre-sNDA meeting (March 16, 2022), FDA noted that there were 11 responders having less than 6 months of follow-up as of the primary data cutoff (DCO) date of August 23, 2021. Therefore, FDA recommended that the Applicant submit additional follow-up data to better characterize the durability of response. On November 11, 2022, the Applicant submitted updated data with a new DCO date of April 5, 2022. All efficacy analysis methods were the same as those described in the SAP and amendments. No p-values were generated for these FDA-requested post-hoc analyses.

Protocol Amendments

The Applicant's Description

The study protocol was amended 5 times. The key features of each amendment are provided in Table 11-5.

Table 11-5. Applicant - Protocol Amendments

Version and Date	Summary of Key Changes
Amendment 1 dated 07-Jun-2017	• Revised the investigational treatment regimen from dabrafenib monotherapy to include trametinib with dabrafenib for children and adolescents with BRAF V600 mutation-positive relapsed or refractory HGG • Guidance provided to the Sponsor by the FDA and CHMP, in addition to updated efficacy data from the ongoing dabrafenib monotherapy study (CDRB436A2102) supported the use of combination treatment in pediatric glioma clinical studies. • Safety related changes were also implemented to include: – Requirement to obtain informed consent/assent for patients who continued treatment beyond progression per RANO criteria. – Added ophthalmic examinations to follow any visual changes in patients receiving trametinib and dabrafenib combination therapy. – Updated dose modification guidance for combination treatment. – Revised cardiac toxicity monitoring and the conditions for re-starting study treatment per FDA advice. – Clarified that skeletal maturation monitoring of wrist or tibia could be assessed by X-ray or MRIs. – Added the collection of seizure AE on study treatment. – Updated the AESIs pertaining to dabrafenib and trametinib.
Amendment 2 dated 23-Feb-2018	• Added a new cohort of BRAF V600 mutant LGG children and adolescent patients whose tumor was unresectable and required systemic treatment. Additionally, the amendment also added a pediatric formulation of dabrafenib as a dispersible tablet. • The LGG cohort was added to enroll approximately 102 pediatric patients with BRAF V600 mutant LGG, randomized 2:1 dabrafenib with trametinib vs carboplatin plus vincristine, with overall response rate (PR+CR) as the primary endpoint. • In addition, taste questionnaires for trametinib and dabrafenib pediatric formulations were implemented for all patients who received the trametinib oral solution and/or dabrafenib oral suspension. The PROMIS PRO questionnaire was added for the LGG cohort of patients. Sparse PK collection was included for a subset of LGG patients.
Amendment 3 dated 07-Aug-2018	• Changed the age range of patients eligible to enroll in the study from ≥ 6 to < 18 years of age to ≥ 12 months to < 18 years of age. This change was possible as the recommended dose for the combination of dabrafenib with trametinib for patients between 12 months and 6 years of age had been determined. • The inclusion and exclusion criteria were updated to clarify the eligible population for the LGG cohort as patients with BRAF V600 mutant LGG, who either have progressive disease following surgical excision, or non-surgical candidates with necessity to begin first systemic treatment because of a risk of neurological impairment with progression. Further, the exclusion criteria specified that LGG patients who had any prior systemic anticancer therapy or antitumor radiotherapy were excluded. • The primary endpoint for the HGG cohort was changed from investigator assessment of ORR to central independent review of ORR. This change could lessen the potential for bias that could be introduced due to investigator assessment in a

Version and Date	Summary of Key Changes
	single arm study. Investigator assessment of ORR was therefore added as a secondary endpoint.
Amendment 4 dated 11-Mar-2019	• Added an additional interim analysis of key safety and pharmacokinetics (PK) data of the adolescent patients (ages ≥ 12 to < 18 years) in the HGG cohort to support a health authority request in the first half of 2019 for data in adolescent patients. • In addition, an exclusion criterion was added to exclude patients with history or current evidence of retinal vein occlusion and central serous retinopathy. This exclusion criterion is standard language for all studies with trametinib and was inadvertently omitted from previous versions of CDRB436G2201. • Optional CSF collection was removed. CSF samples were expected to be very limited (1/30 patients provided a sample), hence, the value of the analyses was limited.
Amendment 5 dated 26-Nov-2019	• Added dose modification requirements for cases of severe cutaneous adverse reactions (SCARs) which had been reported during treatment with dabrafenib in combination with trametinib outside this clinical study. Changed the duration of male and female contraception following the last dose of dabrafenib from 4 weeks to 2 weeks and following the last dose of trametinib from 6 months to 16 weeks. • Further, one of the inclusion criteria was clarified to indicate that local histological diagnosis of HGG was sufficient for study entry and also criteria for patients with Gilbert's syndrome were established.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CR, complete response; CSF, cerebrospinal fluid; HGG, high-grade glioma; LGG, low-grade glioma; MRI, magnetic resonance imaging; ORR, overall response rate; PR, partial response; PRO, patient-reported outcome; PROMIS, patient-reported outcomes measurement information system; RANO, response assessment in neuro-oncology

The FDA's Assessment

FDA agrees with the Applicant's summary of changes.

11.1.2 Study G2201 - Results

Compliance With Good Clinical Practice

The Applicant's Position

The study is being conducted according to ICH E6 Guideline for Good Clinical Practice that have their origin in the Declaration of Helsinki.

The FDA's Assessment

FDA agrees that a declaration of Good Clinical Practice is included in this application.

Financial Disclosure

The Applicant's Position

The details of financial disclosure for Study G2201 are presented in Appendix 23.2.

The FDA's Assessment

FDA agrees that financial disclosures are included without notable conflicts. A financial disclosure certification document was included in Module 1.3.4. Refer to Section 23.2 for details.

Patient Disposition

The Applicant's Position

LGG Cohort

In total, 121 patients were screened for entry into the LGG cohort; of whom 110 patients entered the LGG cohort upon completion of the screening phase and were randomized in a 2:1 ratio to the targeted therapy (D+T) arm (n=73) or the chemotherapy (C+V) arm (n=37).

Table 11-6. Applicant – Study G2201, LGG Cohort, Patient Disposition (FAS-L)

Patient Disposition	D+T N=73 n (%)	C+V N=37 n (%)	All Patients N=110 n (%)
Patient randomized	73 (100)	37 (100)	110 (100)
Treated	73 (100)	33 (89.2)	106 (96.4)
Not treated	0	4 (10.8)	4 (3.6)
Reason for not being treated			
Patient/guardian decision	0	3 (8.1)	3 (2.7)
Physician decision	0	1 (2.7)	1 (0.9)
Treatment ongoing[1]	61 (83.6)	8 (21.6)	69 (62.7)
Discontinued treatment	12 (16.4)	25 (67.6)	37 (33.6)
Reason for discontinuation			
Progressive disease	5 (6.8)	9 (24.3)	14 (12.7)
Completed	0	9 (24.3)	9 (8.2)
Adverse event	3 (4.1)	6 (16.2)	9 (8.2)
Physician decision[2]	2 (2.7)	0	2 (1.8)
New therapy for study indication[3]	1 (1.4)	0	1 (0.9)
Protocol deviation[4]	0	1 (2.7)	1 (0.9)
Patient/guardian decision[5]	1 (1.4)	0	1 (0.9)

Patient Disposition	D+T N=73 n (%)	C+V N=37 n (%)	All Patients N=110 n (%)
Post-treatment follow-up for patients who discontinued treatment			
Crossed-over to dabrafenib plus trametinib		9 (24.3)	9 (8.2)
Did not enter post-treatment follow-up	6 (8.2)	9 (24.3)	15 (13.6)
Entered post-treatment follow-up, ongoing*	5 (6.8)	13 (35.1)	18 (16.4)
Entered post-treatment follow-up, discontinued	1 (1.4)	3 (8.1)	4 (3.6)
Reason for discontinuation			
Completed	0	1 (2.7)	1 (0.9)
Physician decision	0	1 (2.7)	1 (0.9)
Progressive disease	0	1 (2.7)	1 (0.9)
Patient/guardian decision	1 (1.4)	0	1 (0.9)
Survival follow-up			
Did not enter survival follow-up	1 (1.4)	11 (29.7)	12 (10.9)
Entered survival follow-up	6 (8.2)	1 (2.7)	7 (6.4)
Alive	4 (5.5)	0	4 (3.6)
Unknown	2 (2.7)	1 (2.7)	3 (2.7)

Source: Table 14.1-1.3L

[1] Ongoing in randomized phase at the time of the DCO date 23-Aug-2021.

[2] Two patients in the D+T am discontinued due to physician decision. One patient (G2201-(b) (6) had PR as overall response by Investigator assessment on treatment for 2 years. The other patient (G2201-(b) (6) had PR followed by SD as overall response by Investigator assessment on treatment for more than 2 years; this patient discontinued treatment as per Investigator's discussion with patient/family.

[3] One patient (G2201-(b) (6) in the D+T arm discontinued as the patient had radiotherapy.

[4] One patient (G2201-(b) (6) in the C+V arm discontinued due to a protocol deviation for I/E criteria – BRAF V600 mutation criteria was not met.

[5] One patient (G2201-(b) (6) in the D+T arm discontinued due to patient/guardian decision; the patient was on treatment for more than 2 years; the patient had PR followed by PD and the patient's family decided to discontinue treatment.

Abbreviations: C+V, carboplatin plus vincristine; D+T, dabrafenib plus trametinib; FAS-L, full analysis set, LGG cohort; LGG, low-grade glioma

HGG Cohort

In total, 46 patients were screened for entry into the HGG cohort, of whom 41 patients entered the HGG cohort upon completion of the screening phase.

Table 11-7. Applicant – Study G2201, HGG Cohort, Patient Disposition (FAS-H)

Disposition	All Patients N=41 n (%)
Patients treated	41 (100)
Treatment ongoing[1]	21 (51.2)
No RANO progressive disease	19 (46.3)
Continuing post progressive disease	2 (4.9)
Discontinued treatment	20 (48.8)
Reason for discontinuation	
Progressive disease	16 (39.0)
Death	2 (4.9)
Adverse event	1 (2.4)
Physician decision[2]	1 (2.4)
Post-treatment follow-up for patients who discontinued treatment	
Did not enter post-treatment follow-up	15 (36.6)
Entered post-treatment follow-up, ongoing[1]	2 (4.9)
Entered post-treatment follow-up, discontinued	3 (7.3)
Reason for discontinuation	
Death	3 (7.3)
Survival follow-up	
Did not enter Survival follow-up	7 (17.1)
Entered Survival follow-up	8 (19.5)
Alive	2 (4.9)
Dead	6 (14.6)

Source: Table 14.1-1.3H
[1] Ongoing at the time of the 23-Aug-2021 DCO date.
[2] The patient (G2201-(b) (6) had progressive disease and the patient was advised to have surgery by the Investigator.

The FDA's Assessment

FDA agrees with the Applicant's description of patient disposition for the LGG cohort. Among the 73 patients in the D+T arm, 12 (16%) patients discontinued treatment. Among the 37 patients in the C+V arm, 25 (68%) patients discontinued treatment. The most common reason for treatment discontinuation was disease progression in both arms (7% of patients in D+T, 24% in C+V). Per protocol, a total of 9 patients who were in the C+V arm crossed over to D+T arm following confirmed disease progression and received at least one dose of treatment.

The efficacy data from the HGG cohort in Study G2201 were considered supportive and therefore were not independently verified by FDA.

Protocol Violations/Deviations

The Applicant's Position

LGG Cohort

Overall, protocol deviations were reported in 50.0% of patients in the LGG cohort. The protocol deviations were generally well-balanced across the 2 treatment arms. The most frequently reported protocol deviations were related to "treatment deviation" in 18.2% of patients and "other deviations" reported in 23.6% of patients of which "tumor assessment missed or not performed within protocol specified time window" was the most frequently reported (12.7%). Two patients (1 in each treatment arm) did not meet the BRAF V600 evaluation criteria: 1 patient in the D+T arm had BRAF V600 mutation on basis of IHC testing, however this was confirmed before the protocol was amended to allow IHC test results for the eligibility criteria. One patient in the C+V arm was randomized based on the local BRAF V600 status after which it was found that the patient did not have BRAF V600 mutation locally. Central testing was done, and the patient was found to not have the mutation.

Overall, the protocol deviations did not appear to impact the overall efficacy conclusions or safety of the patients in the LGG cohort.

HGG Cohort

Overall, protocol deviations were reported in 73.2% of patients in the HGG cohort. The most frequently reported important protocol deviations were related to "treatment deviation" in 34.1% of patients and "other deviations" were reported in 41.5% of patients of which "tumor assessment missed or not performed within protocol specified time window" was the most frequently reported (17.1%).

Overall, the protocol deviations did not appear to impact the overall efficacy conclusions or safety of the patients in the HGG cohort.

The FDA's Assessment

FDA agrees the reported deviations did not impact the results of this study. No additional protocol deviations were noted during the course of FDA's review.

Analysis Sets

The Applicant's Description

LGG Cohort

All 110 LGG patients were included in the FAS-L (Table 11-8).

Table 11-8. Applicant - Analysis Sets (FAS-L)

Analysis Set	D+T N=73 n (%)	C+V N=37 n (%)	All Patients N=110 n (%)
Full analysis set-L	73 (100.0)	37 (100.0)	110 (100.0)
Safety set-L	73 (100.0)	33 (89.2)	106 (96.4)
Pharmacokinetic analysis set-L	69 (94.5)	0 (0.0)	69 (62.7)
Evaluable analysis set-L	49 (67.1)	19 (51.4)	68 (61.8)
Cross-over set-L	0 (0.0)	9 (24.3)	9 (8.2)

Source: Table 14.1-2.1L
Abbreviations: C+V, carboplatin plus vincristine; D+T, dabrafenib plus trametinib; FAS-L, full analysis set, LGG cohort; LGG, low-grade glioma

HGG Cohort

All 41 patients were included in the FAS-H and Safety set-H (Table 11-9).

Table 11-9. Applicant - Analysis Sets (FAS-H)

Analysis Set	All Patients N=41 n (%)
Full analysis set-H	41 (100.0)
Safety set-H	41 (100.0)
Pharmacokinetic analysis set-H	39 (59.1)
Evaluable analysis set-H	27 (65.9)

Source: Table 14.1-2.1H
Abbreviations: FAS-H, full analysis set, HGG cohort; HGG, high-grade glioma

Table of Demographic Characteristics

The Applicant's Position

Demographic characteristics are summarized in Table 11-10 for LGG and Table 11-11 for HGG.

LGG Cohort

Table 11-10. Applicant – Study G2201 Demographics and Baseline Characteristics (FAS-L)

Demographic Variable	D+T N=73	C+V N=37	All Patients N=110
Age (years)			
n	73	37	110
Mean (SD)	9.3 (4.97)	8.8 (5.01)	9.1 (4.96)
Median	10.0	8.0	9.5
Q1-Q3	5.0-13.0	4.0-13.0	5.0-13.0
Min-Max	1-17	1-17	1-17

Demographic Variable	D+T N=73	C+V N=37	All Patients N=110
Age category-n (%)			
12 months–<6 years	20 (27.4)	14 (37.8)	34 (30.9)
6–<12 years	25 (34.2)	11 (29.7)	36 (32.7)
12–<18 years	28 (38.4)	12 (32.4)	40 (36.4)
Sex-n (%)			
Female	44 (60.3)	22 (59.5)	66 (60.0)
Male	29 (39.7)	15 (40.5)	44 (40.0)
Race-n (%)			
White	55 (75.3)	25 (67.6)	80 (72.7)
Asian	5 (6.8)	3 (8.1)	8 (7.3)
Black or African American	2 (2.7)	3 (8.1)	5 (4.5)
Not reported	2 (2.7)	1 (2.7)	3 (2.7)
Unknown	6 (8.2)	4 (10.8)	10 (9.1)
Other	3 (4.1)	1 (2.7)	4 (3.6)
Ethnicity-n (%)			
Not Hispanic or Latino	48 (65.8)	17 (45.9)	65 (59.1)
Hispanic or Latino	8 (11.0)	4 (10.8)	12 (10.9)
Unknown	5 (6.8)	5 (13.5)	10 (9.1)
Not reported	12 (16.4)	11 (29.7)	23 (20.9)
Weight (kg)			
n	73	33	106
Mean (SD)	43.02 (26.364)	43.81 (26.527)	43.27 (26.291)
Median	36.50	38.20	36.75
Q1-Q3	22.30-61.80	22.40-60.60	22.30-61.80
Min-Max	7.8-115.0	9.0-110.3	7.8-115.0
Body mass index (kg/m^2)			
n	73	33	106
Mean (SD)	21.73 (10.594)	21.43 (6.128)	21.64 (9.403)
Median	19.39	20.13	19.50
Q1-Q3	16.81-24.02	17.37-23.91	16.92-24.02
Min-Max	13.1-97.7	15.5-40.9	13.1-97.7
Body surface area (m^2)			
n	73	33	106
Mean (SD)	1.26 (0.516)	1.27 (0.506)	1.26 (0.510)
Median	1.22	1.26	1.22
Q1-Q3	0.85-1.66	0.86-1.69	0.86-1.69
Min-Max	0.4-2.4	0.5-2.3	0.4-2.4

Demographic Variable	D+T N=73	C+V N=37	All Patients N=110
Lansky and Karnofsky performance status-n (%)			
n[1]	73	33	-
100	44 (60.3)	17 (51.5)	-
90	20 (27.4)	12 (36.4)	-
80	7 (9.6)	2 (6.1)	-
70	2 (2.7)	2 (6.1)	-
<70	0	0	-

Source: Table 14.1-3.1.1L, Table 14.3-2.1L
Body mass index [m^2] is calculated as weight[kg]/(height[m]**2).
[1] Percentages are taken out of n at each visit. If both Lansky and Karnofsky are available, the age-appropriate scale is used.
Abbreviations: C+V, carboplatin plus vincristine; D+T, dabrafenib plus trametinib; FAS-L, full analysis set, LGG cohort; LGG, low-grade glioma; SD, standard deviation

HGG Cohort

Table 11-11. Applicant – Study G2201 Demographics and Baseline Characteristics (FAS-H)

Demographic Variable	All Patients N=41
Age (years)	
N	41
Mean (SD)	12.12 (4.451)
Median	13.00
Q1-Q3	10.00 - 16.00
Min-Max	2.0 - 17.0
Age category-n (%)	
12 months - < 6 years	5 (12.2)
6 - <12 years	10 (24.4)
12 - <18 years	26 (63.4)
Sex-n (%)	
Female	23 (56.1)
Male	18 (43.9)
Race-n (%)	
White	25 (61.0)
Asian	11 (26.8)
Black Or African American	1 (2.4)
Not reported	1 (2.4)
Unknown	3 (7.3)
Ethnicity-n (%)	
Not Hispanic Or Latino	26 (63.4)
Hispanic Or Latino	5 (12.2)
Not reported	7 (17.1)
Unknown	3 (7.3)

Demographic Variable	All Patients N=41
Weight (kg)	
N	41
Mean (SD)	49.82 (27.381)
Median	44.90
Q1-Q3	33.20 - 57.40
Min-Max	11.3 - 155.6
Body mass index (kg/m^2)	
N	40
Mean (SD)	20.58 (7.390)
Median	18.34
Q1-Q3	16.58 - 21.55
Min-Max	10.4 - 48.8
Lansky and Karnofsky performance status - n (%)	
n[1]	41
100	15 (36.6)
90	13 (31.7)
80	7 (17.1)
70	1 (2.4)
<70	5 (12.2)

Source: Table 14.1-3.1.1H, Table 14.3-2.1H
Body mass index [m^2] is calculated as weight[kg]/(height[m]^2).
[1] Percentages are taken out of n at each visit. If both Lansky and Karnofsky are available, the age-appropriate scale is used.
Abbreviations: FAS-H, full analysis set, HGG cohort; HGG, high-grade glioma; SD, standard deviation

The FDA's Assessment

FDA agrees with the Applicant's description of patient demographics. In G2201, a total of 151 patients were enrolled. Of the 41 HGG patients, 25 patients (61%) were White, 11 patients (27%) were Asian, and 1 patient (2%) was African American. Of the 110 LGG patients, 80 patients (73%) were White, 8 patients (7%) were Asian, and 5 patients (5%) were African American. The majority of patients were White, female, with a median age of 10 (6 to <12) years. Generally, the study population demographic characteristics are reflective of the United States populations of patients with LGG and HGG; however, Black patients are underrepresented in study G2201 4.5% of patients in the LGG Cohort in contrast to the United States 2020 census of 12.4% for the Black population (U.S. Census Bureau. Date accessed March 6, 2023). Evaluation of pediatric glioma cases from the SEER database (years: 2000–2016) revealed differences in incidence rates by ethnicity by calculation of age-adjusted incidence rates (AAIRs). The highest AAIRs of pediatric glioma were observed among non-Hispanic Whites (AAIR: 2.91 per 100 000, 95%-CI: 2.84–2.99) and to a lesser degree non-Hispanic Blacks (AAIR: 1.93 per 100 000, 95%-CI: 1.81, 2.05) compared to Hispanic and Asian races (Muskens 2020).

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

The Applicant's Position

Disease Characteristics

LGG Cohort

The predominant tumor histologies at Baseline were pilocytic astrocytoma (30.9%), ganglioglioma (27.3%), and LGG NOS (18.2%). The majority of the patients (80.0%) presented with grade 1 gliomas and 17.3% of patients with grade 2 disease. One patient (0.9%) had grade 4 disease at diagnosis; this patient had primitive neuroectodermal tumor, termed LGG by Investigator and the patient was randomized to the C+V arm. All patients, except for 2, had gliomas with BRAF V600E mutation.

A total of 103 patients (93.6%) patients had locally available mutation status; 100 patients (90.9%) had mutant BRAF V600E locally and 3 patients had local BRAF status of 'other' that were BRAF V600E centrally. Of the remaining 7 patients without locally available mutation status, 5 patients had central BRAF V600E status determined at the time of enrollment, 1 patient withdrew consent, and 1 patient had non-mutant BRAF V600 status determined by central testing and was removed from the study.

Seventy-two patients had centrally available mutation status; 69 patients (62.7%) had mutant BRAF V600E status centrally. Three patients (2.7%) had non-mutant central BRAF V600 status. Nineteen patients (17.3%) did not have centrally confirmed positive BRAF V600 mutation as the sample could not be analyzed due to insufficient quality or quantity (the tumor content in the submitted samples was below 10%). Twelve patients (10.9%) did not have centrally confirmed positive BRAF V600 mutation as the samples were non-evaluable (sample tested but did not yield a valid result due to low tumor content). Seven patients had missing central mutation status (4 patients withdrew consent before central analysis and 3 samples were not submitted in time for analysis).

HGG Cohort

The predominant tumor histology per institution, at the time of initial diagnosis, was glioblastoma multiforme (31.7%). Twenty patients (48.8%) presented with grade 4 gliomas and 13 patients (31.7%) with grade 3 disease. Seven patients had initial diagnoses of grade 1 or grade 2 glioma and subsequently transformed into HGG prior to study entry. All patients had gliomas with BRAF V600E mutation.

As per centrally determined disease diagnosis that was performed, the predominant tumor histology was pleomorphic xanthoastrocytoma with anaplasia (29.3%) followed by diffuse midline glioma (9.8%). The majority (51.2%) of the patients had insufficient tumor tissue to obtain a conclusive central diagnosis and are presented here as 'other' tumor histology. Central

review of available tissue identified 1 patient with tumor most likely LGG. Grading was possible for several samples in 'other' category.

Of 36 patients (87.8%) with available mutation status locally, all patients had mutant BRAF V600E.

Of 37 patients with available mutation status centrally, all patients except 1 had mutant BRAF V600E. One patient had non-mutant central BRAF V600 status. Three patients did not have centrally confirmed positive BRAF V600 mutation as the sample could not be analyzed due to insufficient quality or quantity. One patient did not have centrally confirmed positive BRAF V600 mutation as the sample was non-evaluable (sample tested but did not yield a valid result). Five patients with missing local mutation status were enrolled with central BRAF V600E status determined at the time of screening.

Prior Antineoplastic Therapy

LGG Cohort

Prior antineoplastic therapy was well-balanced across the 2 treatment arms; the majority of patients (84.9% in D+T vs. 78.4% in C+V) had prior surgery; only 2 patients did not have residual disease (1.8%). One patient (1.4%) in the D+T arm was reported to receive prior antineoplatic medication; the patient received dexamethasone daily for symptom control and discontinued dexamethasone 2 months prior to study entry. It should be noted that the investigator incorrectly reported dexamethasone as an antineoplastic therapy instead of a concomitant medication. None of the patients had received radiotherapy.

HGG Cohort

All patients had received at least one form of prior antineoplastic therapy. All patients except one (97.6%) had prior surgery, with the majority of patients (61.0%) with residual disease. In total, 90.2% of patients underwent prior radiotherapy mostly in the adjuvant setting (48.8%), and 80.5% of patients had received chemotherapy mostly in the adjuvant setting (51.2%). The most frequently administered chemotherapies (≥ 10% of patients) were temozolomide (53.7%), cyclophosphamide (14.6%), and vincristine (12.2%).

The majority of patients (36.6%) had experienced stable disease (SD) as the best response to their last therapy.

The FDA's Assessment

FDA agrees with the Applicant's description of disease characteristics.

The majority of the patients (80%) presented with grade 1 gliomas; 17% of patients had grade 2 disease. As noted in the Applicant's discussion above, one patient (0.9%) randomized to the C+V arm was recorded as having grade 4 primitive neuroectodermal tumor, termed LGG by

investigator. Subsequently, pathology in this patient confirmed pleomorphic xanthoastrocytoma WHO Grade 2. Data entry errors for this patient's histology and grading were corrected upon queries after the primary database lock. Two patients' grade of LGG was not entered in the study body report.

The median time since initial diagnosis to study entry was 3.5 months (range: 0.7-199.9). The majority of patients (54%) had radiologic progression as a component of the need for systemic therapy, although this was more common in those randomized to the targeted therapy (D+T) arm (60% vs 40%). Many disease metrics were cited and often overlapping in the G2201 LGG cohort for reason to treat. These included: clinical progression (28.8% in the D+T arm and 18.9% in the C+V arm); abnormal vision (30.1% in the D+T arm and 51.4% in the C+V arm); and neurologic symptoms (42.5% in the D+T arm and 51.4% in the C+V arm). It is unclear how these and other reasons to treat if asymmetrically distributed between treatment arms could affect efficacy results. FDA considers the reason to treat distribution to be unlikely to affect the results in Study G2201.

For the LGG cohort, 65 of the 110 patients enrolled had remnant tumor samples available to analyze for co-occurring alterations. CDKN2A was a co-occurring alteration in 18 out of 65 samples meeting assay criteria requirements. There were 12 patients (16%) in the D+T arm and 6 patients (16%) in the C+V arm with co-occurring CDKN2A alterations. Given the amount of missing information, the actual distribution of co-occuring CDKN2A alterations is unclear, and limited conclusions may be drawn.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position

LGG Cohort

Treatment compliance: No formal measurements of study treatment concentrations were performed for the purpose of establishing compliance with treatment.

Concomitant medications: All patients received at least 1 concomitant medication during the study. The most commonly administered concomitant medications (used in ≥ 20% of patients) were paracetamol (69.9% vs. 66.7%), ondansetron (20.5% vs. 84.8%), bactrim (5.5% vs. 57.6%), ibuprofen (32.9% vs. 21.2%), and dexamethasone (15.1% vs. 24.2%) in the D+T vs. C+V arms, respectively.

Rescue medication: Not applicable, as study protocol did not define any rescue medication.

HGG Cohort

Treatment compliance: No formal measurements of study treatment concentrations were performed for the purpose of establishing compliance with treatment.

Concomitant medications: All patients had received at least 1 concomitant medication during the study. The most commonly administered concomitant medications (used in ≥ 20% of patients) were paracetamol (65.9%), levetiracetam (39.0%), and dexamethasone (36.6%), ondansetron (31.7%), and ibuprofen (22.0%).

Rescue medication: Not applicable, as study protocol did not define any rescue medication.

The FDA's Assessment

FDA agrees with the Applicant's statement regarding concomitant medications.

Elective anti-cancer radiotherapy was not to be performed prior to either documented radiologic progression of disease or at least a total of 36 months of treatment and follow-up, whichever came first.

For patients enrolled into the LGG cohort, elective anti-cancer surgery was not to be performed prior to either centrally confirmed radiologic progression of disease or at least a total of 36 months of treatment plus follow-up, whichever came first. Elective anti-cancer surgery prior to documented radiologic progression did not qualify a patient for cross over therapy within this protocol.

Efficacy Results – Primary Endpoint (Including Sensitiity Analyses)

The Applicant's Position

LGG Cohort

ORR Per Independent Review

The study met the pre-defined success criteria of ORR per Independent review in the LGG cohort. There was a statistically significant and clinically meaningful increase in ORR per Independent review in the targeted therapy (D+T) arm (ORR 46.6%; 95% CI: 34.8, 58.6) compared to the chemotherapy (C+V) arm (ORR 10.8%; 95% CI: 3.0, 25.4), with an odds ratio of 7.19 (95% CI: 2.3, 22.4) and 1-sided p-value <0.001 (Table 11-12).

A higher CBR was demonstrated in the D+T arm (CBR 86.3%; 95% CI: 76.2, 93.2) compared to the C+V arm (CBR 45.9%; 95% CI: 29.5, 63.1). Complete responses (CR) were reported in 2 patients (2.7%) in the D+T arm and 1 patient (2.7%) in the C+V arm. Progressive disease as best response was reported in 11.0% and 32.4% of patients, respectively (Table 11-12).

Table 11-12. Applicant - Independent Reviewer Assessed ORR Using RANO Criteria (FAS-L)

	D+T N=73		C+V N=37		Odds Ratio Between Treatment Groups		p-Values (One-Sided)[3]
Overall Response Rate	**n (%)**	**95% CI[1]**	**n (%)**	**95% CI[1]**	**OR[2]**	**95% CI[2]**	
Best overall response							
Complete response (CR)	2 (2.7)		1 (2.7)				
Partial response (PR)	32 (43.8)		3 (8.1)				
Stable disease (SD)[4]	30 (41.1)		15 (40.5)				
Progressive disease (PD)	8 (11.0)		12 (32.4)				
Unknown (UNK)	1 (1.4)		6 (16.2)				
Overall response rate (ORR: CR+PR)	34 (46.6)	(34.8, 58.6)	4 (10.8)	(3.0, 25.4)	7.19	(2.3, 22.4)	<0.001
Clinical benefit rate (CBR: CR+PR+SD[5])	63 (86.3)	(76.2, 93.2)	17 (45.9)	(29.5, 63.1)	7.41	(2.9, 18.8)	<0.001

Source: Table 14.2-1.1.1L
N: The total number of patients in the treatment group. It is the denominator for percentage (%) calculation.
n: Number of patients who are at the corresponding category.
[1] The exact binomial 95% CI (Clopper and Pearson 1934).
[2] Odds ratio (D+T vs C+V) and 95% confidence interval are from a logistic regression with treatment as the only covariate. Odds ratio > 1 favors D+T.
[3] The p-value is computed from chi-square test (Mantel-Haenszel) at a one-sided 2.5% level of significance
[4] SD: Response SD for 16 weeks or longer is recorded at 15 weeks or later (i.e ≥ 105 days) from randomization date.
[5] SD: Response SD for 24 weeks or longer is recorded at 23 weeks or later (i.e ≥ 161 days) from randomization date.
Abbreviations: C+V, carboplatin plus vincristine; CI, confidence interval; CI, confidence interval; D+T, dabrafenib plus trametinib; FAS-L, full analysis set, LGG cohort; LGG, low-grade glioma; OR, odds ratio

HGG Cohort

The primary objective of ORR per Independent review met the pre-specified success criteria for the HGG cohort, i.e., the lower bound of the 95% CI for targeted therapy (D+T) ORR was greater than the 20% rate as pre-specified threshold in the study protocol. Treatment with D+T was considered to have clinically relevant efficacy. The ORR as determined per Independent review in the FAS was 56.1% (95% CI: 39.7, 71.5; 80% CI: 44.9, 66.8). Note that the 80% CI is reported for these results as they may be useful in determining the contribution of trametinib to dabrafenib therapy in this disease setting. The primary endpoint of ORR per Independent review also met the pre-specified threshold of excluding 32% ORR using an 80% CI.

CR was reported in 12 patients (29.3%) and PR in 11 patients (26.8%). The CBR was 65.9% (95% CI: 49.4, 79.9) (Table 11-13).

Table 11-13. Applicant - Independent Reviewer Assessed ORR Using RANO Criteria (FAS-H)

	All Patients N=41	
Best Overall Response	**n (%)**	**95% CI / 80% CI**
Complete response (CR)	12 (29.3)	
Partial response (PR)	11 (26.8)	
Stable disease (SD)[1]	5 (12.2)	
Progressive disease (PD)	10 (24.4)	
Unknown (UNK)	3 (7.3)	
Overall response rate (ORR: CR+PR)	23 (56.1)	(39.7, 71.5) / (44.9, 66.8)
Clinical benefit rate (CBR: CR+PR+SD[2])	27 (65.9)	(49.4, 79.9) / NA

Source: Table 14.2-1.1.1H
N: The total number of patients in the treatment group. It is the denominator for percentage (%) calculation.
n: Number of patients who are at the corresponding category.
[1] SD: Response SD for 16 weeks or longer is recorded at 15 weeks or later (i.e ≥ 105 days) from treatment start date.
[2] SD: Response SD for 24 weeks or longer is recorded at 23 weeks or later (i.e ≥ 161 days) from treatment start date.
The exact binomial 95% CI/80% CI (Clopper and Pearson 1934) is presented.
Abbreviations: CI, confidence interval; FAS-H, full analysis set, HGG cohort; HGG, high-grade glioma; ORR, overall response rate; RANO, response assessment in neuro-oncology

The FDA's Assessment

FDA agrees with the Applicant's analysis of the primary endpoint of ORR determined by BIRC. FDA notes that CBR is not considered to be a clinically relevant endpoint for efficacy evaluation.

One patient randomized to the chemotherapy arm with non-measurable disease was withdrawn from the study prior to receiving protocol therapy.

The subgroup analyses of ORR for the LGG cohort are discussed in Section 11.1.8 Subpopulations.

We note that the IRC used a single-reader paradigm. Although a dual reader paradigm with adjudication is preferred, randomization mitigates some of the concern over the lack of an adjudication process.

Efficacy Results – Secondary and Other Relevant Endpoints

The Applicant's Position

LGG Cohort

Results of the secondary efficacy endpoints were supportive of the primary endpoint:

- Results of ORR per Investigator assessment were consistent with those observed per Independent review. The ORR per Investigator assessment was higher in the targeted therapy (D+T) arm (ORR 54.8%; 95% CI: 42.7, 66.5) as compared to the chemotherapy (C+V) arm (ORR 13.5%; 95% CI: 4.5, 28.8) with an odds ratio of 7.76 (95% CI: 2.7, 22.2).

- The concordance rate of BOR between Independent review and Investigator assessment was 66.4%.
- The secondary endpoint of ORR per Investigator assessment was further confirmed by the results of predefined supportive analyses.

Progression-free survival: The observed PFS benefit translates to a considerable clinical benefit of targeted therapy (D+T) compared to chemotherapy (C+V) for this clinical population.

- As statistical significance was reached for ORR, the secondary endpoint PFS by Independent review was also tested at a 1-sided alpha of 0.025. The D+T arm demonstrated a statistically significant and clinically meaningful benefit in PFS over C+V with an estimated 69% risk reduction in PFS (HR 0.31; 95% CI: 0.17, 0.55; 1-sided log-rank p-value <0.001). The median PFS per Independent review was longer in the D+T arm (median PFS: 20.1 months; 95% CI: 12.8, NE) compared to the C+V arm (median PFS: 7.4 months; 95% CI: 3.6, 11.8).
- Similar to the Independent review results, the Investigator assessment also showed that the targeted therapy (D+T) arm demonstrated a clinically meaningful benefit in PFS over the chemotherapy (C+V) arm with an estimated 63% risk reduction in PFS (HR 0.37; 95% CI: 0.14, 0.93). The median PFS per Investigator assessment was not reached and could not be estimated in either arm.
- Results of preplanned supportive analyses of PFS were consistent with the main PFS results.

Duration of response: Observed responses in the targeted therapy arm (D+T) were durable. Among patients with confirmed CR or PR, the median DOR per Independent review was 20.3 months in the D+T arm while the median DOR was not estimable in the C+V arm. The number of responders in the C+V arm (n=4 by independent review, n=5 by investigator assessment) was too low to allow meaningful conclusions regarding the DOR.

Time to response: Using descriptive statistics, among patients with confirmed response (CR or PR), the median TTR was 3.6 months vs. 3.8 months by Independent review and 2.8 months vs. 3.8 months by Investigator assessment in the targeted therapy (D+T) vs. chemotherapy (C+V) arm, respectively.

Overall survival: As statistical significance was reached for PFS, the secondary endpoint OS was also tested at a 1-sided alpha of 0.025. OS was not statistically significantly different between the 2 arms (1-sided log rank p-value 0.065). Data are currently very immature with no deaths in the targeted therapy (D+T) arm and 1 death in the chemotherapy (C+V) arm.

Clinical benefit rate: Higher CBR was demonstrated in the targeted therapy (D+T) arm compared to the chemotherapy (C+V) arm by Independent review (CBR: 86.3% vs. 45.9%) and Investigator assessment (CBR: 91.8% vs. 59.5%).

Cross-over phase: A total of 9 patients crossed-over from the C+V arm to the D+T arm. ORR was 33.3% (95% CI: 7.5, 70.1) per Independent review and 66.7% (95% CI: 29.9, 92.5) per Investigator assessment. The CBR was 44.4% (95% CI: 13.7, 78.8) per Independent review and 66.7% (95% CI: 29.9, 92.5) per Investigator assessment.

HGG Cohort

Results of the secondary efficacy endpoints were supportive of the primary endpoint:

ORR per Investigator assessment:

- The ORR per Investigator assessment in the FAS-H was 58.5% (95% CI: 42.1, 73.7; 80% CI: 47.3, 69.1). CR was reported in 10 patients (24.4%) and PR in 14 patients (34.1%).
- The concordance rate of BOR between Independent review and Investigator assessment was 73.2%.

Results of all preplanned supportive and sensitivity analyses demonstrated the robustness and consistency of the ORR results.

Duration of response: Observed responses were durable with targeted therapy (D+T). The median DOR per Independent review was 22.2 months (95% CI: 7.6, NE) and per Investigator assessment was 26.6 months (95% CI: 14.9, NE). Twelve of 23 patients (with CR or PR) continued to be in response at the time of the DCO date. Multiple supportive analyses of DOR confirmed the robustness and consistency of the DOR for patients with confirmed CR or PR.

Time to response: The observed responses were seen early in the course of treatment with targeted therapy (D+T). Using descriptive statistics, among patients with confirmed response (CR or PR), the median TTR per Independent review was 1.9 months (95% CI: 1.0, 10.9) and per Investigator assessment was 1.7 months (95% CI: 0.9, 5.6). Using K-M methodology, the median K-M TTR per Independent review was 8.5 months (95% CI: 2.0, NE) and per Investigator assessment was 3.4 months (95% CI: 1.8, NE).

Progression-free survival: The observed PFS suggests a clinical benefit for this population. The median PFS was 9.0 months (95% CI: 5.3, 24.0) per Independent review and 17.1 months (95% CI: 12.5, NE) per Investigator assessment. Per Independent review, the K-M estimated 6-month and 12-month event-free rates were 66.8% (95% CI: 49.6, 79.2) and 44.1% (95% CI: 27.8, 59.3), and 72.7% (95% CI: 56.1, 83.9) and 67.4% (95% CI: 50.5, 79.7), per Investigator assessment, respectively. Multiple supportive analyses of PFS confirmed the robustness and consistency of these data.

Overall survival: The median OS was 32.8 months (95% CI: 19.2, NE). Fourteen patients (34.1%) died, and 27 patients (65.9%) were censored at the time of the DCO date. The OS data are immature at the time of this primary analysis. The estimated OS rates at 12 and 24 months were 76.3% (95% CI: 59.3, 86.9) and 58.6% (95% CI: 37.6, 74.7).

Clinical benefit rate: The CBR was 65.9% (95% CI: 49.4, 79.9) per Independent review and 73.2% (95% CI: 57.1, 85.8) per Investigator assessment.

The FDA's Assessment

In general, FDA agrees with the Applicant that the results for the secondary endpoints in the LGG cohort supported the primary efficacy findings. As previously mentioned, CBR is not considered to be a clinically relevant endpoint for efficacy evaluation. Given that the HGG cohort was a single-arm cohort, time-to-event endpoints such as PFS and OS are not interpretable and are considered descriptive only.

LGG Cohort

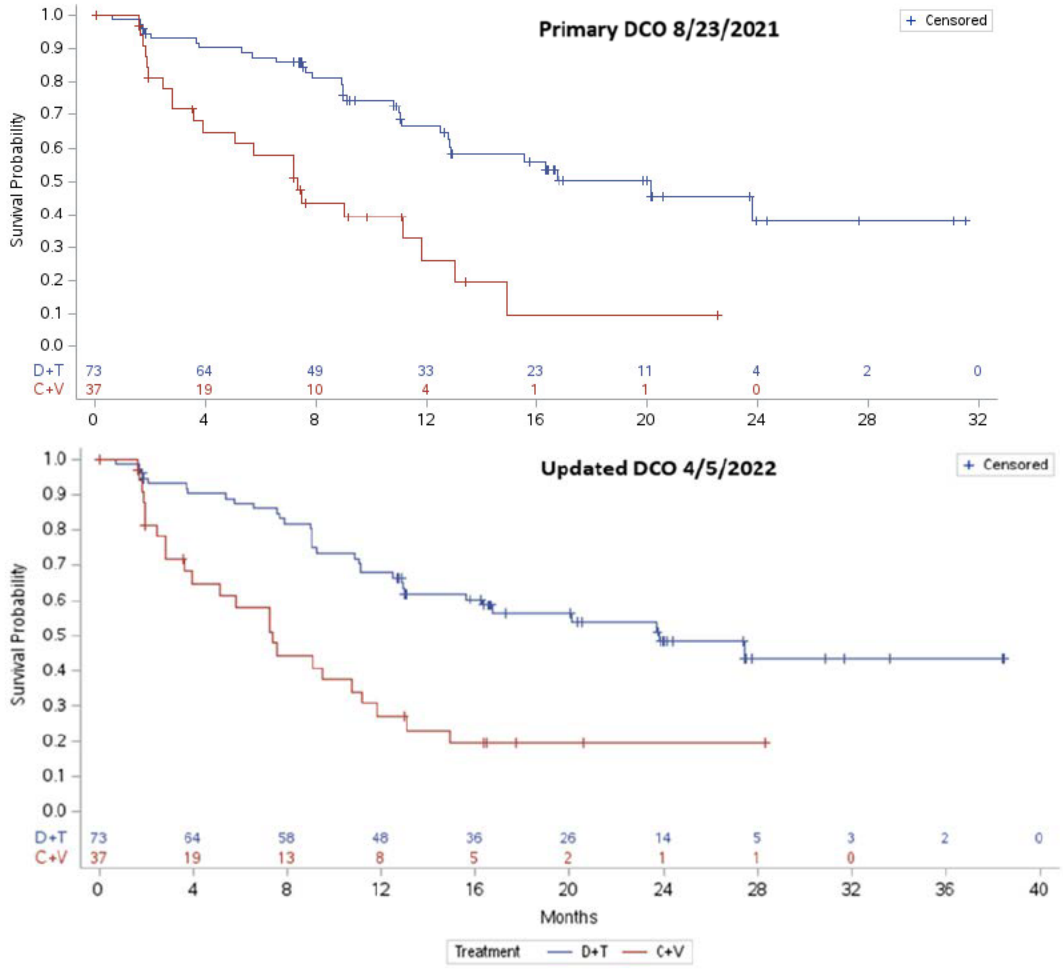
In the LGG cohort, efficacy results for PFS based on the primary and updated DCO dates are presented side-by-side in Table 11-14 and Figure 11-1 below. Note that the lower limit of the 95% CI for the PFS HR at the primary DCO was rounded up from 0.175 to 0.18, whereas the Applicant rounded down to 0.17. With longer follow-up, the PFS data appeared more mature and stable compared to those at the primary DCO. The median PFS at updated DCO date was 23.8 months (95% CI: 12.9, NE) in the D+T arm compared to 7.4 months (95% CI: 3.6, 11.2) in the C+V arm, with a HR of 0.34 (95% CI: 0.20, 0.59). The most common reason for censoring was ongoing follow-up without event in both arms (49% in D+T, 16% in C+V). The Kaplan-Meier curves showed a clear separation between arms starting from approximately 2 months.

Table 11-14. FDA Analysis - Independent Reviewer Assessed PFS (FAS-L), Study G2201

	Primary DCO 8/23/2021		Updated DCO 4/5/2022	
PFS	**D+T (N=73)**	**C+V (N=37)**	**D+T (N=73)**	**C+V (N=37)**
Number of events, n (%)	30 (41)	22 (59)	34 (47)	24 (65)
Median, months (95% CI)[1]	20.1 (12.8, NE)	7.4 (3.6, 11.8)	23.8 (12.9, NE)	7.4 (3.6, 11.2)
HR (95% CI)[2]	0.31 (0.18, 0.55)		0.34 (0.20, 0.59)	

Source: FDA reviewer - generated based on Applicant submitted data
[1] Estimated using Kaplan-Meier method
[2] Estimated using Cox proportional hazards model
Abbreviations: C+V, carboplatin plus vincristine; CI, confidence interval; D+T, dabrafenib plus trametinib; DCO, data cutoff; FAS-L, full analysis set LGG cohort; HR, hazard ratio; NE, not estimable

Figure 11-1. FDA Analysis – Kaplan-Meier Plot of Independent Reviewer Assessed PFS (FAS-L), Study G2201



Source: FDA reviewer - generated based on Applicant submitted data
Abbreviations: C+V, carboplatin plus vincristine; D+T, dabrafenib plus trametinib; DCO, data cutoff; FAS-L, full analysis set LGG cohort; PFS, progression-free survival

As of the updated DCO date, the OS results remained the same with no deaths in the D+T arm and 1 death in the C+V arm. The median DOR per independent review (Table 11-15) in the D+T arm increased to 23.7 months, while the median DOR was not estimable in the C+V arm due to the small number of responders.

Table 11-15. FDA – Independent Reviewer Assessed DOR (FAS-L), Study G2201

	Primary DCO 8/23/2021		Updated DCO 4/5/2022	
DOR	**D+T (N=73)**	**C+V (N=37)**	**D+T (N=73)**	**C+V (N=37)**
DOR, n[1]	34	4	34	4
Median, months (95% CI)[2]	20.3 (12.0, NE)	NE (6.6, NE)	23.7 (14.5, NE)	NE (6.6, NE)
Range, months	1.8+, 29.6+	6.6, 18.8+	3.9, 36.8+	6.6, 24.6+

Source: FDA reviewer - generated based on Applicant submitted data
+ ongoing response
[1] Patients with objective response at the time of primary DCO
[2] Estimated using Kaplan-Meier method
Abbreviations: C+V, carboplatin plus vincristine; CI, confidence interval; D+T, dabrafenib plus trametinib; DCO, data cutoff; DOR, duration of response; FAS, full analysis set; NE, not estimable

As the concordance rate of BOR between Independent review and Investigator assessment was only 66.4%, FDA reviewed the assessment of the concordance between the central independent reviewer (IRC) and local investigator (INV) analysis of ORR and BOR for each patient (Table 11-16 and Table 11-17). There was a similar INV reported ORR (53% [95% CI: 43, 67] D+T vs 14% [95% CI: 4.5, 29] C+V) compared to the ORR determined by IRC review (47% [95% CI: 35, 57] D+T vs 11% [95% CI: 3, 25]). However, for the D+T arm, there was only 59% agreement between IRC review vs INV assessment. A similar number of patients had a discrepancy in BOR of PR to SD and SD to PR (n=12 each), creating a balanced effect (see Table 11-16) among the 110 LGG patients. Response assessments between IRC and INV were more than one step discordant for six patients. The Applicant notes that measurements of response in gliomas is challenging due to irregular shapes of the tumors, presence of cystic cavities, indistinct borders. Reflecting these challenges, specific criteria have been published by consensus panels (RANO) (Chukwueke 2019). The discordance between IRC and INV assessments may be related to the difficulty in measuring LGGs. Of note, the concordance between IRC an INV assessments of ORR in the C+V arm was 81% (Table 11-17). The reason for the higher concordance in the C+V arm is unclear; a smaller sample size may magnify potential differences in concordance.

Additionally, there were a number of patients with a single-time measurement of tumor decrease ≥50% who were counted as SD (Figure 11-2 and Figure 11-3). To qualify for a partial response, the patient's tumor must have a >50% decrease in cross sectional area measured in at least two assessments separated by at least 4 weeks while also having stable or improved clinical status and stable or reduced use of corticosteroids. Of the 16 patients with a best percentage decrease of >50% but who did not have a best overall response of PR or better, 14 had only a single measurement of a percentage decrease of greater than 50% which was followed by a response of PD (N=7, one of which was based on clinical data only), SD without PD or PR confirmation (N=3) or did not have any further response evaluations before the data cut off date (N=4). The additional two patients had assessments of PD prior to the first occurrence of a >50% reduction and thus were not candidates for a BOR of PR or better. The variability in response assessment leading to a lack of confirmation of response reinforces the challenges in response assessment in this tumor type, as discussed above.

Table 11-16. FDA Analysis ORR Concordance: IRC vs. INV (D+T) Arm

D+T		BOR by INV					
(N=73)	n	CR	PR	SD	PD	UNK	Total
BOR by IRC	CR	**0**	**2**	0	0	0	2
	PR	**1**	**19**	12	0	0	32
	SD	2	12	**15**	**1**	**0**	30
	PD	0	4	**1**	**3**	**0**	8
	UNK	0	0	**0**	**0**	**1**	1
	Total	3	37	28	4	1	73
ORR concordance: 43 (59%)							

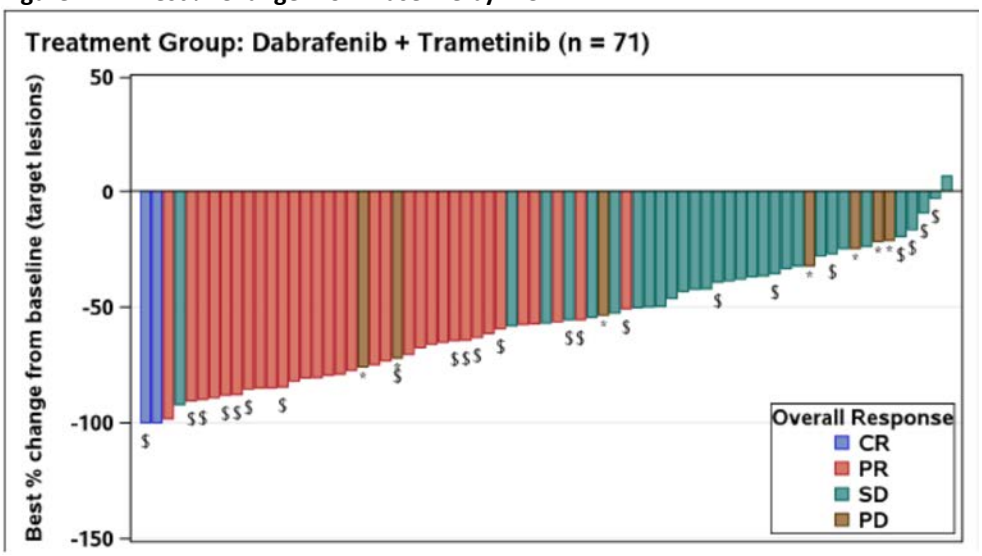
Source: FDA reviewer - generated based on Applicant submitted data
UNK: Unknown, including all other cases (not qualifying for confirmed CR or PR and without SD at or beyond the second post-baseline assessment or progression)
Abbreviations: BOR, best overall response; CR, complete response; D+T, dabrafenib plus trametinib; INV, local investigator; IRC, central independent reviewer; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown

Table 11-17. FDA Analysis of ORR Concordance: IRC vs. INV (C+V)

C+V		BOR by INV					
(N=37)	n	CR	PR	SD	PD	UNK	Total
BOR by IRC	CR	**0**	**1**	0	0	0	1
	PR	**0**	**0**	3	0	0	3
	SD	0	4	**11**	**0**	**0**	15
	PD	0	0	**4**	**7**	**1**	12
	UNK	0	0	**0**	**0**	**6**	6
	Total	0	5	18	7	7	37
ORR concordance: 30 (81%)							

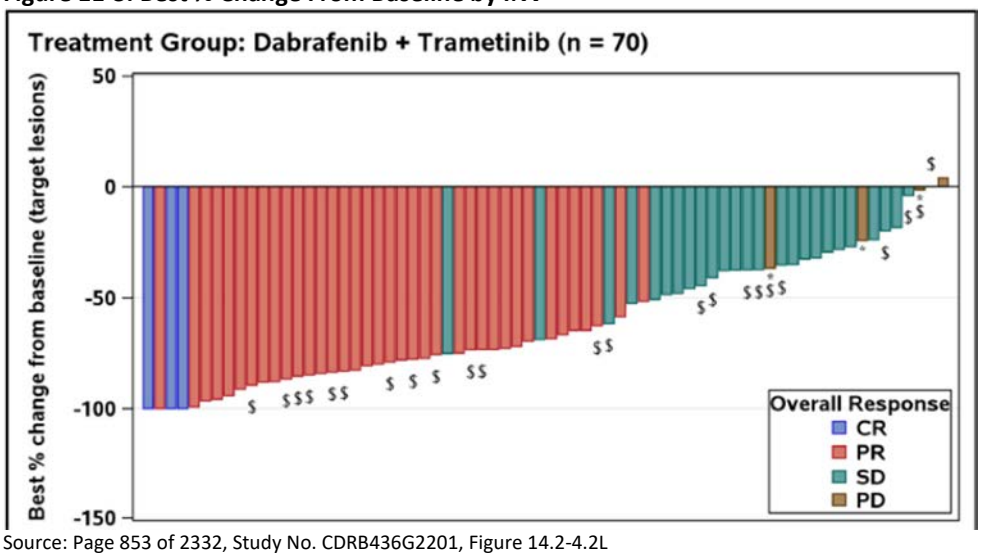
Source: FDA reviewer - generated based on Applicant submitted data
UNK: Unknown, including all other cases (not qualifying for confirmed CR or PR and without SD at or beyond the second post-baseline assessment or progression)
Abbreviations: BOR, best overall response; C+V, carboplatin plus vincristine; CR, complete response; INV, local investigator; IRC, central independent reviewer; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown

Figure 11-2. Best % Change From Baseline by IRC



Source: Page 850 of 2332, Study No. CDRB436G2201, Figure 14.2-4.1L
Decrease shown in best percentage from baseline as read but the investigator.
Only patients with measureable disease at baseline included.
$ Patient is not in the evaluable set
* % change in the target lesion contradicted by by overall lesion response = progressive disease
Abbreviations: CR, complete response; IRC, central independent reviewer; PD, progressive disease; PR, partial response; SD; stable disease

Figure 11-3. Best % Change From Baseline by INV



Source: Page 853 of 2332, Study No. CDRB436G2201, Figure 14.2-4.2L
Decrease shown in best percentage from baseline as read but the investigator.
Only patients with measureable disease at baseline included.
$ Patient is not in the evaluable set
* % change in the target lesion contradicted by by overall lesion response = progressive disease
Abbreviations: CR, complete response; INV, investigator; PD, progressive disease; PR, partial response; SD; stable disease

For PFS, the major discrepancy between IRC and INV was progression vs censored as ongoing without progression, but the proportion of this discrepancy is consistent across treatment arms, and it is unlikely to affect the efficacy conclusion.

Nine patients assigned to the C+V arm with centrally confirmed progression crossed over to the D+T arm. After crossover, the overall response rate in these patients was 33% (95% CI: 8, 70) per independent review.

Considering the discordant measurements between INV and IRC, FDA considers there to be sufficient rationale for how discordant measurements between INV and IRC could occur in glioma response assessments. Given the symmetry of discordance between INV and IRC, there is unlikely to be a significant effect on the efficacy outcomes. The results, presented above in the context of this application, are found to be consistent and supportive of the proposed indication.

HGG Cohort

In the HGG cohort, the updated results for DOR per independent review were consistent with the primary results. The median DOR changed from 22.2 months (95% CI: 7.6, NE) to not estimable (95% CI: 9.2, NE). For the 23 responders, observed DOR was ≥6 months for 78% of patients, ≥12 months for 48% of patients, and ≥24 months for 22% of patients.

Data Quality and Integrity

The Applicant's Position

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets. Two investigator site audits were conducted for this study. The audits results were considered satisfactory for both site audits. There were no known health authority inspections conducted at investigator sites participating in this study. The COVID-19 pandemic had minimal impact on the interpretation of the results of this study.

The FDA's Assessment

FDA agrees with the Applicant's position. The data submitted were organized and adequate to perform a complete review of the efficacy of dabrafenib plus trametinib in patients with pLGG with BRAFV600E mutation. FDA issued information requests during the review cycle and all requests were addressed appropriately.

A small number of RANO assessments were missing due to COVID-19, therefore, no further sensitivity analyses for efficacy are planned.

Dose/Dose Response

The Applicant's Position

Overall analyses are presented in Section 11.1.2, Study G2201 – Results.

The FDA's Assessment

FDA agrees with the Applicant's position.

Durability of Response

The Applicant's Position

Overall analyses are presented in Section 11.1.2, Study G2201 – Results. No additional analyses on durability of response were performed.

The FDA's Assessment

Refer to FDA's assessment of the secondary endpoints and efficacy results above.

Persistence of Effect

The Applicant's Position

Persistence of efficacy is established by the study endpoints DOR/PFS/OS. In line with the study designs and with the currently approved dabrafenib and trametinib indications in the non-adjuvant setting, the recommended duration of treatment in the proposed label will be until loss of favorable benefit-risk as assessed by treating physician or unacceptable toxicity.

No additional analyses on persistence of effect were performed.

The FDA's Assessment

FDA agrees with the Applicant's position regarding study endpoints DOR, PFS, and OS.

In response to an information request, the Applicant provided a summary of outcomes in patients with treatment interruptions in patients demonstrating responses. Treatment interruptions were frequent, and were permitted for up to 28 days. In total, five patients had a response and then discontinued study treatment; these are further described below.

In the LGG cohort, one patient discontinued treatment after a best overall response (BOR) of CR (CDRB436G2201_ (b) (6) The patient had response assessments of CR from evaluations 6 to 10 (between days 337 and 729 post-randomization). Treatment was discontinued on day 729

([redacted]) due to physician decision. After treatment discontinuation, one further response assessment was performed on day 834, which was assessed as PD.

In the LGG cohort, there were four patients who discontinued treatment after a BOR of PR:

- CDRB436G2201_[redacted] The patient had a PR at evaluations 4 and 5 (days 222 and 283 post-randomization), but then was assessed as SD from evaluations 6 through 9 (between days 337 and 479). Treatment was discontinued on day 491 due to initiation of a new cancer therapy; subsequent disease evaluations demonstrated PD.
- CDRB436G2201_[redacted] The patient had a PR from evaluation 2 to 5 (between days 111 and 274 post-randomization), but was then assessed as PD for evaluations 6 and 7 (between days 330 and 386). Treatment was then discontinued on day 398 due to an adverse event (fatigue). After treatment discontinuation, one further response assessment was performed on day 504, which was assessed as PD.
- CDRB436G2201_[redacted] The patient had a PR from evaluations 1 to 5 (between days 55 and 288 post-randomization) but was then assessed as PD for evaluations 6 and 7 (between days 335 and 376). Treatment was discontinued on day 414 due to an adverse event (weight gain). At the time of data cutoff, no further response assessments had been performed since treatment discontinuation.
- CDRB436G2201_[redacted] The patient had a PR from evaluations 2 to 7 (between days 110 and 389 post-randomization), an assessment of PD at evaluation 8 (day 473), assessments of PR at evaluations 9 and 10 (days 502 and 614), an assessment of PD at evaluation 11 (day 669), an assessment of PR at evaluation 12 (day 725), an assessment of PD at evaluation 13 (day 837), and an assessment of PR at evaluation 14 (day 949). Treatment was discontinued on day 953 due to physician decision. After treatment discontinuation, further response assessments were assessed as PD.

The necessary duration of therapy for pediatric patients with BRAF V600E mutant LGG responding to dabrafenib with trametinib therapy is not clearly established. The five patients described above provide some evidence to support continued treatment following initial tumor shrinkage given the progressive disease observed in at least four of the five patients after treatment discontinuation. Available literature also supports continued treatment after tumor response. Elective discontinuation of BRAFi with or without MEKi in pediatric patients with BRAFV600 mutant LGG has been observed and is described in a retrospective analysis of 56 patients (Nobre et al, JCO Precision Oncology 2020). Of these 56 patients, 17 had treatment discontinuation (N=14 patient/physician decision, N=3 toxicity). Thirteen of the 17 patients had rapid progression of their tumors at a median time of 2.3 months after treatment cessation. Nine of the 13 were rechallenged with BRAFi, with 8 (90%) achieving objective response to that therapy. The currently available data are not definitive, but they are supportive of continued therapy for pediatric patients with BRAFV600 mutant LGG who have responded to dabrafenib and trametinib treatment, though an optimal duration of therapy has not yet been determined.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

The Applicant's Position

Patient-reported outcomes were assessed using the PROMIS Parent Proxy Global Health 7+2 for LGG patients. The PRO measured the patient's overall evaluation of his or her physical, mental, and social health. PRO data were collected using an electronic tablet device and administered in the patient's local language. PROs were administered to the patients for completion before any clinical assessments were performed.

Patients in the LGG cohort showed a trend towards improvement for general health and fatigue favoring the targeted therapy (D+T) arm. There was no difference in pain scores among patients receiving D+T or C+V.

The FDA's Assessment

The PRO data for LGG cohort were considered exploratory and therefore were not independently verified by FDA. Patient-reported outcomes for the LGG cohort were administered on Day 1, at Week 5 and every 8 weeks until Week 56, then every 16 weeks thereafter until disease progression per RANO criteria. According to the CSR Table 14.2-7.1L, the majority of participating patients completed the questionnaire, with a minimum completion rate of 89% in the D+T arm and 85% in the C+V arm at the scheduled time points through Week 56.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position

No additional analyses are performed in the current submission.

The FDA's Assessment

Not applicable.

11.1.3 Study A2102

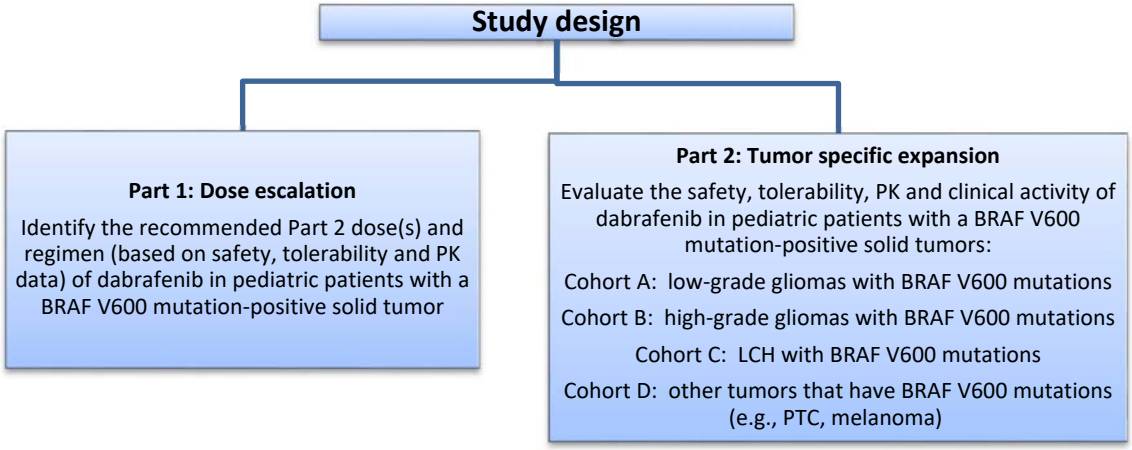
Trial Design

The Applicant's Description

This was a 2-part, Phase I/IIa, multi-center, open label, study in pediatric subjects with advanced BRAF V600 mutation-positive solid tumors. Part 1 was a dabrafenib monotherapy dose escalation study in subjects with any tumor using a modified Rolling 6 Design (RSD). Part 2

was an expansion study to further evaluate the safety, tolerability, and clinical activity of dabrafenib monotherapy in 4 specific tumor types. Subjects participated in only either part 1 or part 2 of the study (Figure 11-4).

Figure 11-4. Applicant – Study A2102 Study Design



Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine kinase; LCH, Langerhans cell histocytosis; PK, pharmacokinetics; PTC, papillary thyroid cancer

Part 1: Dose escalation: this was a repeat dose, dose escalation study. The RSD was built on the classic 3+3 design, but allowed for continued recruitment of subjects while the data from the first 3 subjects in each cohort was collected (up to 6 subjects per cohort). For dose escalation decisions, all available data were used to inform the decision. The starting dose was dabrafenib 3 mg/kg with subsequent dose levels increased or decreased in steps of 0.75mg/kg. The total daily dose was split evenly into a morning and evening dose (BID dosing). The total daily dose did not exceed 300 mg (150 mg BID).

Part 2: Tumor specific expansion: Part 2 had 4 disease-specific cohorts of subjects with BRAF V600 mutation tumors (pediatric LGG; pediatric HGG; Langerhans cell histiocytosis; miscellaneous tumors including melanoma and papillary thyroid carcinoma). At least 40 subjects were recruited into Part 2 with at least 10 subjects each for cohort 1, 2 and 3 and up to 10 subjects in cohort 4. Evaluable response was defined as a subject with a pre-dose and at least 1 post–dose disease assessment. The study attempted to enroll at least 5 pediatric subjects in each cohort who were <6 years of age.

Study End: The study was considered complete when the last enrolled subject was in the study for at least 6 months (without disease progression or withdrew from the study for any reason). At the time of study completion, subjects who were still benefitting from study treatment were offered to participate in a rollover follow-up study. All subjects were followed until 28 days after last dose of study drug. In addition, subjects who discontinued dabrafenib treatment were to be followed every 2 to 3 months.

Discussion on the Study Design

Dose escalation part of the study was to determine the maximum tolerated dose (MTD) and recommend the dose for phase 2 studies (RP2D). An MTD has not been identified for dabrafenib in the adult population. This does not preclude the identification of an MTD in the pediatric population. In this study, modified rolling 6 design (RSD) was employed to determine the MTD. If dose de-escalation had occurred (due to the occurrence of dose limiting toxicity [DLT]) resulting in 6 subjects being entered at the next lower dose level, and there were ≤1 DLT in that next lower dose level, then the MTD would have been defined. The modified RSD (as opposed to the commonly used 3+3 design) was employed as it allows for continuous accrual of subjects into the study and avoids delays in accruing and treating subjects with BRAF V600-mutant tumors as they are identified.

Exposure-response relationships between plasma dabrafenib concentrations and clinical efficacy have been established in adult subjects with melanoma. As per the published data, the molecular biology of mutant BRAF activity is identical between adult and pediatric subjects. Thus, it should be possible to extrapolate adult response data to pediatric subjects, if the pharmacologic exposures achieved in pediatric subjects are similar. In addition, no MTD has been identified in adult subjects with melanoma. Therefore, in addition to monitoring for DLTs, systemic exposure to dabrafenib was used to determine the optimal dose in the pediatric population.

The dose expansion part of the study was conducted to assess the antitumor activity. In the absence of compelling pre-clinical and clinical data to indicate a similar likelihood of response in pediatric BRAF V600 mutation-positive non-melanoma tumors to that seen in adults with BRAF V600 mutation-positive unresectable or advanced melanoma, the introduction of new agents such as dabrafenib into pediatric oncology treatment regimens typically occurs in later lines of therapy. In keeping with this standard, this study was conducted in subjects who experienced recurrent, refractory, or progressive disease after receiving at least one standard therapy. One exception was for subjects with unresectable or metastatic melanoma as there is sufficient clinical data from Phase III adult studies with dabrafenib.

The FDA's Assessment

FDA agrees with the Applicant's description of Study A2102. Single agent dabrafenib data from this study provides supportive evidence for the contribution of trametinib to the combination regimen studied in G2201.

Study Population

The key inclusion criteria were:

- Male or female ≥ 12 months and < 18 years old

- Recurrent disease, refractory disease, or progressive disease after having received at least one standard therapy for their disease

NOTE: Subjects with metastatic (and surgically unresectable) melanoma could have been enrolled for first-line treatment; melanoma subjects with central nervous system involvement may have been enrolled.

- At least one evaluable lesion
- BRAF V600 mutation-positive tumor as confirmed in a CLIA-approved laboratory or equivalent (the local BRAF testing may be subject to further verification by centralized testing that can confirm V600E and V600K mutations only)
- Performance score of >=50% according to Karnofsky/Lansky (a lower performance status could be enrolled if due solely to cancer-related pain, as assessed by the investigator)
- Adequate bone marrow, renal, metabolic, liver, and cardiac function

The key exclusion criteria were:

- Part 2 ONLY: Previous treatment with dabrafenib, another RAF inhibitor, or a MEK inhibitor (exception: prior treatment with sorafenib is permitted)
- Malignancy OTHER than the BRAF mutant malignancy under study
- Had chemotherapy or radiotherapy within 3 weeks (or 6 weeks for nitrosoureas or mitomycin C) prior to administration of the first dose of study treatment
- History of another malignancy; Exception: (a) Subjects who were successfully treated and were disease-free for 3 years, (b) a history of completely resected non-melanoma skin cancer, (c) successfully treated in situ carcinoma, or (d) chronic lymphocytic leukemia in stable remission, are eligible
- Had leukemia
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to dabrafenib and its excipients
- Autologous or allogeneic stem cell transplant within 3 months prior to enrolment [NOTE: subjects with evidence of active graft versus host disease were excluded]
- Presence of active GI disease or other condition (e.g., small bowel or large bowel resection) that would interfere significantly with the absorption of drugs.

Study Endpoints

The Applicant's Description

Study objectives and endpoints are presented in Table 11-18.

Table 11-18. Applicant – Study A2102 Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the safe and tolerable dabrafenib dose(s) for chronic dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures to the dabrafenib adult dose, in subjects with BRAF V600 mutation positive tumors	AEs; ECG; ECHO; changes in laboratory values and vital signs in Part 1 and Part 2. Cmax, area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration [AUC(0-tau) and AUC(0-inf) of dabrafenib
Secondary	
To characterize the pharmacokinetics of dabrafenib, and its metabolites	Ctrough, AUC(0-t), AUC(0-inf), CL/F (dabrafenib only), Cmax, tmax and t½ of dabrafenib and its metabolites, as appropriate
To characterize the longer-term safety and tolerability of dabrafenib	AEs; ECG; changes in laboratory values and vital signs
To assess any preliminary anti-tumor activity of dabrafenib	Tumor response as defined in by investigator assessment
To determine the effect of age and weight on the pharmacokinetics of dabrafenib using a population pharmacokinetics approach	CL/F, V/F, ka, and coefficients for significant covariates
Exploratory	
To evaluate dabrafenib exposure-response relationships for clinical activity and/or safety endpoints, as warranted	Relationship between dabrafenib exposure (PK), and clinical activity and/or safety endpoints
To further characterize the subject population through analysis of tumor DNA, RNA, and protein, or other aberrations from tumor tissue, and to determine whether these are associated with clinical outcome in response to therapy, and assess pharmacodynamic targets.	Mutation analysis (DNA, RNA, and protein testing) of genes related to the BRAF pathway, clinical outcome, and tumor response. Protein assessment of pERK, and other markers of dabrafenib activity if warranted.
To determine the palatability of dabrafenib in pediatric subjects	Palatability questionnaire data

Abbreviations: AE, adverse event; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CL, clearance; ECG, electrocardiogram; ECHO, echocardiogram; PK, pharmacokinetics

The FDA's Assessment

FDA agrees with the Applicant's description of Study A2102.

Statistical Analysis Plan and Amendments

The Applicant's Description

The statistical reporting and analysis plan for Study A2102 was finalized on 13-Nov-2020. SAS version 9.4 was used to perform all data analyses and to generate tables and listings.

All treated population: All subjects who received at least one dose of trametinib and/or dabrafenib. Subjects were not excluded from this population in the case of an incorrect treatment schedule or drug administration or an early termination of treatment.

Safety population: all subjects who received at least one dose of study treatment. All safety data were analyzed using the Safety population.

In this study, the All Treated population and Safety population are identical.

Pharmacokinetic population: subjects fulfilling the All Treated population criteria and for whom pharmacokinetic sample(s) are obtained and analyzed. This population was used for the primary, secondary PK endpoints, and exploratory PK/PD analyses.

DLT Evaluable Population: The DLT Evaluable population is defined as those Part 1 subjects fulfilling the All Treated population criteria, and having received an adequate treatment for the first 28 days to enable an appropriate evaluation of study drug related DLTs. Adequate exposure during the first 28 days will be defined as having received > 75% of planned study drug doses, exclusive of missed doses due to treatment-related toxicity. Subjects who are either withdrawn or dose reduced due to toxicity during the first 28 days will be included in the DLT evaluable population. Any subject from Part 1 in the 'All Treated' population who experiences a DLT, as defined in section 3.3 of the protocol, was also to be included in the DLT evaluable population regardless of exposure.

Response Evaluable Population: all subjects fulfilling the All Treated population criteria with a pre-dose and at least 1 post–dose disease efficacy assessment. For subjects evaluated by RANO criteria, their disease must be 'measurable' at baseline to be included in the Response-evaluable population. This population will be used for sensitivity analysis on the efficacy endpoints.

Efficacy Endpoints and Analyses

The endpoint used to evaluate anti-tumor activity of dabrafenib was the ORR. Efficacy was measured by tumor response, ORR, and DOR. Where appropriate, all lesion and response data were listed by investigator and central independent reviewer assessments for each subject. ORR along with 95% confidence intervals are calculated separately for each of the disease cohorts.

Point estimates and the exact 95% CIs for ORR as assessed by investigator and independent central review were provided for LGG and HGG subjects. For subjects with LCH, the ORR was defined as the proportion of subjects with response of complete resolution or regression by investigator assessment. The ORR point estimate and the 95% CI of ORR were provided. TTR, defined as the time from start of study drug to first documented response (CR or PR, which must be confirmed subsequently), was listed for subjects with a confirmed response (CR or PR). DOR, defined as the time from first documented (CR or PR) to the date of first documented PD or death due to any cause for subjects with a confirmed response (CR or PR), was listed. If a subject did not have an event (PD or death due to any cause), DOR was censored at the date of the last adequate tumor assessment.

Safety Analyses

Unless otherwise specified, all the safety analyses were based on the Safety population. All safety data were reported according to the initial treatment regimen the subject received (initial dose of dabrafenib). Safety analyses were included but not limited to summaries of DLTs, AEs, dose adjustments, and laboratory measures, and were summarized by each initial dose level of dabrafenib for subjects from Part 1 and by cohort for subjects from Part 2. AEs were summarized by maximum toxicity grade for each initial dose level of dabrafenib. The toxicity grade for laboratory data were calculated using NCI-CTCAE v4.0 or higher. The lab data were summarized according to the subjects' baseline grade and maximum grade for each cycle of therapy (done for each initial dose level of dabrafenib).

Exploratory Analyses

Palatability assessments (bitterness, sweetness, appearance, texture, and overall taste) for the suspension formulation, were listed by subject and summarized overall by study part and by dose level for Part 1 and by cohort for Part 2.

Growth analysis Growth data consisted of height, weight, BMI, height velocity and weight velocity. Height, and BMI were summarized at 6-month intervals, using the standard deviation scores (SDS, also called z-score), velocity and velocity SDS. The z-scores allowed identification of potential outliers. Height/BMI SDS and height/weight velocity SDS were summarized by dose/cohort for Part 1 and Part 2 using descriptive statistics (mean, standard deviation, range) for each time window (at Baseline and thereafter allowing informal comparison of growth data), as well as by presenting number of subjects with SDS values lower/higher than 5th/95th percentiles, respectively as applicable**.**

SAP Amendments

No SAP amendments were performed after transition to Novartis.

The FDA's Assessment

FDA acknowledges the Applicant's description. However, FDA did not independently verify the information from Study A2102 given that it is a supportive study.

Protocol Amendments

The Applicant's Description

The study protocol was amended 11 times. Key amendment features are given in Table 11-19.

Table 11-19. Applicant – Study A2102 Protocol Amendments

Version and Date	Summary of Key Changes
Amendment 1.0, 19-Oct-2012	Corrected Inclusion Criteria #6 to ensure consistency with the contraception requirements as outlined in Section 11.1.1; the requirement for male contraception was deleted since the risk of embryofetal developmental toxicity as a consequence of exposure to female pregnant partners is very low. In addition, the dose escalation procedure table provided in Appendix 1 was changed to ensure that escalation of dose when 6 subjects are enrolled occurs only if there are ≤1 subject with a DLT and no subject data pending, and to fix the reference and formatting
Amendment 2.0, 13-Dec-2012	Amendment No. 02 is a country-specific amendment for France which prohibits children younger than 6 years and children older than 6 years with a risk of choking when swallowing capsules from inclusion in the study in France (pending availability of an oral suspension formulation); changes the QTc stopping criteria to 500 msec for French subjects (as compared to 530 msec); adds cardiac monitoring by echocardiogram (ECHO) at Week 4; and highlights that ECHOs are to be performed by the same operator throughout the study, where possible.
Amendment 3.0, 28-Mar-2013	To take into account potential renal effects, Amendment 03 changed the lower age limit of inclusion criterion #2 from subjects 1 month old to ≥ 12 months old, adjusted criteria for adequate renal function in inclusion criterion #7, added guidelines for renal insufficiency and additional laboratory testing. Information on the new suspension formulation was incorporated. The section on dose modification was re-organized for consistency. The Time and Events Table was adjusted to include assessments on Day 22, Week 4 was clarified to be Day 29, and increased chemistry and urinalysis evaluations were added.
Amendment 4.0, 19-Jun-2013	Expanded eligibility to subjects with refractory disease, and allows for BID dosing on Day 1. Clarifications made to glioma scan requirements and BRAF mutation testing timing. Pyrexia management guidelines updated and Prohibited and Cautionary medication section updated.

Version and Date	Summary of Key Changes
Amendment 5.0, 25-Jul-2013	To clarify the dose escalation rules to allow selection of the appropriate dose by age group in the absence of MTD; to include 2 additional dose levels: To clarify that at least 5 subjects less than 6 years old will be enrolled to be consistent with the binding elements of the Pediatric Investigation Plan (PIP) To clarify the general dose modification guidelines; To clarify the DLT evaluable population and PK population; To update the T&E table to specify that ECHOs will be collected for all subjects; To correct Appendix 1.
Amendment 6.0, 30-Jul-2014	Title changed to specify children and adolescents instead of specific years. Lower age range increased to ≥ 12 months from >1 month. Study rationale updated to specify refractory disease. Clarification of the dose escalation rules for selection of the appropriate dose by age group in the absence of MTD. Addition of LCH assessments to the time and events schedule, and addition of the LCH scoring system. Overdose section updated in accordance with most recent information for dabrafenib. SAE definition of protocol-specific SAEs updated for clarity and modified based on additional understanding of the compound
Amendment 7.0, 15-Sep-2016	References to GSK or its staff were deleted and replaced with those of Novartis/Novartis and its authorized agents. Administrative changes to align with Novartis processes and procedures
Amendment 8.0, 19-May-2017	To allow the enrollment of additional subjects in the HGG cohort of Part 2 of the study. This cohort was originally planned to include approximately 10 subjects and has enrolled 21 subjects in Part 2 to date. In view of the promising efficacy in this otherwise very poor prognosis disease, enrollment will remain open until another pediatric HGG study is open for enrollment of this population across all age groups in the same countries (expected by the end of 2018 and no later than mid 2019). Enrollment into the LGG and LCH cohorts have not been extended as subjects may be able to enroll into another pediatric study (Study X2101). Data analysis and statistical consideration updated to align analysis populations with the SAP. Two interim analyses were added to explain a past unplanned interim analysis and a future interim analysis for decision making of development options. Independent review of HGG tumor histology was clarified in the protocol. It has been shown that LGG can be misdiagnosed for HGG, so the independent review was to ensure consistent application of the WHO glioma classification scale to allow for more reliable comparison to historical studies. As a sensitivity analysis, the efficacy data was to be analyzed including only subjects with centrally confirmed HGG.
Amendment 9.0, 17-Sep-2018	Addition of a new pediatric formulation dosage form of dabrafenib 10 mg as dispersible tablets. Update withdrawal of consent language to align with new Global Data Protection Requirements.
Amendment 10.0, 04-Apr-2019	Add additional interim analyses of data to support a regulatory submission

Version and Date	Summary of Key Changes
Amendment 11.0, 21-Aug-2020	Change of the target subject enrollment number for the miscellaneous tumor cohort. The trial has enrolled only four subjects with miscellaneous tumor types (those that are BRAFV600 mutant but are not HGG, LGG, or LCH); two in the dose finding portion, two in the dedicated miscellaneous cohort, over the more than 5 years of enrollment. The miscellaneous cohort was not required for regulatory obligations, and was not required to meet the aims of the clinical trial. Hence, the proposed enrollment target for the miscellaneous cohort was modified from 'at least 10 subjects' to 'up to ten subjects. The protocol was also amended to add updated RANO criteria specifically for low-grade glioma (RANO-LGG; Wen et al 2017) as the basis for independent review.

Abbreviations: BID, twice a day; BRAF, B-Raf proto-oncogene, serine/threonine kinase; DLT, dose-limiting toxicity; GSK, GlaxoSmithKline; HGG, high-grade glioma; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; MTD, maximum tolerated dose; PK, pharmacokinetics; RANO, response assessment in neuro-oncology; SAE, serious adverse event; SAP, statistical analysis plan; WHO, World Health Organization

The FDA's Assessment

FDA acknowledges the Applicant's description. However, FDA did not independently verify the information from Study A2102 given that it is a supportive study.

11.1.4 Study A2102- Results

Compliance With Good Clinical Practices

The Applicant's Position

The study was conducted according to ICH E6 Guideline for Good Clinical Practice that have their origin in the Declaration of Helsinki.

The FDA's Assessment

FDA agrees with the Applicant's position.

Financial Disclosure

The Applicant's Position

As pre-agreed with FDA, Study A2102, is considered covered by the "Financial Disclosure for Clinical Investigators" rule.

The FDA's Assessment

FDA agrees with the Applicant's position.

Patient Disposition

The Applicant's Position

Table 11-20. Applicant – Study A2102 Patient Disposition, Parts 1 and 2 (All Treated Population)

	Part 1				
Part 1 Disposition Reason	**3 mg/kg N=3 n (%)**	**3.75 mg/kg N=10 n (%)**	**4.5 mg/kg N=8 n (%)**	**5.25 mg/kg N=6 n (%)**	**All Subjects N=27 n (%)**
Subjects treated					
Study completion	3 (100)	10 (100)	8 (100)	6 (100)	27 (100)
Died	0	0	0	1 (16.7)	1 (3.7)
Withdrew/discontinued	2 (66.7)	7 (70.0)	5 (62.5)	4 (66.7)	18 (66.7)
Enrolled in a rollover study	0	3 (30.0)	2 (25.0)	1 (16.7)	6 (22.2)
Progressive disease	1 (33.3)	0	1 (12.5)	0	2 (7.4)
Primary reason for withdrawal/discontinuation					
Adverse event	0	0	1 (12.5)	0	1 (3.7)
Investigator's discretion	0	2 (20.0)	1 (12.5)	3 (50.0)	6 (22.2)
Withdrew consent	0	0	1 (12.5)	0	1 (3.7)
Other	0	1 (10.0)	1 (12.5)	0	2 (7.4)
Other: Progressive disease	2 (66.7)	4 (40.0)	1 (12.5)	1 (16.7)	8 (29.6)
	Part 2				
Part 2 Disposition Reason	**LGG N=17 n (%)**	**HGG N=28 n (%)**	**LCH N=11 n (%)**	**Other N=2 n (%)**	**All Subjects N=58 n (%)**
Subjects treated					
Study completion	17 (100)	28 (100)	11 (100)	2 (100)	58 (100)
Died	0	1 (3.6)	0	0	1 (1.7)
Withdrew/discontinued	11 (64.7)	20 (71.4)	4 (36.4)	2 (100)	37 (63.8)
Enrolled in a rollover study	6 (35.3)	6 (21.4)	7 (63.6)	0	19 (32.8)
Progressive disease	0	1 (3.6)	0	0	1 (1.7)
Primary reason for withdrawal/discontinuation					
Adverse event	2 (11.8)	1 (3.6)	1 (9.1)	0	4 (6.9)
Investigator's discretion	5 (29.4)	1 (3.6)	1 (9.1)	0	7 (12.1)
New anti-neoplastic therapy	0	2 (7.1)	0	1 (50.0)	3 (5.2)
Other	2 (11.8)	0	0	0	4 (6.9)
Other: Progressive disease	2 (11.8)	16 (57.1)	2 (18.2)	1 (50.0)	19 (32.8)

Source: Study A2102-Table 14.1-1.1
Percentage is based on N.
Primary reason for withdrawal/discontinuation is from subject completion CRF page.
Other: Progressive disease: this was captured as one of the primary reasons for withdrawal/discontinuation as per the CRF design. Hence, progressive disease for some of the subjects is presented under 'other' reasons instead of 'progressive disease' as one of the reasons for study completion.
Abbreviations: HGG, high-grade glioma; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma

The FDA's Assessment

FDA acknowledges the Applicant's description. However, FDA did not independently verify the results of Study A2102 given that it is a supportive study.

Protocol Violations/Deviations

The Applicant's Position

In Part 1, at least one major PD was reported in 11 subjects (40.7%). The most frequent PDs were due to incorrect dose taken by the patient (5 subjects, 18.5%) and failure to report serious adverse event (SAE) within 24 hours of awareness (3 subjects, 11.1%). In Part 2, at least one major PD was reported in 19 subjects (32.8%). The most frequent PDs were due to at least one incorrect dose (6 subjects, 10.3%), and failure to report SAE within 24 hours of awareness (3 subjects, 5.2%).

The FDA's Assessment

FDA acknowledges the Applicant's description. However, FDA did not independently verify the results of Study A2102 given that it is a supportive study.

Analysis Sets

The Applicant's Position

Analysis sets for part 1, part 2 and pooled disease cohorts are shown in Table 11-21.

Table 11-21. Applicant – Study A2102 Analysis Populations, Parts 1 and 2 (All Treated Population)

Part 1 Analysis Set	3 mg/kg N=3 n (%)	3.75 mg/kg N=10 n (%)	4.5 mg/kg N=8 n (%)	5.25 mg/kg N=6 n (%)	All Subjects N=27 n (%)
All treated population	3 (100)	10 (100)	8 (100)	6 (100)	27 (100)
Safety population	3 (100)	10 (100)	8 (100)	6 (100)	27 (100)
DLT evaluable population	3 (100)	10 (100)	8 (100)	6 (100)	27 (100)
PK population	3 (100)	10 (100)	8 (100)	6 (100)	27 (100)
Response-evaluable population by investigator	3 (100)	9 (90.0)	7 (87.5)	5 (83.3)	24 (88.9)
Response-evaluable population by independent reviewer	2 (66.7)	9 (90.0)	6 (75.0)	6 (100)	23 (85.2)

	3 mg/kg	3.75 mg/kg	4.5 mg/kg	5.25 mg/kg	All Subjects
Part 1	**N=3**	**N=10**	**N=8**	**N=6**	**N=27**
Analysis Set	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
	LGG	**HGG**	**LCH**	**Other**	**All Subjects**
Part 2	**N=17**	**N=28**	**N=11**	**N=2**	**N=58**
Analysis Set	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
All treated population	17 (100)	28 (100)	11 (100)	2 (100)	58 (100)
Safety population	17 (100)	28 (100)	11 (100)	2 (100)	58 (100)
DLT evaluable population	NA	NA	NA	NA	NA
PK population	17 (100)	28 (100)	11 (100)	2 (100)	58 (100)
Response-evaluable population by investigator	17 (100)	21 (75.0)	11 (100)	2 (100)	51 (87.9)
Response-evaluable population by independent reviewer	17 (100)	17 (60.7)	0	2 (100)	36 (62.1)
	LGG BRAF V600	**HGG BRAF V600**	**LCH BRAF V600**		
Pooled Disease Cohort	**N=33**	**N=35**	**N=13**	**Other N=4**	**All Subjects N=85**
Analysis Set	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
All treated population	33 (100)	35 (100)	13 (100)	4 (100)	85 (100)
Safety population	33 (100)	35 (100)	13 (100)	4 (100)	85 (100)
DLT evaluable population	16 (48.5)	7 (20.0)	2 (15.4)	2 (50.0)	27 (31.8)
PK population	33 (100)	35 (100)	13 (100)	4 (100)	85 (100)
Response-evaluable population by investigator	31 (93.9)	27 (77.1)	13 (100)	4 (100)	75 (88.2)
Response-evaluable population by independent reviewer	32 (97.0)	23 (65.7)	0	4 (100)	59 (69.4)

Source: Study A2102-Table 14.1 2.1
Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine kinase; DLT, dose-limiting toxicity; HGG, high-grade glioma; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; PK, pharmacokinetics

The FDA's Assessment

FDA acknowledges the Applicant's description. However, FDA did not independently verify the results of Study A2102 given that it is a supportive study.

Table of Demographic Characteristics

The Applicant's Position

Demographic characteristics of both the parts are presented in Table 11-22.

Table 11-22. Applicant – Study A2102 Demographic and Baseline Characteristics – Parts 1 and 2 (All Treated Population)

Part 1 **Demographic Variable**	**3 mg/kg** **N=3**	**3.75 mg/kg** **N=10**	**4.5 mg/kg** **N=8**	**5.25 mg/kg** **N=6**	**All Subjects** **N=27**
Age (years)					
Mean (SD)	9.33 (5.132)	11.30 (5.355)	6.58 (5.445)	7.17 (3.189)	8.76 (5.144)
Median (Min-Max)	8.00 (5.0 - 15.0)	13.00 (3.0 - 17.0)	5.50 (1.2 - 16.4)	7.50 (3.0 - 11.0)	8.00 (1.2 - 17.0)
Age category-n (%)					
12 months -<2 years	0	0	1 (12.5)	0	1 (3.7)
2-<6 years	1 (33.3)	2 (20.0)	3 (37.5)	2 (33.3)	8 (29.6)
6-<12 years	1 (33.3)	2 (20.0)	3 (37.5)	4 (66.7)	10 (37.0)
12-<18 years	1 (33.3)	6 (60.0)	1 (12.5)	0	8 (29.6)
Sex-n (%)					
Male	2 (66.7)	5 (50.0)	5 (62.5)	3 (50.0)	15 (55.6)
Female	1 (33.3)	5 (50.0)	3 (37.5)	3 (50.0)	12 (44.4)
Body surface area (m^2)					
N	3	10	8	6	27
Mean (SD)	1.2 (0.62)	1.3 (0.33)	1.0 (0.42)	1.0 (0.28)	1.1 (0.39)
Median (Min-Max)	1.0 (0.7 - 1.9)	1.4 (0.8 - 1.8)	0.9 (0.6 - 1.7)	1.0 (0.6 - 1.4)	1.0 (0.6 - 1.9)
Karnofsky performance status-n (%) for subjects ≥16 years of age					
100	0	1 (10.0)	0	0	1 (3.7)
90	0	1 (10.0)	1 (12.5)	0	2 (7.4)
70	0	1 (10.0)	0	0	1 (3.7)
Lansky performance status-n (%) for subjects <16 years of age					
100	1 (33.3)	4 (40.0)	3 (37.5)	3 (50.0)	11 (40.7)
90	1 (33.3)	2 (20.0)	0	1 (16.7)	4 (14.8)
80	0	1 (10.0)	1 (12.5)	1 (16.7)	3 (11.1)
70	0	0	1 (12.5)	1 (16.7)	2 (7.4)
<70	1 (33.3)	0	2 (25.0)	0	3 (11.1)
Part 2 **Demographic Variable**	**LGG** **N=17**	**HGG** **N=28**	**LCH** **N=11**	**Other** **N=2**	**All Subjects** **N=58**
Age (years)					
n	17	28	11	2	58
Mean (SD)	9.65 (5.195)	12.32 (3.692)	5.52 (3.390)	9.50 (10.607)	10.15 (4.957)
Median (Min-Max)	11.00 (2.0 - 17.0)	12.00 (3.0 - 17.0)	5.00 (1.8 - 11.0)	9.50 (2.0 - 17.0)	11.00 (1.8 - 17.0)
Age category-n (%)					
12 months -<2 years	0	0	2 (18.2)	0	2 (3.4)
2-<6 years	5 (29.4)	1 (3.6)	4 (36.4)	1 (50.0)	11 (19.0)
6-<12 years	4 (23.5)	9 (32.1)	5 (45.5)	0	18 (31.0)
12-<18 years	8 (47.1)	18 (64.3)	0	1 (50.0)	27 (46.6)
Sex-n (%)					
Male	9 (52.9)	17 (60.7)	7 (63.6)	2 (100)	35 (60.3)
Female	8 (47.1)	11 (39.3)	4 (36.4)	0	23 (39.7)

Body surface area (m^2)					
n	17	28	10	2	57
Mean (SD)	1.3 (0.44)	1.5 (0.35)	0.8 (0.26)	1.1 (0.78)	1.3 (0.45)
Median (Min-Max)	1.4 (0.7 - 2.0)	1.6 (0.7 - 2.1)	0.8 (0.5 - 1.3)	1.1 (0.5 - 1.6)	1.4 (0.5 - 2.1)
Karnofsky performance status-n (%) for subjects ≥16 years of age					
100	2 (11.8)	6 (21.4)	0	0	8 (13.8)
90	0	0	0	1 (50.0)	1 (1.7)
<70	1 (5.9)	1 (3.6)	0	0	2 (3.4)
Lansky performance status-n (%) for subjects <16 years of age					
100	7 (41.2)	11 (39.3)	6 (54.5)	1 (50.0)	25 (43.1)
90	4 (23.5)	5 (17.9)	3 (27.3)	0	12 (20.7)
80	3 (17.6)	2 (7.1)	0	0	5 (8.6)
70	0	0	1 (9.1)	0	1 (1.7)
<70	0	3 (10.7)	1 (9.1)	0	4 (6.9)

Source: Study A2102-Table 14.1-3.1
A patient may be represented in more than one race category due to multiple races.
Abbreviations: HGG, high-grade glioma; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; SD, standard deviation

The FDA's Assessment

FDA acknowledges the Applicant's description. However, FDA did not independently verify the results of Study A2102 given that it is a supportive study.

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Baseline Characteristics

The Applicant's Position

Disease characteristics varied across subjects and representative of those typically seen in pediatric subjects with recurrent, refractory, or progressive disease after having received at least one standard therapy for their disease. Measurable disease was not required in this dose finding study.

In Part 1, the median time since initial diagnosis was 21.6 months (range: 1 to 151). Four subjects (14.8%) had grade 3 gliomas and two subjects (7.4%) had grade 4 gliomas. In Part 2, median time since initial diagnosis was 44.3 months for LCH, 26.6 months for LGG, 12.0 months for HGG and 8.9 months for 'other tumor'. Based on investigator assessment per RANO, measurable lesions at baseline were present in all 17 subjects with LGG (100%) and in 21 subjects (75.0%) with HGG. All subjects with LCH and other tumors had evaluable only lesions at baseline.

The FDA's Assessment

FDA acknowledges the Applicant's description. However, FDA did not independently verify the results of Study A2102 given that it is a supportive study.

Prior Anti-Cancer Therapy, Radiotherapy and Related Surgeries

The Applicant's Position

All subjects were required to have had at least one prior standard anti-neoplastic therapy (chemotherapy, radiation therapy or surgery) for their disease. In Part 1, all 27 subjects underwent surgery (6 within 6 months and 21 ≥ 6 months) prior to entering the study. All except one patient received chemotherapy as their prior therapy. Ten subjects underwent prior radiotherapy with intent to provide local/regional control (N=4) or with curative intent (N=5). In Part 2, the majority of subjects (47, 81.0%) received chemotherapy as prior therapy. At least 31 subjects underwent prior radiotherapy (11 local/regional, 20 curative). At least 53 of the 58 subjects (91.4%) underwent surgery (26 subjects underwent surgery within 6 months and 27 subjects ≥ 6 months ago) prior to entering the study.

The FDA's Assessment

FDA acknowledges the Applicant's description. However, FDA did not independently verify the results of Study A2102 given that it is a supportive study.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position

Treatment Compliance: Compliance was assessed by the investigator and/or study personnel at each patient visit. The information provided by the patient was captured in the drug accountability form at each visit. Information on treatment compliance was collected, but results were not presented in the CSR.

Concomitant Medications: In Part 1, 13 subjects used concomitant medications during the study that were initiated prior to the start of study drug. Twenty-six subjects began taking at least one concomitant medication after the start of study drug. The most frequently used concomitant medications included ondansetron (48.1%), paracetamol (44.4%), amoxicillin (37%), ceftriaxone, ibuprofen (33.3% each), acetaminophen, dexamethasone, propofol, sodium chloride, and fentanyl (29.6% each), and diphenhydramine, hydrocortisone, morphine (25.9% each). In Part 2, 35 subjects took concomitant medications during the study that were initiated prior to the start of study drug. Fifty-five subjects began taking at least one concomitant medication after the start of study drug. The most frequently used concomitant medications included paracetamol (43.1%), ondansetron (27.6%), and dexamethasone (25.9%).

Rescue medication: Not applicable, as study protocol did not define any rescue medication.

The FDA's Assessment

FDA acknowledges the Applicant's description. However, FDA did not independently verify the results of Study A2102 given that it is a supportive study.

Efficacy Results

The Applicant's Description

Best Overall Response (Secondary Efficacy Endpoint)

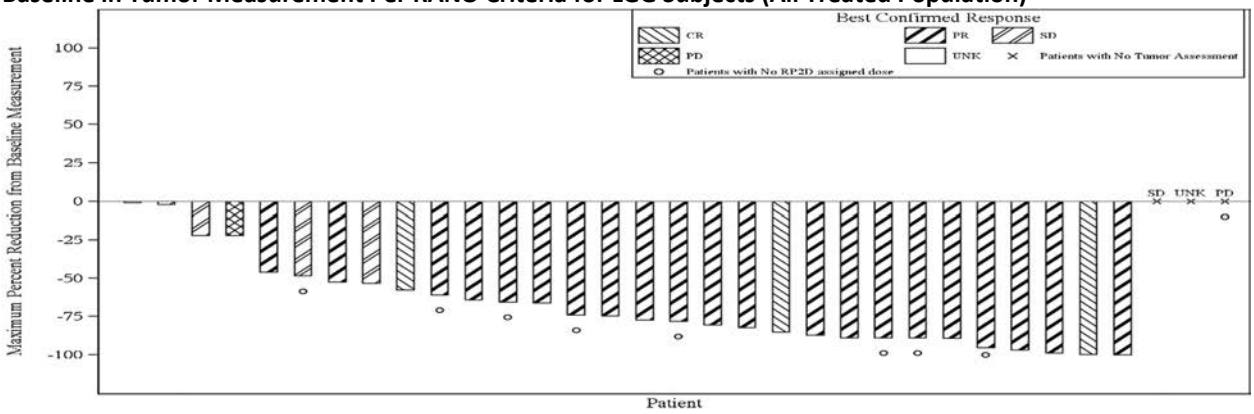
LGG (based on investigator assessment): ORR based on investigator assessment was achieved in 70.8% (95% CI: 48.9, 87.4) of all 24 LGG subjects at RP2D; 3 subjects (12.5%) achieved CR and 14 subjects (58.3%) achieved PR. Among the 33 LGG subjects, the ORR was 72.7% (95% CI: 54.5, 86.7) with CR in 3 subjects, PR in 21 subjects and SD in 5 subjects (15.2%) (Table 11-23). Percentage reduction from baseline sum of the products of perpendicular diameters for LGG subjects is presented in Figure 11-5.

Table 11-23. Applicant – Study A2102 BOR Based on Investigator Assessment Per RANO Criteria for LGG Subjects (All Treated Population)

	Part 1					
	3.75 mg/kg N=4	4.5 mg/kg N=6	5.25 mg/kg N=6	Part 2 LGG N=17	All LGG Subjects at RP2D* N=24	All LGG Subjects N=33
Disease: LGG	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Best overall response						
Complete response	0	0	0	3 (17.6)	3 (12.5)	3 (9.1)
Partial response	3 (75.0)	5 (83.3)	4 (66.7)	9 (52.9)	14 (58.3)	21 (63.6)
Stable disease	1 (25.0)	0	2 (33.3)	2 (11.8)	4 (16.7)	5 (15.2)
Progressive disease	0	1 (16.7)	0	1 (5.9)	1 (4.2)	2 (6.1)
Unknown	0	0	0	2 (11.8)	2 (8.3)	2 (6.1)
ORR (CR+PR)	3 (75.0)	5 (83.3)	4 (66.7)	12 (70.6)	17 (70.8)	24 (72.7)
95% CI for ORR	(19.4, 99.4)	(35.9, 99.6)	(22.3, 95.7)	(44.0, 89.7)	(48.9, 87.4)	(54.5, 86.7)

Source: Study A2102-Table 14.2-1.1a
* All LGG subjects who have been assigned to RP2D across Part 1 and Part 2.
N: The total number of LGG subjects in the corresponding group. It is the denominator for percentage (%) calculation.
n: Number of subjects who are at the corresponding category.
The 95% CI for the frequency distribution of each variable were computed using two-sided exact binomial 95% CIs.
Abbreviations: CI, confidence interval; CR, complete response; LGG, low-grade glioma; ORR, overall response rate; PR, partial response; RP2D, recommended phase II dose

Figure 11-5. Applicant – Study A2102 Investigator-Assessed Percent Change at Maximum Reduction From Baseline in Tumor Measurement Per RANO Criteria for LGG Subjects (All Treated Population)



Source: Study A2102-Figure 14.2-1.1a
Complete response, partial response, stable disease, progressive disease, unknown labels on x-axis represent responses for subjects (subjects ID: (b) (6)) with missing tumor assessment.
Abbreviations: LGG, low-grade glioma; RANO, response assessment in neuro-oncology

LGG (based on Independent assessment): The ORR in the 24 LGG subjects at RP2D based on independent reviewer assessment was the same when measured with the RANO criteria (2010) (Table 11-24) and the RANO criteria (2017): 41.7% (95% CI: 22.1, 63.4) with 10 subjects (41.7%) achieving PR.

Table 11-24. Applicant – Study A2102 Best Overall Response Based on Independent Reviewer Assessment Per RANO Criteria 2010 for LGG Subjects (All Treated Population)

	Part 1			Part 2	
Disease: LGG	**3.75 mg/kg N=4 n (%)**	**4.5 mg/kg N=6 n (%)**	**5.25 mg/kg N=6 n (%)**	**LGG N=17 n (%)**	**All LGG Subjects at RP2D[a] N=24 n (%)**
Best overall response					
Complete response	0	1 (16.7)	0	0	0
Partial response	2 (50.0)	2 (33.3)	2 (33.3)	8 (47.1)	10 (41.7)
Stable disease	2 (50.0)	2 (33.3)	4 (66.7)	6 (35.3)	11 (45.8)
Non-CR/Non-PD	0	0	0	0	0
Progressive disease	0	0	0	1 (5.9)	1 (4.2)
Unknown	0	1 (16.7)	0	2 (11.8)	2 (8.3)

	Part 1			Part 2	
Disease: LGG	**3.75 mg/kg N=4 n (%)**	**4.5 mg/kg N=6 n (%)**	**5.25 mg/kg N=6 n (%)**	**LGG N=17 n (%)**	**All LGG Subjects at RP2D[a] N=24 n (%)**
Overall response rate (ORR: Complete response + Partial response)	2 (50.0)	3 (50.0)	2 (33.3)	8 (47.1)	10 (41.7)
95% CI for ORR	(6.8, 93.2)	(11.8, 88.2)	(4.3, 77.7)	(23.0, 72.2)	(22.1, 63.4)

Source: Study A2102-Table 14.2 1.1b
[a] All LGG subjects who have been assigned to RP2D across Part 1 and Part 2.
[b] the subjects did not have more than one post-baseline assessment.
N: The total number of LGG subjects in the corresponding group. It is the denominator for percentage (%) calculation.
n: Number of subjects who are at the corresponding category.
The 95% CI for the frequency distribution of each variable were computed using two-sided exact binomial 95% CIs.
Abbreviations: CI, confidence interval; CR, complete response; LGG, low-grade glioma; PD, progressive disease; RANO, response assessment in neuro-oncology; RP2D, recommended phase II dose

The concordance between 2010 and 2017 RANO criteria based on independent reviewer assessment of response for LGG subjects was 60.6%. Concordance between investigator and independent reviewer assessment of BOR for LGG subjects was 48.5% for both 2010 and 2017 RANO criteria.

HGG: The ORR based on investigator assessment was 25% (95% CI: 10.7, 44.9) for 28 HGG subjects treated at the recommended Phase II dose (RP2D); 5 subjects (17.9%) achieved CR and 2 subjects (7.1%) achieved PR. The ORR observed in subjects treated at RP2D was similar to the ORR observed in subjects with HGG treated at any dose (28.6%; 95% CI: 14.6, 46.3) (Table 11-25). RANO 2010 criteria was used for evaluation of HGG tumors (Wen et al 2010) as it was not substantially altered in the RANO 2017 (Wen et al 2017). Percentage reduction from baseline tumor measurements is presented in Figure 11-6.

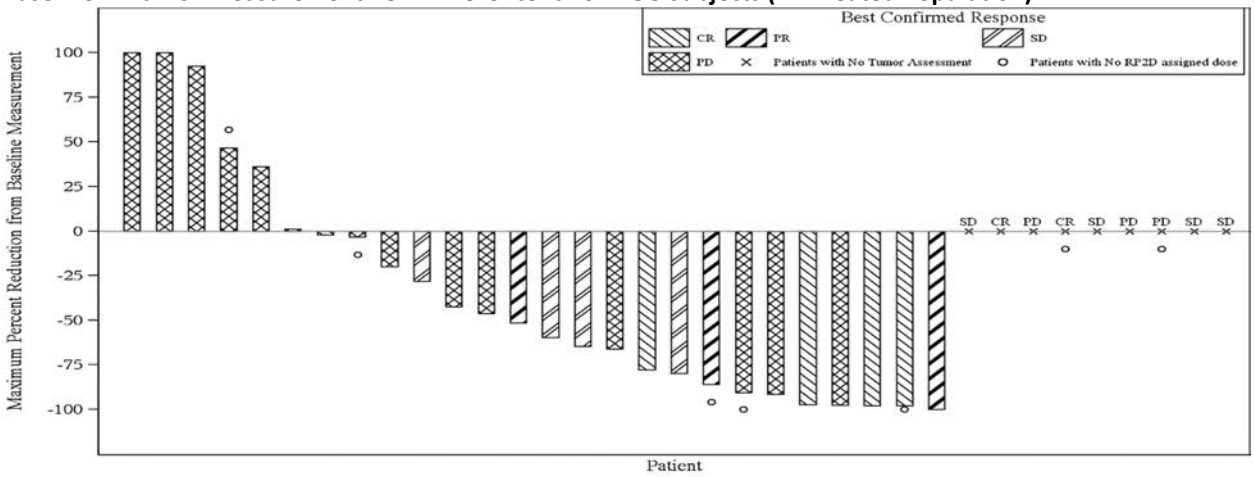
Table 11-25. Applicant – Study A2102 BOR Based on Investigator Assessment Per RANO 2010 Criteria for HGG Subjects (All Treated Population)

	Part 1		Part 2		
Disease: HGG	**3 mg/kg N=3 n (%)**	**3.75 mg/kg N=4 n (%)**	**HGG N=28 n (%)**	**All HGG at RP2D* N=28 n (%)**	**All HGG N=35 n (%)**
Best overall response (BOR)					
Complete response (CR)	2 (66.7)	0	5 (17.9)	5 (17.9)	7 (20.0)
Partial response (PR)	0	1 (25.0)	2 (7.1)	2 (7.1)	3 (8.6)
Stable disease (SD)	0	0	8 (28.6)	8 (28.6)	8 (22.9)
Non-CR/Non-PD	0	0	0	0	0
Progressive disease (PD)	1 (33.3)	3 (75.0)	13 (46.4)	13 (46.4)	17 (48.6)

	Part 1		Part 2		
	3 mg/kg	3.75 mg/kg	HGG	All HGG at RP2D*	All HGG
	N=3	N=4	N=28	N=28	N=35
Disease: HGG	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
ORR (CR+PR)	2 (66.7)	1 (25.0)	7 (25.0)	7 (25.0)	10 (28.6)
95% CI for ORR	(9.4, 99.2)	(0.6, 80.6)	(10.7, 44.9)	(10.7, 44.9)	(14.6, 46.3)

Source: Study A2102-Table 14.2 1.2a
* All HGG subjects who have been assigned to RP2D across Part 1 and Part 2
N: The total number of HGG subjects in the corresponding group. It is the denominator for percentage (%) calculation.
n: Number of subjects who are at the corresponding category.
The 95% CI for the frequency distribution of each variable were computed using two-sided exact binomial 95% CIs.
Abbreviations: BOR, best overall response; CI, confidence interval; HGG, high-grade glioma; RANO, response assessment in neuro-oncology; RP2D, recommended phase II dose

Figure 11-6. Applicant – Study A2102 Investigator-Assessed Percent Change at Maximum Reduction From Baseline in Tumor Measurement Per RANO Criteria for HGG Subjects (All Treated Population)



Source: Study A2102-Figure 14.2-1.2a
Complete response, partial response, stable disease, progressive disease, unknown labels on x-axis represent responses for subjects (subjects ID: (b) (6)) who lack measurable lesions preventing calculation of percent reduction of lesion cross sectional area.
Abbreviations: HGG, high-grade glioma; RANO, response assessment in neuro-oncology

The ORR based on independent reviewer assessment in all 28 HGG subjects at RP2D was 42.9% (95% CI: 24.5, 62.8); 4 subjects (14.3%) achieved CR and 8 subjects (28.6%) achieved PR.

LCH: The ORR for LCH subjects based on investigator assessment (adapted from Histiocyte Society Evaluations and Treatment Guidelines; Minkov et al 2009) at RP2D was 72.7% (95% CI: 39.0, 94.0). The ORR observed in subjects treated with RP2D was similar to the subjects treated at any dose (76.9%, 95% CI: 46.2, 95.0). Six subjects had complete resolution and 4 had regressive disease (Table 11-26). Nine of the 10 responses were ongoing at study completion and 12 of the 13 subjects overall were progression free at study completion.

Table 11-26. Applicant – Study A2102 Response Rate of LCH Subjects Based on Investigator Assessment (All Treated Population)

	Part 1		Part 2	All LCH Subjects	All LCH
	3.75 mg/kg	4.5 mg/kg	LCH	at RP2D*	Subjects
	N=1	N=1	N=11	N=11	N=13
Disease: LCH	n (%)	n (%)	n (%)	n (%)	n (%)
Best overall response					
Complete resolution	1 (100)	1 (100)	4 (36.4)	4 (36.4)	6 (46.2)
Regressive disease	0	0	4 (36.4)	4 (36.4)	4 (30.8)
Stable disease	0	0	3 (27.3)	3 (27.3)	3 (23.1)
Overall response rate (ORR: Complete resolution + regressive disease)	1 (100)	1 (100)	8 (72.7)	8 (72.7)	10 (76.9)
95% CI for ORR	(2.5, 100)	(2.5, 100)	(39.0, 94.0)	(39.0, 94.0)	(46.2, 95.0)

Source: Study A2102-Table 14.2-1.3a
* All LCH subjects who have been assigned to RP2D across Part 1 and Part 2.
N: The total number of LCH subjects in the corresponding group. It is the denominator for percentage (%) calculation.
n: Number of subjects who have response of complete resolution or regression from the start of treatment until disease progression or the start of new anti-cancer therapy.
The 95% CI for the frequency distribution of each variable were computed using two-sided exact binomial 95% CIs.
Abbreviations: LCH, Langerhans cell histiocytosis

Other Solid Tumors

Responses were confirmed by the independent reviewer assessment. Two subjects were enrolled in Part 1: a 14-year-old patient with papillary thyroid carcinoma treated in the 3.75 mg/kg/day cohort achieved stable disease, and a 2-year-old with neuroblastoma treated in the 4.5 mg/kg/day cohort experienced disease progression. Two subjects with 'other solid tumor' types were enrolled in Part 2: a 2-year-old patient with neuroblastoma had PD, and a 17-year-old patient with undifferentiated sarcoma tumor had only one post baseline tumor assessment before discontinuing treatment and thus a response could not be determined.

Sensitivity Analysis

A sensitivity analysis was conducted based on the response-evaluable population

LGG subjects: The ORR based on investigator assessment in all 23 response evaluable LGG subjects at RP2D was 73.9% (95% CI: 51.6, 89.8); 3 subjects (13%) achieved CR and 14 subjects (60.9%) achieved PR. The ORR based on independent reviewer assessment according to both 2010 and 2017 RANO criteria in all 24 response evaluable LGG subjects at RP2D was 41.7% (95% CI: 22.1, 63.4). Ten subjects (41.7%) achieved PR as per both 2010 and 2017 RANO criteria. Stable disease was the best response in 11 subjects (45.8%) per RANO 2010 criteria and 12 subjects (50%) per the RANO 2017 criteria.

HGG subjects: The ORR based on investigator assessment was similar in the response evaluable HGG subjects treated at RP2D (N=21) and those treated at any dose (N=27).

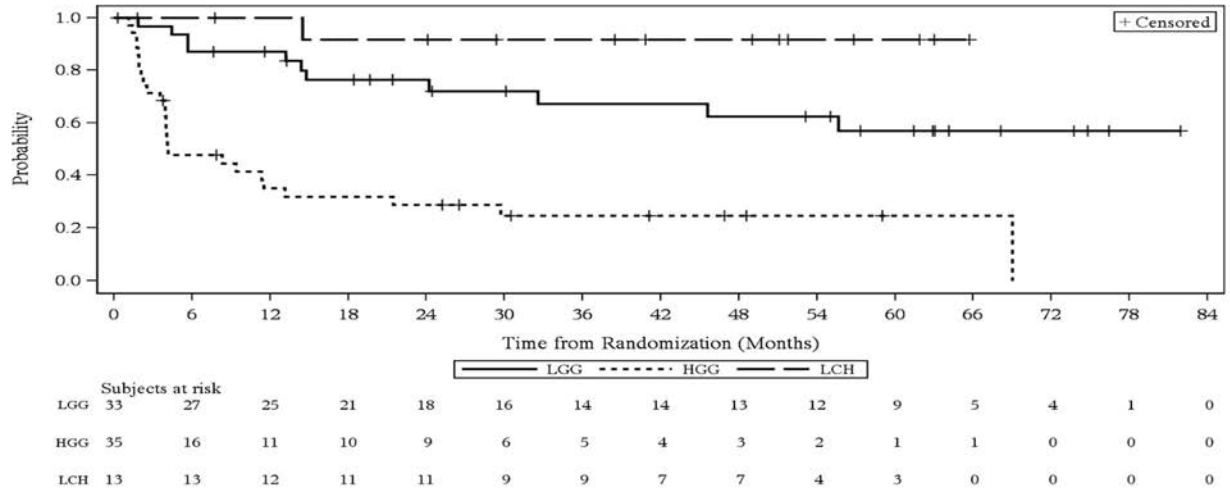
The ORR based on investigator assessment in all 21 response-evaluable HGG subjects at RP2D was 28.6% (95% CI: 11.3, 52.2) and in all 27 response-evaluable HGG subjects at any dose was 33.3% (95% CI: 16.5, 54.0). The BOR of CR and PR was reported in 6 subjects (22.2%) and 3 subjects (11.1%), respectively in all 27 HGG subjects.

The ORR based on independent reviewer assessment in all 17 response-evaluable HGG subjects at RP2D was 47.1% (95% CI: 23.0, 72.2) and 52.2% (95% CI: 30.6, 73.2) in those treated at any dose. The BOR of partial response and stable disease was reported in 12 subjects (52.2%) and 4 subjects (17.4%), respectively in all 23 HGG subjects.

Progression Free Survival- Pooled Disease Cohorts

Based on investigator assessment, the median PFS was 4.2 months (95% CI: 3.9, 13.1) for HGG cohort and was not reached for all other cohorts. The PFS for HGG cohort was 2.3 months (95% CI: 1.7, 4.0) at 25th percentile and 29.7 months (95% CI: 9.4, 69.0) at 75th percentile (Figure 11-7).

Figure 11-7. Applicant - Study A2102 Kaplan-Meier PFS Curves by Investigator Assessment by Cohort – Pooled Disease Cohorts (All Treated Population)

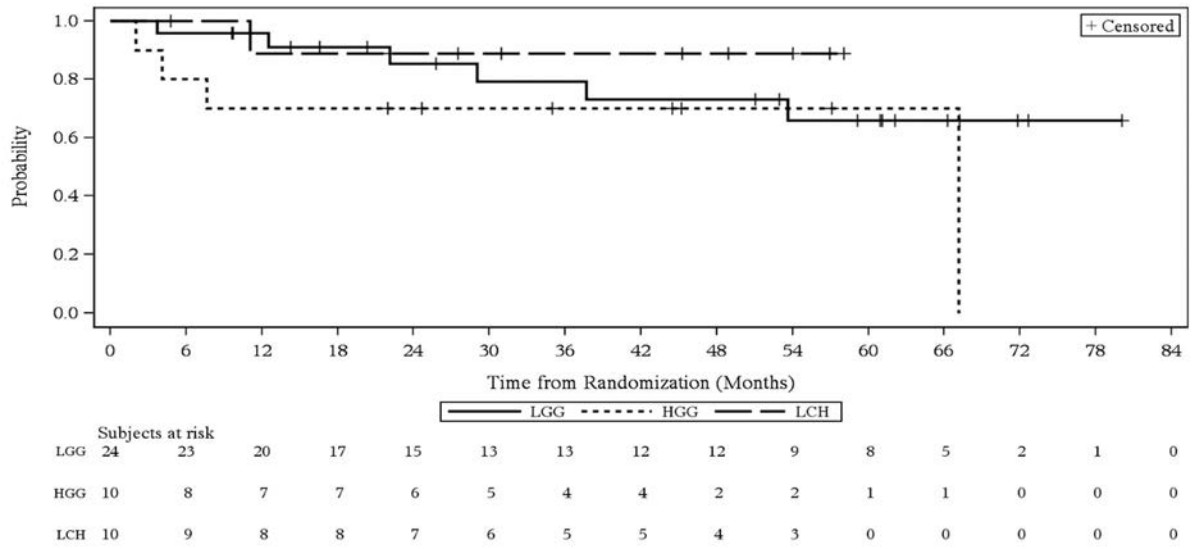


Source: Study A2101-Figure 14.2-1.4.1
Abbreviations: HGG, high-grade glioma; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; PFS, progression-free survival

Duration of Response - Pooled Disease Cohorts

Based on investigator assessment, the median duration of response for HGG cohort was 67.2 months (95% CI: 1.9, 67.2) and was not reached for all other cohorts (Figure 11-8).

Figure 11-8. Applicant - Study A2102 Kaplan-Meier DOR Curves by Investigator Assessment by Cohort – Pooled Disease Cohorts (All Treated Population)



Source: Study A2101-Figure 14.2-1.5.1
Abbreviations: DOR, duration of response; HGG, high-grade glioma; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma

The FDA's Assessment

FDA acknowledges the Applicant's description. See Section 11.1.8 for a discussion of the study results and their support for the determination of the contribution of each component to the combination treatment regimen.

Data Quality and Integrity

The Applicant's Position

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets. With no COVID-19 related deaths reported up to the LPLV (04-Dec-2020), there were no changes to the analysis due to COVID-19.

11.1.5 Study X2101

Trial Design

The Applicant's Description

This study was a 4-part, Phase I/IIa, multi-center, open-label clinical study in pediatric subjects with refractory or recurrent solid tumors. Approximately 142 subjects were planned to be

enrolled in the study (approximately 48 subjects in Part A, at least 40 subjects in Part B, approximately 24 subjects in Part C and at least 30 subjects in Part D).

Part A (trametinib monotherapy dose escalation, approx. 48 subjects) was a repeat dose, dose escalation and expansion phase to evaluate safety, tolerability, and PK of trametinib monotherapy in three age range cohorts (1 month to < 2 years, 2 to ≤ 12 years, and over 12 years of age) to establish the toxicity profile, PK, and RP2D of trametinib in each age cohort.

Part B (trametinib monotherapy dose expansion, at least 40 subjects) aimed to evaluate the safety, tolerability, and preliminary clinical activity of trametinib in tumor-specific pediatric populations in 4 disease cohorts (B1: Refractory or relapsed neuroblastoma; B2: Recurrent or unresectable LGG with BRAF tandem duplication with fusion; B3: Neurofibromatosis Type -1 associated plexiform neurofibromas (NF-1 with PN) that are unresectable and medically significant; B4: BRAF V600 mutant tumors)

Part C (trametinib + dabrafenib dose escalation, approx. 24 subjects) was a limited dose escalation phase in subjects with recurrent, refractory, or unresectable BRAF V600 mutated tumors, which aimed to establish the RP2D of combination therapy.

Part D (trametinib + dabrafenib dose expansion, at least 30 subjects) was added with protocol amendment 5 and aimed to evaluate the safety, tolerability, and preliminary activity of trametinib + dabrafenib in subjects with recurrent, refractory, or unresectable BRAF V600 mutated tumors (LGG and Langerhans cell histiocytosis [LCH]).

The FDA's Assessment

FDA agrees with the Applicant's position**.** FDA did not independently confirm these analyses. However, primary data from this study was used to support approval of the tissue agnostic indication for dabrafenib and trametinib, and efficacy results from this study are described in Section 14.6 of the product labels. Efficacy results from the single agent trametinib arm provide supportive evidence for the contribution of dabrafenib to the combination regimen studied in G2201. Safety results from patients in this study (Parts C and D) contribute to the pooled safety population described in Section 11.2.

Study Population

Key Inclusion Criteria

1. Written informed consent
2. Male or female between 1 month and < 18 years of age (inclusive) (Parts C and D: 12 months to < 18 years; Part A extension: 1 month to < 6 years; Part C extension: 12 months to < 6 years).

3. Disease that was relapsed/refractory to all potentially curative standard treatment regimens or had a current disease for which there was no known curative therapy, or therapy proven to prolong survival with an acceptable quality of life.
4. Prior therapy: The subject's disease (i.e., cancer, NF-1 with PN, or LCH) must had relapsed after or failed to respond to frontline curative therapy or there must not be other potentially curative treatment options available. Subjects who recovered to grade ≤ 1 from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to enrollment.
5. Karnofsky/Lansky performance status score ≥ 50% scale.

Specific Eligibility Criteria, Part A

6. For the initial dose escalation to identify the maximum tolerable or PK target dose, age between 2 years and < 18 years (inclusive) at the time of signing the informed consent form (ICF). Children < 2 years of age were enrolled once the age specific expansion cohorts were opened.
7. Histologically confirmed solid tumors. In subjects with brain stem gliomas the requirement for histological confirmation waived if a biopsy was not performed. For plexiform neurofibromas, histologic confirmation of tumor was not necessary in the presence of consistent clinical and radiological findings, but was to be considered if malignant degeneration of a PN was clinically suspected.
8. Measurable or evaluable tumors. Subjects with neuroblastoma that was only detectable by meta-iodobenzylguanidine (MIBG) scan were eligible. Subjects with neuroblastoma that was only detected by bone marrow aspirate/biopsy or elevated homovanillic acid / vanillylmandelic acid (HVA/VMA) were not eligible.
9. Adequate bone marrow function.

Specific Eligibility Criteria, Part B

10. Tumor tissue (archived or fresh) required and was shipped to Novartis or site-specific laboratory except in subjects where tumor biopsy was not possible.
11. Histologically confirmed Solid Tumor Cohort (B1) Specific Criteria:
    - B1: Refractory or relapsed neuroblastoma
    - B2: Recurrent or unresectable LGG with BRAF tandem duplication with fusion
    - B3: Neurofibromatosis Type -1 associated plexiform neurofibromas (NF-1 with PN) that are unresectable and medically significant
    - B4: BRAF V600 mutant tumors

Specific Eligibility Criteria, Part C

12. Tumors that were documented by clinical laboratory improvement amendments or equivalent certified laboratory test to harbor BRAF V600 mutation at diagnosis or relapse
13. Measurable or evaluable disease
14. Adequate bone marrow function

Specific Eligibility Criteria, Part D: Subjects that met general eligibility criteria as well as the specific criteria listed below were eligible for enrollment in Part D.

15. Measurable or evaluable disease
16. Recurrent or refractory BRAF V600 mutant LGG or LCH tumors
17. Adequate bone marrow function

Exclusion Criteria

18. Lactating or pregnant female.
19. History of another malignancy including resected non-melanomatous skin cancer.
20. Subjects with NF-1 associated optic pathway tumors were excluded if they are actively receiving therapy for the optic pathway tumor or did not met criteria for PN or malignant solid tumor
21. Subjects with a history of NF-1 related cerebral vascular anomaly (such as Moyamoya)
22. Subjects with NF-1 who actively received therapy for the optic pathway tumor
23. Subjects with NF-1 and only PN lesions (only applicable to Part B)
24. Part B, C and D: Previous treatment with dabrafenib or any BRAF inhibitor, trametinib or another MEK inhibitor, or an ERK inhibitor (exception: prior treatment with sorafenib was permitted). Subjects who had received prior dabrafenib or another BRAF inhibitor enrolled into Part B4. Subjects who had prior dabrafenib or BRAF inhibitor therapy was enrolled in Part C or Part D if they had prior benefit to dabrafenib or BRAF inhibitor monotherapy, as determined by the investigator. (Note: Subjects enrolled in Parts A or B were not eligible to participate in Parts C or D)
25. For subjects with solid tumors that were not primary CNS tumors or NF-1 associated plexiform neurofibromas, subjects with symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression were excluded.
26. Unresolved toxicity of National Cancer Institute Common Terminology Criteria for adverse events, version 4.03 (NCI-CTCAE v4.03) grade 2 or higher from previous anti-cancer therapy, except alopecia.

27. History or evidence of cardiovascular risk

The FDA's Assessment

FDA acknowledges the Applicant's position. FDA did not independently confirm these analyses.

Study Endpoints

The Applicant's Description

The study objectives and their respective endpoints are presented in Table 11-27.

Table 11-27. Applicant – Study X2101 Objectives and Endpoints

Objective	Endpoint
To determine the safe and tolerable trametinib dose(s) for chronic dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures (Cτ) to the recommended adult dose	Adverse events (AEs); ECG; ECHO; changes in laboratory values and vital signs. Steady state Cτ of trametinib
To characterize the pharmacokinetics of trametinib	Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F) Cmax, tmax and Cavg, as appropriate
To characterize the safety and tolerability of trametinib	AEs; ECG; changes in laboratory values and vital signs
To assess any preliminary anti-tumor activity of trametinib	Tumor response to trametinib as defined in study protocol by investigator assessment.
To determine the effect of covariates such as age and weight on the pharmacokinetics of trametinib using a population pharmacokinetics approach	CL/F, volume of distribution (V/F), absorption rate (ka), and coefficients for significant covariates
To characterize the pharmacokinetics of trametinib and dabrafenib when administered in combination	Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F) Cmax, tmax and Cavg of trametinib and dabrafenib when administered in combination, if the data permit
To characterize the safety and tolerability of trametinib and dabrafenib when administered in combination	AEs; ECG; ECHO; changes in laboratory values and vital signs.
To determine the safe and tolerable dabrafenib dose(s) when administered in combination with the recommended trametinib dose for chronic continuous daily dosing in pediatric subjects (infants, children and adolescents) that achieves similar exposures to the recommended adult dose	AEs; ECG; ECHO; changes in laboratory values and vital signs. Steady state Cτ of trametinib; steady state AUC(0-12) of dabrafenib
To assess any preliminary anti-tumor activity of trametinib and dabrafenib when administered in combination	Tumor response to dabrafenib and trametinib combination as defined in study protocol by investigator assessment.
To determine the acceptability and palatability of trametinib and dabrafenib in pediatric subjects	Palatability questionnaire data

Objective	Endpoint
To further characterize the subject population through analysis of archival tumor tissue and circulating markers, to determine whether these biomarkers are associated with clinical outcome in response to therapy	Mutation analysis (DNA, RNA, and protein testing) of genes related to the MAPK pathway, clinical outcome, and tumor response.
To evaluate trametinib exposure response relationships for clinical activity and/or safety endpoints, as warranted	
To evaluate exposure-response relationships for clinical activity and safety endpoints for trametinib when administered as combination with dabrafenib	

Abbreviations: ECG, electrocardiogram; ECHO, echocardiogram

The FDA's Assessment

FDA acknowledges the Applicant's position. FDA did not independently confirm these analyses.

Statistical Analysis Plan and Amendments

The Applicant's Description

The statistical analysis plan was finalized on 18-Nov-2020. SAS version 9.3 was used to perform all data analyses and to generate tables and listings.

All treated population: all subjects who received at least one dose of study medication

Safety population: all subjects who received at least one dose of trametinib and/or dabrafenib. This population was used for all baseline and demographic summaries, and for safety data analyses.

Pharmacokinetic population: all subjects in the 'All treated' population from whom a PK sample was obtained and analyzed and was evaluable. For a concentration to be evaluable the subject has to receive a dose of the planned treatment and provide at least one primary PK parameter. Only confirmed PK concentrations were used in the analyses.

DLT Evaluable Population: The DLT evaluable population included subjects participating in the dose determining portion of the study (Part A and 3+3 design portion of Part A extension, Part C and Part C extension), fulfill the 'All treated' population criteria and received an adequate treatment in the first 28 days which enabled an appropriate evaluation of study treatment related to DLTs.

Response Evaluable Population: The Response-evaluable population was defined as those subjects who fulfilled the 'All treated' population criteria with a pre-dose and at least one post-dose disease efficacy assessment (unless disease progression was observed before that time) or have discontinued for any reason. In addition, for subjects evaluated by RANO criteria, their disease must have been measurable at baseline to be included in the Response-evaluable population. This population was used for sensitivity analysis on the efficacy endpoints.

Efficacy Criteria and Analysis

All efficacy analyses were based on the 'All treated' population unless otherwise specified. All analyses were summarized by dose levels in Part A and Part C, by disease cohorts in Part B and Part D, and by 5 disease cohorts as listed below.

- Glioma fusion subjects on trametinib monotherapy*
- BRAF V600 mutant glioma subjects on trametinib monotherapy
- BRAF V600 mutant glioma subjects on combination therapy
- NF-1 with PN subjects on trametinib monotherapy*
- LCH subjects on combination therapy

*Note: The results for these non-BRAF V600 mutation positive disease types are not discussed

ORR by disease type: Objective response rate (ORR) was defined as the proportion of subjects with a disease assessment at baseline and a confirmed BOR of CR or PR according to disease-specific criteria. ORR was calculated based on the 'All treated' population using investigator assessment of tumor response.

BOR for each subject was determined from the sequence of overall responses according to the rules for RECIST v1.1, RANO and Dombi criteria.

Efficacy was assessed using the RANO criteria for LGG and the definition of disease state, response criteria and response definition for LCH, adapted from Histiocyte Society Evaluations and Treatment Guidelines; Minkov et al 2009.

Evaluation of anti-cancer activity by disease assessment included imaging (e.g., CT scan, MRI, bone scan, plain radiography) and physical examination (as indicated or palpable/superficial lesions). Efficacy assessment methods and measurement modalities are provided in, which included updated RANO 2017 criteria (Wen et al 2017).

The pooled disease type investigator assessed BOR response data for the all treated population is presented as the efficacy objective. Supportive analysis for each pooled disease type includes:

- Investigator assessed BOR of the response evaluable population,
- Investigator assessed PFS,
- Independent reviewer assessed BOR of the all treated population and the response evaluable population,
- Independent reviewer assessed PFS
- Concordance analysis, as applicable.

SAP Amendments

SAP amendments are described in Table 11-28.

Table 11-28. Applicant – Study X2101 SAP Amendments

Date/Amendment Version	Section and Title Impacted (Current)
6-Aug-2019/ Version 1.1	Table 1.2 Study objectives and end-points: Exploratory end-point added. Section 2.10: Description for growth analysis added Appendix section 5.5: Formulae for calculation of SDS and velocity values and time-windows to be considered added.
22-May-2020/ Amendment 1	2.4.1 Study treatment/compliance: Duration of exposure to combination partner updated 2.7 Analysis of secondary efficacy objective(s): Analysis text updated to mention the analysis by disease cohort Also, derivation of BOR and ORR updated for each disease cohort 2.7.4 Supportive analyses: New section added 2.8 Safety analysis: Updated the analysis text to mention the analysis by disease cohort 2.10 Other exploratory analysis: Added part for time to event analysis for progression-free survival (PFS) and duration of response (DoR), Added the updated sections in document history. Updated as per sponsor comments.
18-Nov-2020/ Amendment 2	1 Introduction: Updated the SAP has been written in accordance with Novartis SOPs only 1.1 Study Design: Clarified scope of the Addendum restricted to IA3 analysis only 2.2 Analysis Set: Response Evaluation Population updated 2.3 Patient disposition, demographics, and other baseline characteristics Central BRAF V600 mutation status 2.3.1 Patient Disposition: Protocol deviations related to COVID-19 added 2.4.1 Study treatment/compliance: Duration of exposure to combination partner updated 2.7 Analysis of secondary efficacy objective(s): Analysis text updated to mention the analysis by disease cohort Also, derivation of BOR and ORR updated for each disease cohort 2.7.4 Supportive analyses: New section added, Concordance analysis is described 2.8 Safety analysis: Updated the analysis text to mention the analysis by disease cohort 2.8.3 Safety analysis: Updated Hy's law definitions 2.10 Other exploratory analysis: Added part for time to event analysis for progression-free survival (PFS) and duration of response (DoR) Clarified naming convention of NF-1 cohort as NF-1 with PN throughout the document Added 2 references at the end: Renamed Final Analysis set to All Treated Patients throughout the document

Abbreviations: BOR, best overall response; BRAF, B-Raf proto-oncogene, serine/threonine kinase; NF-1, neurofibromatosis type-1; ORR, overall response rate; PN, plexiform neurofibromas; SAP, statistical analysis plan; SDS, standard deviation score; SOP, standard operating procedure

The FDA's Assessment

FDA acknowledges the Applicant's position. FDA did not independently confirm these analyses.

Protocol Amendments

The Applicant's Description

The study protocol was amended 9 times. Key amendment features are given in Table 11-29.

Table 11-29. Applicant – Study X2101 Protocol Amendments

Version, Date, Sponsor	Summary of Key Changes
Amendment 1, 05-Mar-2014, GSK	This amendment was made in response to FDA comments, as well as review from various clinical sites. Subjects must have been less than 18 years of age to enroll. Part B Leukemia cohort was removed. Part B cohort B1 was restricted to subjects with relapsed or refractory neuroblastoma and Part B cohort B4 was added to allow subjects with BRAF V600 mutant solid tumors to be treated with trametinib monotherapy. Guidelines and dose modifications for trametinib events of special interest were updated and RANO criteria were added for disease response assessment for CNS tumors.
Amendment 2, 14-Apr-2015, GSK	This amendment was made in response to MHRA comments, as well as review from clinical sites. Eligibility criteria was revised to clarify that subjects with NF-1 associated PNs and subjects with LCH were eligible. At the request of regulatory, the timeframe for pregnancy testing prior to enrollment was shortened from 14 to 7 days in applicable subjects. Exclusion criteria were changed to exclude only optic pathway tumors that were being actively treated. Cardiovascular exclusion criteria were updated to be consistent with requirements in other dabrafenib and trametinib studies; Removal of RPED (retinal pigment epithelium detachment) as an exclusion criterion, based on current safety data that only requires history of RVO (retinal vein occlusion) as an exclusion; Removal of heparin-sensitivity as an exclusion as there are no known drug-drug interactions between heparin and trametinib or dabrafenib. MRIs were required in Part B for PN subjects. Updated to clarify that there were no prohibited medications in Parts A and B.
Amendment 3, 05-Jan-2016, GSK	This amendment was made to expand the description of Part C to include the dabrafenib RP2D levels and rationale along with the observed safety in pediatric subjects on dabrafenib monotherapy. Updated safety information from adult combination studies was included.
Amendment 4, 20-Sep-2016, Novartis	As of 02-Aug-2016, 64 subjects had received study treatment in 5 countries and 10 subjects had completed or discontinued study treatment. Subsequent to the acquisition of GlaxoSmithKline (GSK) compound GSK1120212 and GSK2118436 by Novartis, the purpose of this protocol Amendment 4 was to delete or replace references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and to make administrative changes to align with Novartis processes and procedures.

Version, Date, Sponsor	Summary of Key Changes
Amendment 5, 08-Mar-2017, Novartis	As of 08-Mar-2017, 86 subjects had received study treatment in 5 countries and 21 subjects had discontinued study treatment. The purpose of this amendment was to add 2 new specific BRAF V600 mutant disease cohorts (LGG and LCH) for study combination therapy of dabrafenib and trametinib to obtain preliminary efficacy information in these diseases, as well as additional safety, tolerability, and PK data for the combination. The added cohorts in Part D were part of an agreement with the US FDA. The 2 dose escalation portions of the protocol (Part A and Part C) were extended to allow additional dose exploration of trametinib in subjects under 6 years of age in an effort to obtain target exposure comparable to adults in this age group.
Amendment 6, 17-Sep-2018, Novartis	As of 15-Aug-2018, 128 subjects were enrolled, and enrollment was completed in Cohort C Extension (total 6 subjects) as well as Cohort D1 LGG (total 20 subjects) according to the current protocol. Due to the completion of enrollment in Cohort C Extension, RP2D/MTD had been declared for combination therapy of dabrafenib and trametinib in subjects under 6 years of age. The purpose of this amendment was the addition of a new pediatric formulation dosage form of dabrafenib 10 mg as dispersible tablets and to update the withdrawal of consent language to align with the new Global Data Protection Requirements.
Amendment 7, 04-Apr-2019, Novartis	As of 06-Feb-2019, 133 subjects had received study treatment in 5 countries. Parts A, B, C and D had enrolled 50, 39, 18 and 26 subjects, respectively. The cohorts open to enrollment were: B1 (neuroblastoma), C (BRAF V600 melanoma), and D2 (LCH). All other cohorts had completed enrollment and were closed. 59 subjects had discontinued study treatment. The purpose of this amendment was to add additional interim analyses of data to support health authority requests/publication requests.
Amendment 8, 23-Jan-2020, Novartis	As of 21-Nov-2019, 138 subjects had received study treatment in 5 countries. Parts A, B, C and D had enrolled 50, 41, 18 and 29 subjects, respectively. The cohorts open to enrollment were: C (BRAF V600 melanoma), and D2 (LCH). All other cohorts had completed enrollment and were closed. Seventy-one subjects in Parts A, B, C and D had discontinued study treatment. The main purpose of this amendment was to add dose modification requirements for cases of severe cutaneous adverse reactions (SCARs) which have been reported during treatment with dabrafenib in combination with trametinib outside this clinical study. This change was made in order to align with updated information available in dabrafenib and trametinib Investigator's Brochure Edition 11. The definition of 'Study Completion' had also been amended, reducing the minimum treatment duration from 12 months to 6 months. The primary analysis for safety and efficacy (response rate) was not impacted, but this change allowed for an earlier final analysis of this study. Longer term follow-up of study subjects will be available through the rollover follow-up study (CDRB436G2401). Dabrafenib powder for oral suspension (150 mg stickpack, 10 mg/mL in oral suspension), and trametinib 0.125 mg tablets were removed, as the manufacturing of these formulations was discontinued, and they are no longer in use in Study X2101. Subjects were switched to either the oral liquid formulations (dabrafenib dispersible tablets and trametinib powder for oral solution), or if appropriate, to the solid dose formulations.

Version, Date, Sponsor	Summary of Key Changes
	The contraception requirement post end of treatment, for subjects on dabrafenib monotherapy was updated to 2 weeks, in line with the latest Investigator Brochure.
Amendment 9, 21-Aug-2020, Novartis	As of 17-Jul-2020, 139 subjects had received study treatment in 5 countries. Parts A, B, C and D had enrolled 50, 41, 18 and 30 subjects, respectively. All cohorts had completed enrollment and were closed. Eighty subjects in Parts A, B, C and D had discontinued study treatment and 13 had enrolled into the Study G2401 Rollover and Follow-up study. The purpose of this amendment was to add updated RANO criteria specifically for low-grade glioma (RANO-LGG; Wen et al 2017) as the basis for independent review. These more recent RANO-LGG criteria allowed for the identification of measurable target lesions in subjects with LGG that may not be gadolinium enhancing and are best seen by T2/FLAIR imaging sequences. These updated RANO - LGG criteria were utilized in supplemental independent RANO response determination for those subjects with LGG. Note that the independent response determinations that were originally intended to be applied using the older RANO criteria were retained for analysis purposes. Also note that the response category of 'minor response' was not used in this study. In addition, the contraception information had been updated following results from a trametinib PK study which showed that no loss of efficacy of combined hormonal contraceptives (norethindrone and ethinyl estradiol) was expected when co-administered with trametinib monotherapy.

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine kinase; CNS, central nervous system; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; MTD, maximum tolerated dose; PK, pharmacokinetics; PN, plexiform neurofibromas; RANO, response assessment in neuro-oncology; RP2D, recommended phase II dose; US, United States

The FDA's Assessment

FDA acknowledges the Applicant's position. FDA did not independently confirm these analyses.

11.1.6 Study X2101 - Results

The Applicant's Description

Note: Study X2101 included efficacy data regarding trametinib monotherapy dosing arms (Parts A and B) consisting of subjects with BRAF V600 mutation-positive cancers. Parts C and D of the study assessed combination therapy as part of a limited dose escalation (Part C) or disease expansion cohort (Part D). In particular, the ORR and CBR (CR+PR+SD) for subjects with BRAF V600 mutant LGG treated with dabrafenib + trametinib combination therapy appears substantially better than what would be expected with cytotoxic chemotherapy, which was standard of care before the introduction of BRAF and MEK inhibitors.

As this submission primarily focuses on combination therapy of dabrafenib plus trametinib (received by subjects enrolled in Parts C and D), the results (except for patient disposition) only for Part C and Part D are summarized.

The FDA's Assessment

FDA acknowledges the Applicant's position. FDA did not independently confirm these analyses.

Compliance With Good Clinical Practices

The Applicant's Position

The study was conducted according to ICH E6 Guideline for Good Clinical Practice that have their origin in the Declaration of Helsinki.

The FDA's Assessment

FDA acknowledges the Applicant's position.

Financial Disclosure

The Applicant's Position

As pre-agreed with FDA, Study X2101, is considered covered by the "Financial Disclosure for Clinical Investigators" rule.

The FDA's Assessment

FDA acknowledges the Applicant's position.

Patient Disposition

The Applicant's Description

All subjects completed the study within each respective part. A total of 139 pediatric subjects were enrolled of which 50 subjects (36.0%) were receiving benefit from treatment and subsequently enrolled in a separate roll over study, 1 subject died during post-treatment follow-up, and 88 subjects (63.3%) withdrew or discontinued. The primary reasons for study discontinuation were 'other' reasons (30 subjects, 21.6%) and adverse events (28 subjects, 20.1%). Details per study part are found in Table 11-30.

Table 11-30. Applicant – Study X2101 Subject Disposition (All Treated Population)

Subject Disposition	All Part A Subjects N=50 n (%)	All Part B Subjects N=41 n (%)	All Part C Subjects N=18 n (%)	All Part D Subjects N=30 n (%)
Subjects treated				
Study completion*	50 (100)	41 (100)	18 (100)	30 (100)
Enrolled in a rollover study	13 (26.0)	7 (17.1)	10 (55.6)	8 (26.7)
Died during the post-treatment period	1 (2.0)	0	-	-
Withdrew/discontinued	36 (72.0)	34 (82.9)	8 (44.4)	22 (73.3)
Primary reason for study discontinuation				
Lack of efficacy	3 (6.0)	7 (17.1)	1 (5.6)	1 (3.3)
Adverse event	11 (22.0)	9 (22.0)	4 (22.2)	4 (13.3)
Withdrawal consent	3 (6.0)	2 (4.9)	1 (5.6)	1 (3.3)
Investigator discretion	5 (10.0)	2 (4.9)	1 (5.6)	1 (3.3)
Progressive disease	0	2 (4.9)	-	-
Other	14 (28.0)	12 (29.3)	3 (16.7)	1 (3.3)

Source: Study X2101-Table 14.1-1.1.1, Table 14.1-1.1.2, Table 14.1-1.1.3, Table 14.1-1.1.4

The FDA's Assessment

FDA acknowledges the Applicant's position. FDA did not independently confirm these analyses.

Protocol Violations/Deviations

The Applicant's Description

Note: Only Parts C and D are discussed in detail, as they enrolled patients in the target population for this submission (recurrent, refractory, or unresectable BRAF V600 mutated tumors treated with dabrafenib + trametinib combination therapy).

Part C: At least one protocol deviation was reported in 11 subjects (61.1%). The protocol deviations reported were drug supply method changed due to COVID-19 (5 subjects, 27.8%), failure to re-consent appropriately (5 subjects, 27.8%), visit done outside of study site due to COVID-19 (5 subjects, 27.8%) assessment/procedure changed due to COVID-19 (3 subjects, 16.7%), tumor assessment missed due to COVID-19 (1 subject, 5.6%), exclusion criteria was met but was enrolled in study (1 subject, 5.6%), failure to supply initial consent into the study (1 subject, 5.6%), and visit conducted outside of visit window (1 subject, 5.6%) (Study X2101-Table 14.1-1.2.3, Table 14.1-1.2.7).

Part D: At least one protocol deviation was reported in 15 subjects (50.0%). The protocol deviations reported were assessment/procedure changed due to COVID-19 (7 subjects, 23.3%), failure to re-consent appropriately (6 subjects, 20.0%), drug supply method changed due to COVID-19 (5 subjects, 16.7%), visit done outside of study site due to COVID-19 (4 subjects,

13.3%), incorrect dose administered (2 subjects, 6.7%), and visit conducted outside of visit window (1 subject, 3.3%) (Study X2101-Table 14.1 1.2.4, Table 14.1 1.2.8).

The FDA's Assessment

FDA acknowledges the Applicant's position. FDA did not independently confirm these analyses.

Analysis Sets

The Applicant's Description

Definitions of each of the analysis sets are provided in Section 11.1.3. The number of subjects in each of the analysis sets in Part C and D are provided in the Table 11-31.

Table 11-31. Applicant – Study X2101 Analysis Populations Parts C and D (All Treated Population)

	Part C	Part D		
Populations	**All Part C Subjects N=18 n (%)**	**LGG N=20 n (%)**	**LCH N=10 n (%)**	**All Part D Subjects N=30 n (%)**
All treated population	18 (100)	20 (100)	10 (100)	30 (100)
Safety population	18 (100)	20 (100)	10 (100)	30 (100)
PK population	18 (100)	20 (100)	9 (90.0)	29 (96.7)
DLT evaluable population	18 (100)			
Response-evaluable population by investigator	14 (77.8)	20 (100)	10 (100)	30 (100)
Response-evaluable population by independent reviewer	16 (88.9)	17 (85.0)	0	17 (56.7)

Source: Study X2101-Table 14.1-2.1.3, and Table 14.1-2.1.4
Abbreviations: DLT, dose-limiting toxicity; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; PK, pharmacokinetics

The FDA's Assessment

FDA acknowledges the Applicant's position. FDA did not independently confirm these analyses.

Table of Demographic Characteristics

The Applicant's Description

The demographic characteristics of subjects in parts C and D are presented in Table 11-32.

Table 11-32. Applicant – Study X2101 Demographics and Baseline Characteristics Part C and D (All Treated Population)

	Part C	Part D		
	All Part C Subjects	LGG	LCH	All Part D Subjects
	N=18	N=20	N=10	N=30
Characteristics	n (%)	n (%)	n (%)	n (%)
Age (years)				
Mean (SD)	8.3 (5.57)	10.5 (3.79)	5.6 (3.63)	8.8 (4.35)
Median (min-max)	8.0 (1.4-17)	10.5 (2-16)	4.0 (2-13)	9.0 (2-16)
Age category, n (%)				
<2 years	1 (5.6)	0	0	0
2 - < 6 years	7 (38.9)	2 (10.0)	6 (60.0)	8 (26.7)
6 - <12 years	3 (16.7)	9 (45.0)	3 (30.0)	12 (40.0)
≥12 years	7 (38.9)	9 (45.0)	1 (10.0)	10 (33.3)
Sex, n (%)				
Female	10 (55.6)	10 (50.0)	2 (20.0)	12 (40.0)
Male	8 (44.4)	10 (50.0)	8 (80.0)	18 (60.0)
Weight (kg)				
Mean (SD)	38.19 (26.258)	50.54 (25.628)	20.64 (8.049)	40.57 (25.610)
Median (min-max)	30.70 (12.8-101.5)	50.15 (15.3-116.6)	19.60 (11.5-36.2)	33.05 (11.5-116.6)
Karnofsky and Lansky performance status n (%)				
100	9 (50.0)	13 (65.0)	7 (70.0)	20 (66.7)
90	6 (33.3)	6 (30.0)	1 (10.0)	7 (23.3)
80	3 (16.7)	0	1 (10.0)	1 (3.3)
70	0	1 (5.0)	0	1 (3.3)
<70	0	0	1 (10.0)	1 (3.3)

Source: Study X2101-Table 14.1-3.1.3, Table 14.1-3.1.4
Abbreviations: LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; SD, standard deviation

The FDA's Assessment

FDA acknowledges the Applicant's position. FDA did not independently confirm these analyses.

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

The Applicant's Description

Disease Characteristics - Part C

The majority of subjects (14 subjects, 77.8%) had LGG. There were 2 HGG (anaplastic pleomorphic xanthoastrocytoma, anaplastic ganglioglioma), 1 LCH and a juvenile xanthogranulomatosis tumor. The median time since initial diagnosis was 39.1 months (range: 3.4 to 112.6 months) (Table 11-33).

Table 11-33. Applicant – Study X2101 Disease Characteristics, Disease Burden at Baseline - Part C (All Treated Population)

Disease Burden or Characteristics at Baseline	All Part C Subjects N=18
Primary tumor type n (%)	
Bone	1 (5.6)
Brain*	15 (83.3)
CNS*	1 (5.6)
Langerhans cell histiocytosis (LCH)	1 (5.6)
Time since initial diagnosis of primary tumor type (days)	
n	18
Mean	1183.5 (974.83)
Median (Minimum - Maximum)	1189.0 (104 - 3425)
Time since last progression to start of study treatment (days)	
n	14
Mean (SD)	219.6 (530.83)
Median (Minimum - Maximum)	45.5 (7 - 2006)
Metastatic disease at Screening	
Yes	1 (5.6)
No	17 (94.4)
Type of lesion at baseline based on investigator assessment per RECIST-n (%)	
Non-target only	1 (5.6)
Both target and non-target	1 (5.6)
Not applicable	16 (88.9)
Type of lesion at baseline based on independent reviewer assessment per RECIST-n (%)	
Non-target only	1 (5.6)
Both target and non-target	1 (5.6)
Not applicable	16 (88.9)
Type of lesion at baseline based on investigator assessment per RANO-n (%)	
Measurable only	9 (50.0)
Non-measurable only	4 (22.2)
Both measurable and non-measurable	3 (16.7)
Not applicable	2 (11.1)
Type of lesion at baseline based on independent reviewer assessment per RANO 2010-n (%)	
Measurable only	4 (22.2)
Non-measurable only	7 (38.9)
Both measurable and non-measurable	2 (11.1)
Unknown	3 (16.7)
Not applicable	2 (11.1)
Type of lesion at baseline based on independent reviewer assessment per RANO 2017-n (%)	
Measurable only	16 (88.9)
Not applicable	2 (11.1)

Source: Study X2101-Table 14.1-4.1.3
* There was no intended distinction in the collected data field for primary tumor type between Brain and CNS.
Abbreviations: RANO, response assessment in neuro-oncology

Disease Characteristics - Part D

The disease characteristics were as expected for the enrolled disease cohorts. The primary tumor type was LGG (20 subjects, 66.7%) which included 11 subjects with pilocytic astrocytomas and 5 subjects with gangliogliomas. Ten subjects had LCH (10 subjects, 33.3%). The median time since initial diagnosis was 33.9 months (range: 5.8 to 137.0 months) (Table 11-34).

Table 11-34. Applicant – Study X2101 Disease Characteristics, Disease Burden at Baseline - Part D (All Treated Population)

Disease Characteristics or Burden at Baseline	LGG N=20 n (%)	LCH N=10 n (%)	All Subjects N=30 n (%)
Primary tumor type n (%)			
Brain*	19 (95.0)	0	19 (63.3)
CNS*	1 (5.0)	0	1 (3.3)
Langerhans Cell Histiocytosis (LCH)	0	10 (100)	10 (33.3)
Time since initial diagnosis of primary tumor type (days)			
n	20	10	30
Mean	1554.9	1439.8	1516.5
SD	998.75	1314.52	1092.18
Median	1020.0	1032.0	1032.0
Minimum	657	176	176
Maximum	3767	4166	4166
Time since last progression to start of study treatment (days)			
n	13	5	18
Mean	64.7	64.8	64.7
SD	46.81	37.69	43.37
Median	50.0	61.0	51.0
Minimum	8	13	8
Maximum	176	112	176
Metastatic disease at Screening			
Yes	1 (5.0)	0	1 (3.3)
No	19 (95.0)	10 (100)	29 (96.7)
Type of lesion at baseline based on investigator assessment per RECIST-n (%)			
Target only	0	1 (10.0)	1 (3.3)
Non-target only	0	6 (60.0)	6 (20.0)
Both target and Non-target	0	2 (20.0)	2 (6.7)
Unknown	0	1 (10.0)	1 (3.3)
Not applicable	20 (100)	0	20 (66.7)
Type of lesion at baseline based on independent reviewer assessment per RECIST-n (%)			
Non-target only	0	6 (60.0)	6 (20.0)
Both target and Non-target	0	1 (10.0)	1 (3.3)
Unknown	0	3 (30.0)	3 (10.0)
Not applicable	20 (100)	0	20 (66.7)

Disease Characteristics or Burden at Baseline	LGG N=20 n (%)	LCH N=10 n (%)	All Subjects N=30 n (%)
Type of lesion at baseline based on investigator assessment per RANO-n (%)			
Measurable only	15 (75.0)	0	15 (50.0)
Both measurable and Non-measurable	5 (25.0)	0	5 (16.7)
Not applicable	0	10 (100)	10 (33.3)
Type of lesion at baseline based on independent reviewer assessment per RANO 2010-n (%)			
Measurable only	2 (10.0)	0	2 (6.7)
Non-measurable only	12 (60.0)	0	12 (40.0)
Both measurable and non-measurable	4 (20.0)	0	4 (13.3)
Unknown	2 (10.0)	0	2 (6.7)
Not applicable	0	10 (100)	10 (33.3)
Type of lesion at baseline based on independent reviewer assessment per RANO 2017-n (%)			
Measurable only	16 (80.0)	0	16 (53.3)
Non-measurable only	3 (15.0)	0	3 (10.0)
Both measurable and non-measurable	1 (5.0)	0	1 (3.3)
Not applicable	0	10 (100)	10 (33.3)

Source: Study X2101-Table 14.1-4.1.4
* There was no intended distinction in the collected data field for primary tumor type between Brain and CNS.
Abbreviations: LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; RANO, response assessment in neuro-oncology; SD, standard deviation

The FDA's Assessment

FDA acknowledges the Applicant's position. FDA did not independently confirm these analyses.

Prior Antineoplastic Medication

The Applicant's Description

In Part C, 14 subjects (77.8%) had prior anti-cancer therapy, 1 subject (5.6%) had prior anti-cancer radiotherapy and 14 subjects (77.8%) had prior cancer related surgical procedures. In Part D. 29 subjects (96.7%) had prior chemotherapy, no subjects had prior anti-cancer radiotherapy and 21 subjects (70.0%) had prior cancer related surgical procedures.

The FDA's Assessment

FDA acknowledges the Applicant's position. FDA did not independently confirm these analyses.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Description

Treatment compliance: Information on treatment compliance was collected, but no results were presented in the CSR.

Concomitant medications: In Part C, 15 subjects (83.3%) were taking a medication prior to start of study drug and 17 subjects (94.4%) started a concomitant medication after the start of study drug. In Part D, all 30 subjects (100.0%) were taking a medication prior to start of study. All 30 subjects (100.0%) started a concomitant medication after the start of study drug.

Rescue medication: Not applicable, as study protocol did not define any rescue medication.

The FDA's Assessment

FDA acknowledges the Applicant's position. FDA did not independently confirm these analyses.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Description

The primary objective was to determine MTD/RP2D based on DLT and target exposure. The RP2Ds for trametinib were determined as 0.032 mg/kg/day for ages < 6 years and 0.025 mg/kg/day for ages ≥ 6 years (capped at the adult daily dose of 2 mg). The RP2Ds were established through observations of DLTs and similar exposures achieved at these dose levels in pediatric subjects compared to those achieved in adults successfully treated at the approved daily dose of 2 mg. The RP2Ds for dabrafenib when given in combination with trametinib were confirmed as dabrafenib 2.63 mg/kg BID for ages< 12 years and dabrafenib 2.25mg/kg BID for ages ≥12 years.

The FDA's Assessment

FDA acknowledges the Applicant's position. FDA did not independently confirm these analyses.

Secondary Efficacy Results

The Applicant's Description

Best Overall Response by Study Design Part

In Part C, 2 subjects (11.1%) achieved CR and 7 subjects (38.9%) achieved PR. The ORR based on investigator assessment is 50.0% (95% CI: 26.0, 74.0). The CBR based on investigator assessment was 88.9% (95% CI: 65.3, 98.6). In Part D, 5 subjects (16.7%) achieved CR and 12 subjects (40.0%)

achieved PR in the RP2D. The ORR based on investigator assessment is 56.7% (95% CI: 37.4, 74.5). The CBR based on investigator assessment was 93.3% (95% CI: 77.9, 99.2) (Table 11-35).

Table 11-35. Applicant – Study X2101 Investigator Assessed BOR Parts C and D (All Treated Population)

	Part C				Part D		
	TMT 0.025 mg/kg/day + 50% DRB RP2D N=3 n (%)	TMT 0.025 mg/kg/day + 100% DRB RP2D N=9 n (%)	TMT 0.032 mg/kg/day + 100% DRB RP2D N=6 n (%)	All Part C Subjects N=18 n (%)	LGG N=20 n (%)	LCH N=10 n (%)	All Part D Subjects N=30 n (%)
Best overall response							
Complete response (CR)	0	0	2 (33.3)	2 (11.1)	2 (10.0)	3 (30.0)	5 (16.7)
Partial response (PR)	2 (66.7)	3 (33.3)	2 (33.3)	7 (38.9)	9 (45.0)	3 (30.0)	12 (40.0)
Stable disease (SD)	1 (33.3)	5 (55.6)	1 (16.7)	7 (38.9)	8 (40.0)	3 (30.0)	11 (36.7)
Progressive disease (PD)	0	1 (11.1)	0	1 (5.6)	0	0	0
Non-CR/Non-PD (NN)	0	0	0	0	0	0	0
Unknown	0	0	0	0	1 (5.0)	0	1 (3.3)
Missing	0	0	1 (16.7)	1 (5.6)	0	1 (10.0)	1 (3.3)
ORR (CR+PR)	2 (66.7)	3 (33.3)	4 (66.7)	9 (50.0)	11 (55.0)	6 (60.0)	17 (56.7)
ORR 95% CI	(9.4, 99.2)	(7.5, 70.1)	(22.3, 95.7)	(26.0, 74.0)	(31.5, 76.9)	(26.2, 87.8)	(37.4, 74.5)
Clinical benefit rate (CBR: CR+PR+SD)	3 (100)	8 (88.9)	5 (83.3)	16 (88.9)	19 (95.0)	9 (90.0)	28 (93.3)
CBR 95% CI	(29.2, 100)	(51.8, 99.7)	(35.9, 99.6)	(65.3, 98.6)	(75.1, 99.9)	(55.5, 99.7)	(77.9, 99.2)

Source: Study X2101-Table 14.2-1.1.1c, Table 14.2-1.1.1d

ORR is calculated as the number of subjects deemed to have treatment response relative to the total number of subjects treated in that cohort which is complete response + partial response.

The 95% CI for the frequency distribution of each variable was computed using two-sided exact binomial 95% CIs.

Abbreviations: BOR, best overall response; CI, confidence interval; DRB, dabrafenib; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; ORR, overall response rate; RP2D, recommended phase II dose; TMT, trametinib

Best Overall Response as Assessed by Investigator and Independent Reviewer

Higher ORR and prolonged median PFS was observed by both the Investigator and Independent Reviewer in BRAF V600 mutated LGG when treatment dabrafenib + trametinib combination therapy was used instead of trametinib monotherapy (Table 11-36). There were no subjects with BRAF V600 mutation-positive LCH treated with trametinib monotherapy.

The concordance between the investigator and independent review for best response by RANO criteria was at least 58% in the LGG cohorts, with higher concordance observed when using the RANO 2017 criteria. Independent evaluation was not conducted in the LCH cohort.

OS was not a pre-specified endpoint of the study but there were no deaths during the study.

Table 11-36. Applicant – Study X2101 Secondary Efficacy Endpoints and Supportive Analyses

	LGG BRAF V600 Mutation		LCH BRAF V600 Mutation
Parameter	**Trametinib N=13**	**Dabrafenib+Trametinib N=36**	**Dabrafenib+Trametinib N=12**
ORR by investigator - % (95% CI)	38.5% (13.9, 68.4)	52.8% (35.5, 69.6)	58.3% (27.7, 84.8)
ORR by independent reviewer – % (95% CI)			Response assessment for subjects with LCH was conducted by investigators without attempting independent confirmation. LCH disease assessment and response to therapy is very dependent upon investigator evaluation.
RANO 2010 criteria	15.4% (1.9, 45.4)	19.4% (8.2, 36.0)[1]	
RANO 2017 criteria	15.4% (1.9, 45.4)	25.0% (12.1, 42.2)[1]	
Median PFS by investigator - months (95% CI)	26.9 (3.2, NR)	NR	There were no progression events for these subjects while on study
Median PFS by independent reviewer - months (95% CI)			
RANO 2010 criteria	13.8 (1.8, NR)	NR	
RANO 2017 criteria	16.4 (3.2, NR)	36.9 (36.0, NR)	

Source: Study X2101-Tables 14.2-1.1.3, 14.2-1.1.4, 14.2-1.1.5, 14.2-1.1.8, 14.2-1.1.9, 14.2-4.1.2, 14.2-4.1.3, 14.2-4.1.4, 14.2-4.1.7, 14.2-4.1.8 and Figure 14.2-3.4

[1] There were a small number of responders in the combination arm based on independent or investigator review and consequently the 95% CIs for ORR were wide and overlapped between investigator and independent radiology review. This would indicate that the point estimates for ORR may be highly sensitive to any changes in the underlying data. Of note, the clinical benefit rate was similar when assessed by investigator or independent review (94.4% vs 88.9%, respectively).

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine kinase; CI, confidence interval; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; NR, not reached; ORR, overall response rate; PFS, progression-free survival; RANO, response assessment in neuro-oncology

The FDA's Assessment

FDA acknowledges the Applicant's position. FDA did not independently confirm these analyses. See Section 11.1.8 for a discussion of the study results and their support for the determination of the contribution of each component to the combination treatment regimen.

Data Quality and Integrity

The Applicant's Description

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets. No investigator site audits were conducted for this study. There were no known health authority inspections conducted at investigator sites participating in this study. The COVID-19 pandemic had minimal impact on the interpretation of the results of this study.

The FDA's Assessment

FDA agrees with the Applicant's description.

11.1.7 Integrated Review of Effectiveness

The FDA's Assessment

The demonstration of the effectiveness of dabrafenib and trametinib in combination for pediatric patients with LGG with BRAF V600E mutation was based on the results of the LGG cohort o Study G2201. The primary analysis of ORR per independent review demonstrated a statistically significant improvement in patients treated with dabrafenib and trametinib (47% [95% CI: 35, 59]) compared to those treated with carboplatin and vincristine (11% [95% CI: 3.0, 25], p <0.001).

The ORR benefit was consistent across clinically relevant subgroups and supported by the results of analyses of secondary endpoints of PFS, DOR, and ORR per investigator assessment. PFS per independent review was tested hierarchically following ORR. The median PFS was 20.1 months (95% CI: 12.8, NE) in the dabrafenib plus trametinib arm compared to 7.4 months (95% CI: 3.6, 11.8) in the carboplatin plus vincristine arm, with a HR of 0.31 ([95% CI: 0.18, 0.55], p <0.001). The Kaplan-Meier curves for PFS showed a clear separation between arms starting from approximately 2 months. The median DOR per independent review was 20.3 months (95% CI: 12.0, NE) for the 34 responders in the dabrafenib plus trametinib arm whereas the median was not estimable for the 4 responders in the carboplatin plus vincristine arm. The ORR benefit was also confirmed by the analysis of ORR per investigator assessment with an improvement with dabrafenib plus trametinib (55% [95% CI: 43, 67]) compared to carboplatin plus vincristine (14% [95% CI: 4.5, 29]).

With an additional 7.4 months of follow-up, the ORR benefit was sustained with a longer median DOR in the dabrafenib plus trametinib arm (23.7 months [95% CI: 14.5, NE]) compared to the primary analysis. The median PFS in the dabrafenib plus trametinib arm increased to 23.8 months (95% CI: 12.9, NE).

Overall, these results provide adequate evidence of effectiveness of dabrafenib in combination with trametinib for the treatment of pediatric patients 1 year of age and older with BRAF V600E mutated LGG who require systemic therapy.

11.1.8 Assessment of Efficacy Across Trials

Primary Endpoints

The Applicant's Position

The efficacy results across the studies G2201, X2101 and A2102 show that the D+T combination therapy demonstrates improved efficacy as compared to dabrafenib or trametinib monotherapy in both LGG and HGG pediatric patients with BRAF V600 mutation-positive gliomas.

The information on the primary endpoints is presented under each study mentioned in the section above.

The FDA's Assessment

FDA agrees with the Applicant's position. Overall, the results observed in G2201 support the improved efficacy of dabrafenib and trametinib over treatment with either dabrafenib or trametinib as a single agent in this patient population. There appears to be an improved ORR with combination therapy compared to treatment with trametinib as a single agent, as shown in the table below. Although the ORR observed in patients treated with dabrafenib as a single agent in A2102 is similar to that observed in patients treated with the combination in G2201 (42% vs. 47% with overlapping 95% confidence intervals), the improved durability of responses observed with the combination compared with dabrafenib as a single agent is supportive of the need for combination BRAF and MEK inhibition to maintain tumor response.

Table 11-37. FDA Analysis of ORR From Trials A2102, X2101, and G2201

Treatment for Pediatric Patients With BRAFV600E Mutant LGG	ORR (CR+PR) 95% CI
Dabrafenib monotherapy A2102, N=24 (RP2D)	42% (22, 63)
Trametinib monotherapy X2101, N=13	15% (1.9, 45)
Combination D+T therapy G2201, N=73	47% (35, 59)

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine kinase; CI, confidence interval; CR, complete response; D+T, dabrafenib plus trametinib; LGG, low-grade glioma; ORR, overall response rate; PR, partial response; RP2D, recommended phase II dose

Secondary and Other Endpoints

The Applicant's Position

The information on the secondary and exploratory endpoints is presented under each study mentioned in the section above.

The FDA's Assessment

Refer to FDA's discussion of secondary endpoints in specific trials in Sections 8.1.1 – 8.1.6. We note that DOR appears improved with combination therapy compared to treatment with dabrafenib alone, as described in the table below. In Study A2102, the median DOR assessed by independent review per RANO 2017 was 12.8 months (95% C:I 3.8,NE) and the median follow-up duration was NE (95% CI: 6.6, NE) whereas the median follow-up duration for D+T therapy in G2201 (18.4 months [95% CI: 13.1, 25.7]). The nearly one-year improvement in DOR with combination therapy compared with dabrafenib as a single agent is supportive of the need for dual BRAF and MEK inhibition.

Table 11-38. FDA Comparison of DOR From Trials A2102, X2101, and G2201

Treatment for Pediatric Patients With BRAFV600E Mutant LGG	Median DOR (Months) (95% CI)
Dabrafenib monotherapy A2102, N=24 (RP2D)	12.8 (3.8, NE)
Trametinib monotherapy X2101, N=13	NR (NE, NE)
Combination D+T therapy G2201, N=73 (Updated)	23.7 (14.5, NE)

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine kinase; CI, confidence interval; D+T, dabrafenib plus trametinib; DOR, duration of response; LGG, low-grade glioma; NE, not estimable; NR, not reached; RP2D, recommended phase II dose

Subpopulations

The Applicant's Position

The ORR across all three studies was also analyzed in subgroups based on age categories (<2 years; 2 to <6 years; 6 to <12 years; and 12 years over). Furthermore, efficacy was generally consistent across subgroups for age and no meaningful differences in efficacy outcomes by age subgroups were observed.

The FDA's Assessment

FDA acknowledges the Applicant's position. However, the ORR data by subgroup for Study A2102, Study X2101, and HGG cohort from Study G2201 were not independently verified by FDA.

Additional subgroup analyses for LGG cohort from Study G2201 are summarized in Table 11-39 below. The results demonstrated a consistent improvement in ORR per independent review across subgroups. Given the small sample size in some subgroups, the confidence intervals for these ORRs were wide. No formal statistical testing was performed for subgroup analyses and the results from this descriptive analysis should be interpreted with caution.

Table 11-39. FDA - Independent Reviewer Assessed ORR by Subgroup (FAS-L), Study G2201

	D+T		C+V	
Subgroup	**(CR+PR)/N**	**ORR% (95% CI)**	**(CR+PR)/N**	**ORR% (95% CI)**
Overall	34/73	47 (35, 59)	4/37	11 (3.0, 25)
Age group				
12 months - <6 years	11/20	55 (32, 77)	2/14	14 (1.8, 43)
6 - <12 years	12/25	48 (28, 69)	1/11	9 (0.2, 41)
12 - <18 years	11/28	39 (22, 59)	1/12	8 (0.2, 38)
Gender				
Female	21/44	48 (32, 63)	2/22	9 (1.1, 29)
Male	13/29	45 (26, 64)	2/15	13 (1.7, 40)
Race				
White	27/55	49 (35, 63)	3/25	12 (2.5, 31)
Non-White	7/18	39 (17, 64)	1/12	8 (0.2, 38)
Radiographic progression as indication to treatment				
Yes	18/44	41 (26, 57)	3/15	20 (4.3, 48)
No	16/29	55 (36, 74)	1/22	4.5 (0.1, 23)

Source: FDA reviewer - generated based on Applicant submitted data
Data cutoff date: August 23, 2021
Abbreviations: C+V, carboplatin plus vincristine; CI, confidence interval; CR, complete response; D+T, dabrafenib plus trametinib; FAS-L, full analysis set LGG cohort; LGG, low-grade glioma; ORR, overall response rate; PR, partial response

Additional Efficacy Considerations

The FDA's Assessment

See Section 11.1.9.

11.1.9 Integrated Assessment of Effectiveness

The Applicant's Position

Combination therapy with D+T directed at a well-defined driver mutation provides meaningful clinical benefit that is superior to standard of care chemotherapy in pediatric patients with BRAF V600 mutation-positive LGG. Similarly, meaningful clinical benefit is demonstrated in pediatric patients with BRAF V600 mutation-positive relapsed or refractory HGG.

In patients with BRAF V600 mutant LGG, treatment D+T demonstrated robust efficacy with respect to ORR compared to treatment with C+V (p<0.001), with an odds ratio of 7.19. The PFS

analysis also demonstrated a statistically significant and clinically meaningful risk reduction of 69% with D+T treatment over the C+V treatment (HR: 0.31; p<0.001). In patients who responded, the median TTR was 3.6 months. The observed response was durable and sustained for more than a median of 20 months. The combination (D+T) therapy as first line of treatment demonstrated significant and durable efficacy that was superior to standard chemotherapy (C+V) in BRAF V600 mutation-positive LGG patients. Treatment response was also demonstrated in the cross-over patients who had progressed on C+V. The patient reported outcomes showed improvement in the health-related quality of life of patients.

Efforts were made to mitigate the risk of inadequate treatment for patients assigned to the control arm in this open label study, including the potential for premature discontinuation of that treatment. The dose intensity and the efficacy of the control arm treatment in this study was consistent with published results from other studies of this control therapy.

In the patients with HGG, treatment with D+T demonstrated robust efficacy with respect to ORR and PFS with ORR exceeding the protocol-specified threshold of 20%. The treatment response was achieved rapidly in patients who responded (median TTR: 1.9 months) and was sustained for median of more than 20 months. The combination (D+T) therapy as second line of treatment demonstrated significant and durable efficacy that was higher than the historical control in the molecularly unselected HGG patients. Also, the combination therapy with D+T demonstrated better efficacy compared to the dabrafenib monotherapy when trametinib is added to dabrafenib in HGG patients. Remarkably, the observed ORR for patients with BRAF V600 mutant relapsed refractory HGG is similar to that for patients undergoing first systemic therapy for their BRAF V600 mutant LGG with D+T treatment.

Furthermore, efficacy was generally consistent across subgroups for age and no meaningful differences in efficacy outcomes by age subgroups were observed.

The supportive studies demonstrated consistent efficacy (ORR) achieved with either D+T (Study X2101) or monotherapies (Study X2101 and Study A2102) in glioma patients. The addition of dabrafenib to trametinib resulted in longer PFS in patients receiving second line therapy.

(b) (4)

Taken together, the available efficacy data provides comprehensive and robust evidence in support of the proposed indication.

The FDA's Assessment

In general, FDA agrees with the Applicant's integrated assessment of effectiveness.

The data provided in this submission, primarily the LGG cohort from Study G2201, supports the clinical benefit of treatment with dabrafenib and trametinib compared to standard of care

chemotherapy in pediatric patients 1 year and older with BRAF V600E mutated LGG who require systemic therapy. The observed ORR benefit was consistent across subgroups and supported by the results of analyses of PFS and DOR based on both independent review and investigator assessment. The OS data was immature as of the updated data cutoff, and did not permit definitive conclusions, which is expected given the follow-up time for the applications and the known survival outcomes in pediatric patients with LGG. Given the patient population and natural history of pLGG, a post-marketing commitment will be included in the approval letter to provide the results of final analyses of PFS and OS when all patients have been followed for two years.

Evaluation of the contribution of each component to the treatment effect of the combination regimen used comparison to prior trials of dabrafenib and trametinib as single agents in patients with glioma. Although the size of the trials is small and there are limitations to comparisons made across trials, the results suggest an improved ORR (compared to trametinib alone) and DOR (compared to treatment with dabrafenib alone) with the combination of dabrafenib and trametinib. Further, the body of scientific evidence across other tumor types supports the use of the combination over either product as a single agent in patients with BRAF V600E-driven tumors. FDA determined that a randomized trial comparing each component head-to-head was not warranted based on the evidence described above in patients with glioma and in other tumor types, and considers the contribution of dabrafenib and trametinib to the treatment effect observed in G2201 to be adequately established.

11.2 Review of Safety

The Applicant's Position

A comprehensive assessment of safety data relevant to the use of D+T for the treatment of BRAF V600E mutation-positive glioma in pediatric patients 1 year of age and older is provided in the subsequent sections below (Section 11.2.4).

Overall, the safety findings in the pediatric patients treated with D+T were consistent with the known safety profile of D+T in adult patients with advanced BRAF V600 mutation-positive solid tumors. The most frequently reported adverse event(s) (AE)s (incidence of ≥ 20%) by PT in the combination therapy pool were: pyrexia (64.9%), headache (39.2%), vomiting (38.0%), dry skin (32.2%), diarrhea (29.8%), fatigue (28.7%), nausea (25.1%), rash (23.4%), and cough (20.5%). The overall assessment of AEs and growth and development data revealed weight gain as a new adverse drug reaction (ADR) for pediatric population. No other new safety signals were identified from the analysis of the safety data.

The FDA's Assessment

Refer to Section 11.2.11 and 12.2 for FDA's conclusions regarding the safety review.

11.2.1 Safety Review Approach

The Applicant's Position

This overall pediatric safety evaluation for D+T is primarily based on pooled safety data from the pivotal Study G2201 and the combination therapy arm of Study X2101. In total, 171 pediatric patients aged 1 to 17 years with advanced tumors including LGG and HGG were included in this analysis. The safety evaluation is supplemented by a comparison of the safety profiles of targeted therapy with D+T (73 patients) and C+V chemotherapy (33 patients) in the G2201 LGG cohort, by a review of dabrafenib and trametinib monotherapy safety findings in studies A2102 (n=85) and X2101 (n=91), and by the well-established safety profile of D+T combination therapy in adults for other indications from both the clinical development (since 2009) experience and the post-marketing setting (since 2013) (refer to Section 10.1 for details of the clinical studies provided). Data from these studies allow for an informed assessment of the safety profile of D+T and an evaluation of the overall benefit-risk in pediatric patients. The safety data for pediatric patients with relapsed or refractory BRAF V600 mutant HGG comes from a single arm cohort (N=41). This number represents a relatively large population considering the low rate of BRAF V600 mutation in this already rare tumor type, and provides adequate safety data for an effective benefit-risk assessment in this population. The safety data for pediatric patients with relapsed or refractory BRAF V600 mutant HGG comes from a single arm cohort (N=41).

Overall, this approach is considered appropriate for the detection and characterization of common AEs and to provide guidance on adverse event management for pediatric patients with BRAF V600E mutation-positive glioma.

The FDA's Assessment

FDA generally agrees with the Applicant's description of the primary and supportive safety data sets included in the NDA. FDA's safety review approach was based on the LGG cohort of Study G2201 as the primary safety population, including 73 patients who received dabrafenib and trametinib compared to 33 patients who received carboplatin and vincristine. FDA's analysis of the pooled safety population included 166 patients who received the recommended phase 2 doses (RP2D) of dabrafenib and trametinib whereas the Applicant's pooled safety population included patients who received any dose of dabrafenib and trametinib. The pooled population included patients who received dabrafenib and trametinib in the LGG cohort (n=73), those who were initially randomized to carboplatin and vincristine in the LGG cohort and crossed over to receive dabrafenib and trametinib (n=9), patients in the HGG cohort of G2201 (n=41) and patients in Study X2101 (n=43) who received dabrafenib and trametinib at the respective RP2Ds.

11.2.2 Review of the Safety Database

Overall Exposure

The Applicant's Position

The duration of exposure for all four clinical studies is presented in Table 11-40.

Table 11-40. Applicant - Duration of Exposure to Dabrafenib and Trametinib Across Studies (All Treated Patients)

Studies	Dabrafenib Median (Range) Weeks	Trametinib Median (Range) Weeks
Combination therapy pool (N=171)	76.9 (1.3 to 228.1)	75.7 (1.3 to 228.1)
Study G2201		
LGG (n=73)	75.7 (2.7 to 149.7)	75.7 (2.7 to 149.7)
LGG crossover patients (n=9)	59.9 (18.4 to 132.7)	59.9 (19.0 to 132.7)
HGG (n=41)	72.7 (1.3 to 172.1)	72.7 (1.3 to 172.1)
Study A2102		
Part 1 (n=27)	90.3 (5.6 to 356.0)	-
Part 2 (n=58)	85.9 (0.3 to 296.0)	-
Study X2101*		
Part A (n=50)	-	106.0 (2.6 to 276.4)
Part B (n=41)	-	82.9 (1.4 to 240.0)
Part C (n=18)	90.5 (8.1 to 228.1)	90.5 (8.0 to 228.1)
Part D (n=30)	108.2 (9.1 to 168.3)	105.9 (9.1 to 168.3)

Source: SCS Appendix 1-Table 2.1-1, SCS Appendix 1-Table 2.2-1, Study G2201-Section 10.1.6.1 and Section 10.2.6.1, Study A2102-Section 10.6.1, Study X2101-Section 10.6.1, Study G2201-Table 14.4-3.1L
* The exposure for Study X2101 was displayed in days in the CSR and was converted to weeks (days/7) for this table.

Exposure to dabrafenib and trametinib was considered appropriate to allow for an adequate assessment of safety in patients who are representative of the intended target population.

The FDA's Assessment

FDA agrees that exposures to dabrafenib and trametinib in the pooled safety population allowed for an adequate assessment of safety. Based on the combination therapy pool of n=166, the median duration of exposure in the combination therapy pool for dabrafenib was 17.4 months (range 0.3 to 50 months) while the median duration of exposure for trametinib was 17.2 months (range 0.3 to 39.6 months).

Relevant Characteristics of the Safety Population

The Applicant's Position

The key safety population consists of 171 pediatric patients (1 to < 18 years) treated with D+T. The safety data from patients treated with D+T in Study G2201 (n=123; LGG: 73, LGG crossover: 9, and HGG: 41) were pooled with data from Study X2101 D+T arm (n=48; LGG: 36 and LCH: 12) in view of the similar age distribution and the fact that the safety profile of D+T has been shown to be consistent across multiple tumor types. This population included 4 children aged < 2 years, 40 children aged 2 to < 6 years, 55 children aged 6 to < 12 years, and 72 adolescents aged 12 to < 18 years. Median ages across the individual disease cohorts ranged from 8 to 13 years, and majority of patients (>85%) had Karnofsky and Lansky performance status of ≥ 80 at enrolment.

Additionally, data from Studies X2101 and A2102 in pediatric patients treated with trametinib monotherapy and dabrafenib monotherapy, respectively, provide information on the safety of these monotherapies in pediatric patients.

Table 11-41. Applicant - Safety Databases for Combination Therapy Pool and Supportive Monotherapy

Population	Studies
Combination therapy pool	All patients treated with D+T combination therapy in studies G2201 and X2101
Dabrafenib monotherapy	A2102
Trametinib monotherapy	X2101 (monotherapy patients only)

Abbreviations: D+T, dabrafenib plus trametinib

The FDA's Assessment

FDA agrees with the description of the relevant characteristics of the safety populations. FDA's pooled safety population (n=166) included four children aged < 2 years, 37 children aged 2 to < 6 years, 53 children aged 6 to < 12 years, and 72 adolescents aged 12 to < 18 years.

In addition, FDA did not confirm analyses for Study A2102 as this study provided supportive information on the safety of dabrafenib as a single agent. Patients enrolled in this study were not included in the pooled safety population.

Adequacy of the Safety Database

The Applicant's Position

The safety discussions and conclusions in this submission are mainly based on the D+T pediatric safety pool with data from the pivotal Study G2201 and the combination therapy parts of Study X2101. In this overview, the key safety conclusions are derived from the pooled data from 171 pediatric patients treated with the proposed dosing regimen of D+T ("combination therapy

pool") across these 2 studies, regardless of the patient's tumor. The safety findings are further supported with data from pediatric patients treated with monotherapies in supportive studies.

Results are placed in context of the well-characterized and established safety profile of D+T combination therapy in the currently approved adult solid tumor indications.

These safety data in pediatric patients (1 to < 18 years) treated with D+T are considered adequate for the proposed sNDA.

The FDA's Assessment

FDA agrees with the Applicant's assessment of the adequacy of the safety database to support review of the NDAs.

11.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported in any of the clinical study reports.

The FDA's Assessment

FDA agrees that the application, including safety datasets and individual case narratives, was adequate to support the safety analysis and that there were no data integrity concerns.

Categorization of Adverse Event

The Applicant's Position

Safety was evaluated in patients who received at least one dose of study treatment and summarized according to the treatment received.

The evaluation included on-treatment recording of AEs and SAEs (including severity and relationship to study drugs, graded according to NCI-CTCAE v4.03), AESIs, dose modifications and treatment discontinuations due to AEs, vital signs, ECGs, echocardiograms, performance status by Karnofsky/Lansky and clinical laboratory evaluations. In addition, data for dermatological and ophthalmological evaluations, seizure events, sexual maturation, growth and development, bone age, and palatability were collected.

Safety analyses were also performed for AEs by age subgroups in the combination therapy pool: < 2 years, 2 years to < 6 years, 6 years to < 12 years, and 12 years to < 18 years. No safety analysis by formulation received was performed. All studies used both currently approved solid and proposed liquid formulations. Administration of the type of formulation depended upon the ability to swallow solid dose forms as well as the necessity to achieve the intended mg/kg dose, with liquid formulations administered to those under six years of age and some additional lower weight patients. The type of formulation was occasionally changed during the course of the study, hence a safety analysis by formulation was avoided to reduce the ambiguity of AEs association to formulation type. Therefore, safety data in < 6 years age subgroup can be considered as a surrogate for safety profile of the liquid formulations.

AEs were coded to the PT level by different MedDRA versions and assessment of the intensity of AEs had different CTCAE grading for different studies as the studies were performed at various times (Table 11-42). To produce the Summary of Clinical Safety analyses, lower-level terms from all studies were mapped to MedDRA version 24.0, which was the version used for the pivotal Study G2201, while the CTCAE grading version used was the same as in the original studies. Separate summaries are also presented for SAEs, fatal SAEs, AEs that led to discontinuation of study drug, and AEs that required dose reductions/interruptions. The summaries are also presented by study drug relationship.

Table 11-42. Applicant - MedDRA and CTCAE Versions Used in the Studies

Studies	MedDRA Versions	CTCAE Grading
G2201	24.0	4.03
A2102	23.1	4.0
X2101	23.1	4.0

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities

AESI are collections of AE PTs that have been identified as meriting enhanced data presentation due to their possible clinical impact, based on development experience predominantly in adult clinical trials. Each AESI is composed of a selected group of AE PTs that are of specific clinical interest in connection with dabrafenib and trametinib treatment. The AESI groupings are defined at program level on the basis of the current safety information available for D+T. AESIs were identified for this combination based on a clinical review of a comprehensive list of MedDRA terms. Summaries were produced for the combination therapy pool for the following AESIs with D+T, following the search strategy defined for Study G2201.

The FDA's Assessment

FDA agrees with the Applicant's description of AE categorization. The FDA review was completed using MedDRA preferred terms (PTs) and CTCAE grade as well as custom grouped terms (GT) when performing independent analyses of AEs.

Routine Clinical Tests

The Applicant's Position

Laboratory monitoring in the pivotal Study G2201 and supportive Studies A2102 and X2101 consisted of monitoring of hematology and blood chemistry at visits specified in the individual study protocols. The laboratory values were graded in CTCAE v4.0 for Studies A2102, X2101 and CTCAE v4.03 for Study G2201 (Table 11-42). Parameters without a grading were classified as low or high per laboratory normal ranges.

Overall, the routine clinical and laboratory evaluations performed were adequate to assess the safety of pediatric patients (1 to < 18 years) treated with D+T.

The FDA's Assessment

For Study G2201, multiple safety assessments were conducted including physical examinations, vital signs, height and weight, performance status according to Karnofsky for patients >16 years of age or Lansky for patients ≤ 16 years of age at screening, and laboratory evaluation (hematology, clinical chemistry, urinalysis, pregnancy and assessments of female fertility, hepatitis screening). For growth plate evaluation, an X-ray or MRI of tibia was performed at screening, weeks 24 and 48, followed by every 12 months and at end of treatment. Cardiac imaging/echocardiograms and ophthalmic examinations were performed at screening, week 5, followed by every 16 weeks and at end of treatment. ECGs were performed at screening, week 5, followed by every 16 weeks and at end of treatment. Skin examinations were performed prior to initiation of study treatment, and during the study on a monthly basis throughout therapy and at end of treatment. After discontinuation of study treatment, skin examinations were performed at 3 and 6 months after the last dose of study treatment or until the start of a new anti-neoplastic therapy. Routine laboratory monitoring included complete blood count, liver function test which includes alkaline phosphatase alanine aminotransferase and aspartate aminotransferase as well as electrolytes and urinalysis. Creatine phosphokinase was not routinely monitored.

For Study X2101, dermatologic skin examinations were performed at screening and day 22 followed by every 4 weeks starting on week 9. For growth plate evaluation, a plain radiograph of wrist or tibial growth plate was performed on day 1, weeks 9 and 25, and then every 6 months. Ophthalmologic examinations were performed at screening, day 28, weeks 17 and 25 followed by every 12 weeks. Electrocardiograms were performed at screening, weeks 8 and 25 followed by every 12 weeks. Echocardiograms were performed at screening, day 28, weeks 17 and 25 followed by every 12 weeks. Hematology and chemistry evaluations were performed weekly until week 9, after which they were checked every 4 weeks, and then every 12 weeks after week 49.

11.2.4 Safety Results

This safety evaluation of combination therapy in pediatric patients is primarily based on the pooled data from 171 pediatric patients treated with the proposed dosing regimen of D+T ("combination therapy pool") across these Studies G2201 and X2101 and the results are presented in the sections below.

Deaths

The Applicant's Position

A total of 18 deaths were reported across the three pediatric studies (total N=371); 15 patients treated with D+T in Study G2201, 2 patients treated with dabrafenib monotherapy in Study A2102, and 1 patient treated with trametinib monotherapy in Study X2101. Seven of these were considered on-treatment deaths and 11 occurred post-treatment as defined by study protocol. Five of the 7 on-treatment deaths were attributed to the underlying disease; 3 patients in Study G2201 HGG cohort, 1 in the Study G2201 LGG cohort and 1 in Study A2012. Two patients in Study G2201 HGG cohort died secondary to AEs.

One patient, who crossed-over from C+V to D+T in the Study G2201 LGG cohort, died due to disease progression in the cross-over phase 23 days after last dose of treatment with D+T, after having received 156 days of D+T treatment. The on-treatment death in Study A2102 was reported in a 10-year-old patient with glioma (gliomatosis cerebri) on dabrafenib monotherapy due to a depressed level of consciousness concurrent with disease progression 2 weeks after the last dose of the study medication. None of these deaths were considered related to study drug.

The FDA's Assessment

FDA confirmed the information above and reviewed all narratives for on-treatment deaths. Of the 15 patients treated with dabrafenib and trametinib on Study G2201 who had a fatal adverse event, 14 patients were in the HGG cohort and 1 patient was in the LGG cohort. Narratives were provided for 6 patients (including 5 patients with HGG and 1 patient with LGG) who had fatal events within thirty days of discontinuation of study treatment. There were 5 fatal events which were attributed to disease progression (4 patients in the HGG cohort and 1 patient in the LGG cross-over cohort); of these patients one also had a fatal adverse event of apnea and one also had a fatal adverse event of increased intracranial pressure. One patient died of encephalomyelitis. The remaining 9 patients with HGG on Study G2201 with a fatal adverse event that occurred after 30 days of discontinuing study therapy died due to the study indication.

The narratives for patients with on-treatment deaths are reviewed in further detail below.

Table 11-43. FDA Analysis of Treatment-Emergent Deaths in Study 2201

Patient ID	Brief Narrative (Bolded AE is the Condition to Which the Investigator Attributed the Patient's Death)	FDA's Assessment of Causality
G2201 (b) (6)	This is a 15-year-old Caucasian male with HGG who received dabrafenib 100 mg BID + trametinib 1 mg daily who developed headache, vomiting, and was diagnosed with Grade 2 increased intracranial pressure on Day 318. The patient then developed fevers and was hospitalized and intubated. Chest X-ray showed pulmonary edema and the patient was treated with steroids and antibiotics. On Day 320 the patient's fevers and pulmonary edema resolved. A CT scan of the brain showed increased lesion volume and on Day 322 treatment was interrupted and discontinued. The patient died 21 days after the last dose of the study treatment, due to **Grade 5 increased intracranial pressure** and **disease progression.**	The history and imaging are consistent with disease progression.
G2201- (b) (6)	This is a 15-year-old Asian male with BRAFV600 mutation positive HGG who received dabrafenib 75 mg BID + trametinib 0.75 mg daily, who was hospitalized before participation in the trial and underwent Ommaya reservoir placement for a pre-existing hydrocephalus exacerbation followed by CSF drainage on Day−16. On Day 8 of treatment, the patient developed fevers with desaturation, hypotension, and tachycardia. On Day 9 the patient developed dyspnea and was started on high flow oxygen therapy, nasal airway insertion and bi-level positive airway pressure (BIPAP) therapy. Chest X-ray showed atelectasis and CSF culture showed presence of gram-negative bacilli. The patient was treated with meropenem. On Day 10, the study treatment was temporarily interrupted, and on Day 12 the patient died due to **Grade 5 encephalomyelitis**.	Given the history of patient's hospitalization, imaging, and CSF culture this event is likely due to sepsis associated encephalitis.
G2201- (b) (6)	This is a 13-year-old Caucasian male with BRAFV600 mutation positive HGG who received dabrafenib 125 mg BID + trametinib 1.5 mg daily and was hospitalized on Day 113 of treatment for Grade 4 facial nerve paralysis which was treated with steroids. MRI showed disease progression which matched the clinical progression of symptoms. Facial nerve paralysis resolved after 2 days. On Day 160, the patient discontinued study treatment, and on Day 167 the patient died due to **disease progression**.	The history, hospitalization and imaging are consistent with disease progression.

Patient ID	Brief Narrative (Bolded AE is the Condition to Which the Investigator Attributed the Patient's Death)	FDA's Assessment of Causality
G2201 (b) (6)	This is a 17-year-old Caucasian female with BRAF V600 mutation positive HGG who received dabrafenib 150 mg BID + trametinib 2 mg daily. The patient had multiple hospitalizations for hyperesthesia, skin irritation, erythema nodosum which was treated with topical steroids. The patient underwent multiple dose modifications. On Day 76 the patient was hospitalized for Grade 3 paresis, Grade 4 blindness, Grade 3 musculoskeletal pain, Grade 3 headache, and Grade 3 pain in left shoulder. CT scan demonstrated disease progression. The patient was treated with steroids and the study treatment remained interrupted. On Day 77 trametinib was restarted at a reduced dose of 0.5 mg daily and on Day 78 dabrafenib was restarted at a reduced dose of 50 mg BID. On Day 80 the patient developed an erythematous rash (grade not reported), and treatment was permanently discontinued. Fourteen days after the last dose of study treatment, the patient died due to **Grade 3 paresis** and **disease progression.**	The history and imaging are consistent with disease progression.
G2201 (b) (6)	This is an 8-year-old Caucasian male with BRAFV600 mutation positive LGG who initially received treatment with C+V. The patient was hospitalized on Day 64 for cerebrospinal fluid circulation disorder and underwent surgical shunt revision. Due to disease progression the patient crossed over to treatment with D+T 60 mg BID and trametinib 0.5 mg daily on Day 113. On Day 131 dabrafenib dose was increased to 70 mg BID and on Day 132 trametinib dose was increased to 0.75 mg daily. On Day 237 the patient developed Grade 1 nausea, vomiting and Grade 3 cerebral salt wasting syndrome which was treated with steroids. On Day 245 treatment was discontinued due to disease progression. Seven days after the last dose of dabrafenib and three days after the last dose of trametinib, the patient was hospitalized with second episode of Grade 3 cerebrospinal fluid circulation disorder. VP-shunt revision was performed after which there was no improvement in symptomatic brain pressure. Brain CT scan showed generalized brain edema following partial tumor resection. Twenty-seven days after the last dose of dabrafenib and twenty-three days after the last dose of trametinib, the patient died due to **disease progression**	The history and imaging are consistent with disease progression.

Patient ID	Brief Narrative (Bolded AE is the Condition to Which the Investigator Attributed the Patient's Death)	FDA's Assessment of Causality
G2201-(b) (6)	This is a 14-year-old Caucasian female with BRAF V600 mutation positive HGG who received dabrafenib 100 mg BID + trametinib 1 mg daily. The patient had multiple hospitalizations for several issues including increased intracranial pressure. The patient underwent multiple dose modifications during the study. On Day 697, an MRI scan showed progressive disease and so the study treatment was permanently discontinued. The patient died due to **study indication and Grade 5 apnea**.	The history and imaging are consistent with disease progression.

Abbreviations: BID, twice a day; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CSF, cerebrospinal fluid; CT, computed tomography; HGG, high-grade glioma; LGG, low-grade glioma; MRI, magnetic resonance imaging; VP, ventriculoperitoneal

Serious Adverse Events

The Applicant's Position

Table 11-44. Applicant - Serious Adverse Events (at Least 1% in All Patients Group) by Preferred Term - Combination Therapy Pool (Safety Set)

	All Patients N=171	
Preferred Term	All Grades n (%)	Grade 5 n (%)
Number of patients with at least one event	79 (46.2)	3 (1.8)
Pyrexia	26 (15.2)	0
Vomiting	6 (3.5)	0
Headache	5 (2.9)	0
Seizure	4 (2.3)	0
Apnoea	3 (1.8)	1 (0.6)
Dehydration	3 (1.8)	0
Ejection fraction decreased	3 (1.8)	0
Hydrocephalus	3 (1.8)	0
Hypotension	3 (1.8)	0
Tonsillitis	3 (1.8)	0
Intracranial pressure increased	2 (1.2)	1 (0.6)
C-reactive protein increased	2 (1.2)	0
Dysarthria	2 (1.2)	0
Erythema nodosum	2 (1.2)	0
General physical health deterioration	2 (1.2)	0
Paresis	2 (1.2)	0
Procedural complication	2 (1.2)	0
Upper respiratory tract infection	2 (1.2)	0
Urinary tract infection	2 (1.2)	0

	All Patients N=171	
Preferred Term	**All Grades n (%)**	**Grade 5 n (%)**
Varicella	2 (1.2)	0

Source: SCS Appendix 1-Table 3.9-1
Numbers (n) represent counts of patients.
A patient with multiple severity grades for an adverse event is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.0 (A2102, X2101) and CTCAE version 4.03 (G2201)

The SAEs observed with D+T treatment in pediatric patients were in line with the overall AE profile and current safety knowledge of combination therapy with D+T. Serious adverse events were reported in 46.2% of the pediatric patients (79/171) treated with D+T, of whom 3 patients (1.8%) had grade 5 SAEs (apnea, intracranial pressure increased and encephalomyelitis in 1 each). The most frequently reported SAEs (occurring in ≥ 2% of patients) were pyrexia (15.2%), vomiting (3.5%), headache (2.9%), and seizure (2.3%). Overall, 29/171 patients (17.0%) reported SAEs suspected to be study treatment-related. Pyrexia was the most common (incidence of ≥ 2%) study treatment-related SAE.

In Study G2201 LGG cohort, the incidence of SAEs was similar between the D+T and C+V arms. Pyrexia was most common SAE in both arms, reported at lower frequency with D+T treatment. Serious AEs were more frequent in the pHGG patients compared to the pLGG patients. Headache, which may also be associated with the disease pathophysiology, and pyrexia were the most commonly reported SAEs in pHGG patients.

Overall, 29/171 patients (17.0%) in the combination therapy pool reported SAEs suspected to be study treatment-related. The most frequently reported SAEs suspected to be study treatment related (incidence >1%) were pyrexia (10.5%), ejection fraction decreased (1.8%), and dehydration, erythema nodosum and hypotension (1.2% each). No treatment-related fatal SAE was reported.

The FDA's Assessment

FDA performed an independent analysis of the incidence of SAEs in the pooled and primary safety population. In FDA's analysis, serious adverse events in the pooled safety population occurred in 78 patients (47%). The most frequently reported SAEs (occurring in ≥ 2% of patients) were pyrexia (14%), vomiting (4%), hemorrhage 4%, and headache (3%).

In Study G2201, SAEs occurred in 29 patients (40%) in the D+T arm compared to 15 patients (45%) in the C+V arm. The most frequently reported SAEs by preferred term (PT) in the D+T arm were pyrexia (14%), hemorrhage (4.1%), vomiting (4.1%), urinary tract infection (4.1%), apnea (2.7%), hydrocephalus (2.7%), procedural complication (2.7%), tonsilitis (2.7%), and seizure (2.7%). Notable SAEs occurring in single patients on the D+T arm were retinal disorder, embolism, hypernatremia, and toxic shock syndrome. Pyrexia was the most frequently reported SAE in both arms with a slightly higher incidence in the C+V arm (14% in D+T vs. 21% in C+V).

Pyrexia was the most frequently reported SAE in both arms with slightly higher incidence in the C+V arm (14% in D+T vs. 21% in C+V).

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position

In the combination therapy pool, discontinuations due to AEs were low. Among the 13/171 (7.6%) patients who discontinued, most (9 out of 13) were patients with LGG. Most patients discontinued due to AEs in the SOC of investigations (5/13 patients) and skin and subcutaneous tissue disorders (4/13 patients). AE of rash and ALT increased led to treatment discontinuation in 2 patients each. In Study G2201 LGG cohort, treatment discontinuation due to AEs had a lower incidence in the D+T arm (4.1%) than in the C+V arm (18.2%).

The FDA's Assessment

In the Study G2201 LGG cohort, adverse events leading to treatment discontinuation in the D+T arm occurred in 3 patients, which included chills (1.4%), fatigue (1.4%), pyrexia (1.4), weight increased (1.4%) and headache (1.4%).

In the C+V arm, discontinuations occurred in 5 patients (15%). Adverse events in the C+V group resulting in permanent discontinuation included infusion-related reaction (6%), neutropenia (3%), hypersensitivity (3%), and urticaria (3%).

Overall, 13/166 (8%) patients in the pooled safety population discontinued treatment due to adverse events. The most common adverse events leading to discontinuation of study treatment were increased transaminases, weight increased, and ejection fraction decreased in five patients each (2.9%). Discontinuations due to rash, pyrexia, and paronychia occurred in four patients each (2.4%).

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position

In the combination therapy pool, dose reductions due to AEs occurred in 25/171 patients (14.6%). The most frequently reported AE leading to dose reductions was pyrexia, reported in 8 patients (4.7%).

Dose interruptions due to AEs occurred in 121/171 patients (70.8%) in the combination therapy pool. The most frequently reported AEs leading to dose interruptions (>5% incidence) were pyrexia (49.7%) and vomiting (9.4%). Dose interruptions and subsequent dose reductions were stipulated in the study protocols to manage AEs, including pyrexia events.

The incidences of AEs requiring dose adjustments by PT in the combination therapy pool were in line with the known safety profile of D+T.

The FDA's Assessment

In FDA's analysis of the pooled safety population, dose reductions of either dabrafenib or trametinib or both due to an adverse event occurred in 24/166 patients (13%). Dose reductions of dabrafenib occurred in 12 patients (7%). The most frequently reported adverse event leading to dose reductions with dabrafenib (≥5% incidence) was pyrexia (35%). Dose reductions of trametinib occurred in 10 patients (6%). The most frequently reported adverse event leading to dose reductions with trametinib was rash (1.8%), headache (1.2%), abdominal pain (1.2%) and pyrexia (1.2%).

Dose interruptions of either dabrafenib or trametinib or both due to adverse events occurred in 119/166 patients (72%) in the pooled safety population. Dose interruption of dabrafenib occurred in 84 patients (51%) and the most frequently reported adverse event leading to dose interruption of dabrafenib (≥5% incidence) was pyrexia (35%). Dose interruption of trametinib occurred in 82 patients (49%) and the most frequently reported adverse event leading to dose interruption of trametinib (≥5% incidence) was pyrexia (34%).

Significant Adverse Events

Data and the Applicant's Position

Overall, 46.2% of patients had SAEs, including 3 (1.8%) patients (from HGG cohort of Study G2201) who had fatal outcomes (not treatment related). Thirteen (7.6%) patients had AEs leading to discontinuation of the study treatment. No treatment-related fatal SAE was reported (Table 11-45).

Table 11-45. Applicant - Overview of Fatal and Other Serious or Significant Adverse Events – Combination Therapy Pool (Safety Set)

	All Patients N=171	
Category	**All Grades n (%)**	**Grade ≥3 n (%)**
Adverse events	169 (98.8)	98 (57.3)
Treatment-related	154 (90.1)	50 (29.2)
SAEs	79 (46.2)	58 (33.9)
Treatment-related	29 (17.0)	16 (9.4)
Fatal SAEs	3 (1.8)	3 (1.8)
Treatment-related	0	0
AEs leading to discontinuation	13 (7.6)	6 (3.5)
Treatment-related	11 (6.4)	5 (2.9)
AEs leading to dose adjustment/interruption	125 (73.1)	64 (37.4)
AEs requiring additional therapy	135 (78.9)	56 (32.7)

Source: SCS-Table 2-2
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.03.
Abbreviations: AE, adverse event; n, number of patients; SAE, serious adverse event

The FDA's Assessment

FDA's analysis of treatment emergent adverse events in the pooled safety population is provided in Table 11-46. An analysis of TEAEs for the G2201 LGG cohort is provided in Table 11-47. The most common adverse reactions (> 20%) in the pediatric pooled safety population were pyrexia (66%), rash (54%), headache (40%), vomiting (38%), musculoskeletal pain (36%), diarrhea (30%), fatigue (31%), dry skin (31%), epistaxis and other bleeding events (25%), nausea (26%), abdominal pain (24%) and dermatitis acneiform (23%). In the pooled safety population, events of hemorrhage occurred in 25% of patients; the most common type of bleeding was epistaxis (16%). Serious events of bleeding occurred in 3.6% of patients and included gastrointestinal hemorrhage (1.2%), cerebral hemorrhage (0.6%) uterine hemorrhage (0.6%), post-procedural hemorrhage (0.6%) and epistaxis (0.6%).

The most common adverse reactions in the LGG cohort (≥15%) were pyrexia (68%), rash (51%), headache (47%), fatigue (33%), musculoskeletal pain 34%, vomiting (34%), hemorrhage (25%), diarrhea (29%), dry skin (26%), abdominal pain (25%), nausea (25%), dermatitis acneiform (22%), dizziness (15%), upper respiratory tract infection (15%), and weight increased (15%).

Table 11-46. FDA Analysis of Treatment-Emergent Adverse Events in the Pooled Safety Population[a]

	Dabrafenib With Trametinib N=166 n (%)	
TEAE	**All Grades**	**Grades 3-4**
Patients with TEAEs	166(100)	96 (58)
Pyrexia[b]	109 (66)	15 (9)
Rash[c]	89 (54)	4 (2.4)
Headache	68 (41)	5 (3.0)
Musculoskeletal pain[d]	59 (36)	1 (0.6)
Vomiting[e]	65 (39)	5 (3.0)
Fatigue[f]	52 (31)	0 (0.0)
Diarrhea[g]	52 (31)	3 (1.8)
Abdominal pain[h]	40 (24)	2 (1.2)
Hemorrhage[i]	41 (25)	2 (1.2)
Dermatitis acneiform[j]	39 (23)	0 (0.0)
Dizziness[k]	24 (14)	0 (0.0)
Cough[l]	33 (20)	0 (0.0)
Stomatitis[m]	17 (10)	1 (0.6)
Urinary tract infection[n]	9 (5)	3 (1.8)
Neuropathy peripheral[o]	15 (9)	0 (0.0)
Arrhythmia[p]	12 (7)	1 (0.6)
Ejection fraction decreased	9 (5)	1 (0.6)
Hypothyroidism	5 (3.0)	0 (0.0)
Edema[q]	13 (8)	0 (0.0)
Detachment of retinal pigment epithelium	1 (0.6)	0 (0.0)
Hypotension	6 (3.6)	4 (2.4)
Dyspnea	5 (3.0)	0 (0.0)
Hypertension	4 (2.4)	2 (1.2)

	Dabrafenib With Trametinib N=166 n (%)	
TEAE	**All Grades**	**Grades 3-4**
Lower respiratory tract infection	1 (0.6)	0 (0.0)

Source: FDA Primary Analysis Adverse Events Analysis Dataset (adae.xpt)
[a] NCI CTCAE version 4.03
[b] Includes pyrexia and body temperature increased.
[c] Includes rash, rash macular, rash maculo-papular, rash pustular, rash papular, rash erythematous, eczema, erythema multiforme, dermatitis, dermatitis exfoliative, skin exfoliation, palmar-plantar erythrodysaesthesia syndrome and dermatitis bullous.
[d] Includes pain in extremity, arthralgia, back pain, myalgia, pain in extremity, arthralgia, bone pain, non-cardiac chest pain, neck pain, musculoskeletal pain, musculoskeletal discomfort, and musculoskeletal stiffness.
[e] Includes vomiting and retching.
[f] Includes fatigue and asthenia.
[g] Includes diarrhea, colitis, enterocolitis, and enteritis.
[h] Includes abdominal pain and upper abdominal pain.
[i] Includes epistaxis, post procedural hemorrhage, hematuria, upper gastrointestinal hemorrhage, anal hemorrhage, rectal hemorrhage, cerebral hemorrhage, gastrointestinal hemorrhage, catheter site hemorrhage, and uterine hemorrhage.
[j] Includes dermatitis acneiform, acne and acne pustular.
[k] Includes dizziness and vertigo.
[l] Includes cough and productive cough.
[m] Includes stomatitis, cheilitis, mouth ulceration, aphthous ulcer, mucosal inflammation, and glossitis.
[n] Includes urinary tract infection, cystitis, urinary tract infection bacterial, and Escherichia urinary tract infection.
[o] Includes peripheral motor neuropathy, dysaesthesia, hyperaesthesia, paresthesia, hypoaesthesia and peripheral sensory neuropathy.
[p] Includes sinus tachycardia, sinus bradycardia, electrocardiogram PR prolongation, atrioventricular block first degree, and electrocardiogram QT prolonged.
[q] Includes localized edema, edema peripheral, face edema, and periorbital edema.
Abbreviations: TEAE, treatment-emergent adverse event

Table 11-47. FDA Analysis of Adverse Reactions (≥15%) in Pediatric LGG Patients Who Received TAFINLAR in Combination With Trametinib in Study G2201[a]

	MEKINIST Plus Dabrafenib N=73		Carboplatin Plus Vincristine N=33	
Adverse Reactions	**All Grades (%)**	**Grade ≥3 (%)**	**All Grades (%)**	**Grade ≥3 (%)**
Gastrointestinal				
Vomiting	34	1	48	3
Diarrhea[b]	29	0	18	6
Nausea	25	0	45	0
Abdominal Pain[c]	25	0	24	0
Constipation	12	0	36	0
Stomatitis[d]	10	0	18	0
General				
Pyrexia[e]	68	8	18	3
Fatigue[f]	33	0	39	0
Nervous system				
Headache[g]	47	1	33	3
Dizziness[h]	15	0	9	3
Peripheral neuropathy[i]	7	0	45	6
Vascular disorders				
Hemorrhage[j]	25	0	12	0

	MEKINIST Plus Dabrafenib N=73		Carboplatin Plus Vincristine N=33	
Adverse Reactions	**All Grades (%)**	**Grade ≥3 (%)**	**All Grades (%)**	**Grade ≥3 (%)**
Skin				
Rash[k]	51	2.7	18	3
Dry skin	26	0	3	0
Dermatitis acneiform[l]	22	0	0	0
Alopecia	3	0	24	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[m]	34	0	30	0
Pain in jaw	1.4	0	18	0
Metabolism and nutrition disorders				
Decreased appetite	5	0	24	0
Respiratory, thoracic, and mediastinal disorders				
Oropharyngeal pain	11	0	18	0
Psychiatric disorders				
Anxiety	1.4	0	15	3
Immune system disorders				
Hypersensitivity	0	0	15	3
Infections and infestations				
Upper respiratory tract infection	15	0	6	0
Injury, poisoning and procedural complications				
Infusion related reaction	0	0	15	3
Investigations				
Weight increased	15	7	0	0

Source: FDA Primary Analysis Adverse Events Analysis Dataset (adae.xpt)
[a] NCI CTCAE version 4.03
[b] Includes diarrhea, colitis, enterocolitis, and enteritis.
[c] Includes abdominal pain and upper abdominal pain.
[d] Includes stomatitis, cheilitis, mouth ulceration, aphthous ulcer, and glossitis.
[e] Includes pyrexia and body temperature increased.
[f] Includes fatigue and asthenia.
[g] Includes headache and migraine with aura.
[h] Includes dizziness, and vertigo.
[i] Includes peripheral neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paresthesia, neuralgia, hypoaesthesia and peripheral sensory neuropathy.
[j] Includes epistaxis, post procedural hemorrhage, hematuria, upper gastrointestinal hemorrhage, and hemorrhage intracranial.
[k] Includes rash, rash macular, rash maculo-papular, rash pustular, rash papular, rash erythematous, eczema, erythema multiforme, dermatitis, dermatitis exfoliative, skin exfoliation, palmar-plantar erythrodysaesthesia syndrome and dermatitis bullous.
[l] Includes dermatitis acneiform, acne and acne pustular.
[m] Includes back pain, myalgia, pain in extremity, arthralgia, bone pain, non-cardiac chest pain, neck pain and musculoskeletal stiffness.
Abbreviations: LGG, low-grade glioma

The AE of ejection fraction decreased occurred in 2.7% of patients in the D+T arm. Hypertension was uncommonly reported (3% of the C+V arm and no patients in the D+T arm). A pooled term search for ocular disorders indicated only one event of retinal pigment epithelial detachment in one patient (1.4%) on the D+T arm.

The Applicant's Position

ADR identification for D+T combination therapy in pediatric patients was based on the ADR defined in the adult population in a large phase III safety data pool (n=1076). Any additions or updates to the ADRs identified in adults were made following medical review of the combination therapy pool AE data in pediatric patients.

The ADRs observed in pediatric patients were consistent with the previously reported ADRs in adult population and across different approved indications, except for a newly identified ADR of weight increased identified for the pediatric population. Weight gain was identified in patients who had either weight increased reported as an AE (26/171; very common) [SCS Appendix 1-Table 3.16-1] or had weight gain represented by an increase of ≥2 BMI-for-age percentile category change (51/171). A total of 8 patients had both ≥ 2 BMI-for-age percentile categories and the AE of weight increased (grade 1 or 2). Overall, 9 patients had weight gain with a positive temporal relationship with study drug treatment, ≥ 2 BMI-for-age percentile category change, > 20% increase in BMI-for-age from baseline and absence of confounding factors. Therefore, causal association with study drugs could not be ruled out in these 9 cases and weight increased is considered a new ADR.

High prevalence of weight gain in pediatric brain tumor survivors has been reported in the literature and is attributed to hypothalamic-pituitary dysfunction (van Schaik et al 2021). These 9 patients identified above did not have evidence of hypothalamic pituitary dysfunction and/or hypothalamic pituitary lesions.
No other new safety signals have been identified.

The overall ADR profile in pediatric patients, except newly identified weight gain, was consistent with the previously reported ADRs in adult population and across different approved indications.

The FDA's Assessment

The FDA agrees that weight gain in pediatric patients treated with dabrafenib and trametinib was identified as a new safety signal. Of the 166 patients included in the pooled safety population, 24 patients reported at least one adverse event (AE) of 'weight increased.' The Applicant notes that risks factors for weight gain include having a diagnosis of low-grade glioma and that hypothalamic pituitary disfunction may also contribute to weight gain. Based on additional information provided by the Applicant during FDA's review, 17 patients had evidence of hypothalamic pituitary dysfunction indicated by their past and/or current medical condition(s) and/or concomitant medication(s); 13 were from Study G2201, four were from Study X2101 Parts C and D, treated at RP2D, and two patients were identified solely on the basis of use of levothyroxine.

There were seven patients in the pooled safety population with Grades 3 to 4 adverse events of weight gain. Among the eight patients who had both an increase of ≥ 2 BMI-for-age percentile categories and the AE of weight increased, there was one patient with diabetes insipidus.

In total, eleven patients with a positive temporal relationship of weight gain with study drug treatment had no evidence of hypothalamic pituitary dysfunction, suggesting that there may be an alternative cause for the events of increased weight.

As part of the review of these adverse events, growth charts were provided by the Applicant and reviewed by FDA; a small number of charts raised concern for measurement or data entry error based on unrealistic patterns of weight gain or loss. FDA concluded that there may be a causal relationship with the study drugs and that weight gain should be identified as a new adverse drug reaction.

Laboratory Findings

The Applicant's Position

Data from standard laboratory evaluations, i.e., hematology, biochemistry, ECG, and vital signs, were in line with the known safety knowledge with D+T and did not reveal any significant safety concern.

The FDA's Assessment

FDA's analysis of selected laboratory abnormalities that worsened from baseline in the LGG cohort of Study G2201 is provided in Table 11-48 below.

Table 11-48. FDA Analysis of Select Laboratory Abnormalities (≥20%) That Worsened From Baseline in Patients With BRAF V600E Mutation-Positive Low-Grade Glioma Who Received Trametinib in Combination With Dabrafenib in Study G2201[a]

	Trametinib Plus Dabrafenib N=73		Carboplatin Plus Vincristine N=33	
Laboratory Abnormality	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Hepatic				
Increased alkaline phosphatase	55	0	13	0
Increased AST	37	1.4	55	0
Increased ALT	29	3	61	9
Chemistry				
Decreased magnesium	34	4.1	76	6
Increased magnesium	32	0	24	3
Increased potassium	15	4.2	21	6
Decreased calcium	14	4.1	22	9
Decreased potassium	8	1.4	70	0
Decreased phosphate	7	2.7	33	3
Decreased sodium	5	1.4	27	6
Increased serum fasting glucose	0	0	44	0
Hematology				
Decreased leukocytes	59	0	91	18
Decreased hemoglobin	46	0	94	36
Decreased neutrophils	44	17	84	75
Decreased platelets	30	0	73	18
Increased lymphocytes	24	0	13	3.1
Decreased lymphocytes	16	1.4	56	6

Source: Primary analysis, adlb.xpt dataset
[a] The denominator used to calculate the rate varied from 70 to 73 in D+T arm and 10 to 33 in C+V arm based on the number of patients with a baseline value and at least one post-treatment value.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BRAF, B-Raf proto-oncogene, serine/threonine kinase

Laboratory findings in the pooled safety population were similar. The most common (≥ 2%) Grade 3 or 4 laboratory abnormalities in the pooled safety population were decreased neutrophil count (20%), increased alanine aminotransferase (3.1%), and aspartate aminotransferase increased (3.1%).

Vital Signs

The Applicant's Position

Study G2201, LGG cohort: Clinically notable systolic BP (high, low) and weight gain were reported more frequently in the D+T arm compared to the C+V arm. Post-baseline, 26 patients (35.6%) in the D+T group and 10 patients (30.3%) in the C+V group had clinically notable high systolic BP. Fifteen patients (20.5%) had low systolic BP in the D+T group. Weight gain was evaluated based on increase from baseline of ≥ 2 BMI-for-age percentile categories. Post-

baseline, 26 patients (35.6%) in the D+T arm and 2 patients (6.1%) in the C+V arm had clinically notable weight gain. Weight gain was identified as a new ADR.

Study G2201, HGG cohort: Clinically notable high SBP occurred in 11 patients (26.8%), low SBP in 10 patients (24.4%), weight gain (assessed as an increase from baseline of ≥ 2 BMI-for-age percentile categories) was reported in 11 patients (26.8%), and weight loss (assessed as a decrease from baseline of ≥ 2 BMI-for-age percentile categories) was reported in 3 patients (7.3%).

Study A2102: There were no trends of change from baseline in SBP, DBP, heart rate, RR, and temperature over time. The median heart rate decreased from baseline slightly over time for patients in Part 1. This trend was not seen in Part 2 data. The significance of this decrease in heart rate is not known.

Study X2101: Approximately 23% of patients from Part C (2/18) and Part D (9/30) had body temperature increase ≥ 38.5 Celsius, and also pyrexia was the most frequently reported AE suspected to be related to study drug in Part D. Notable increases in weight (defined as increased of > 10% from baseline in the study), were observed in 83.3% (15/18) and 86.7% (26/30) of patients in Parts C and D, respectively.

Overall, apart from the new ADR of weight gain, no new safety concerns were identified.

The FDA's Assessment

FDA agrees with the Applicant's analysis of vital signs. Refer to Section 11.2.1 for further discussion on weight gain.

Electrocardiograms (ECGs)

The Applicant's Position

Study G2201, LGG cohort: Two patients (2.7%) in the D+T arm had increase in QTcF > 60 ms from baseline. One patient in each treatment arm had new QTcF between > 450 and ≤ 480 ms. None of these 3 patients in the D+T group had cardiac-related AEs reported. No AEs related to ECG abnormalities were reported except for 1 patient in D+T arm with an AE of electrocardiogram T wave abnormal (grade 2, suspected to be study drug related); no action with the study treatment was taken and the AE was resolving at the time of the data cut-off date. This was not the patient who presented QTcF between > 450 and ≤ 480 ms.

Study G2201, HGG cohort: Post-baseline, 2 patients (5.0%) had an increase in QTcF of >60 ms. One patient had new QRS > 120 ms post-baseline. No AEs related to ECG abnormalities were noted except 1 patient with an AE of ECG PR prolongation (grade 1, not suspected to be study drug related) that led to study treatment interruption; the AE resolved in 3 days.

Study A2102: No patient had a new QTcB value of ≥ 501 ms in any of the treatment arms. A total of 4 out of 13 (30.8%) patients in Part 1 and 5 out of 30 (16.7%) patients in Part 2 had an increase of > 60 ms from baseline.

Study X2101: Overall, 2 patients in Part A and 1 patient each in Parts B, C, and D had new QTcB notable values of > 500 ms, and 1 patient in each part of the study had a new QTcF notable value of > 500 ms.

The FDA's Assessment

FDA agrees with the Applicant's description of the incidence and severity of QT prolongation.

The Applicant's Position

Effects on QT interval are as presented under section 'Electrocardiography' above.

In dedicated thorough QT studies in adult patients, dabrafenib was associated with a minor not clinically significant QT effect (Nebot et al 2018Nebot et al 2018) and trametinib was devoid of cardiac repolarization effects (Patnaik et al 2016).

There were no clinically significant concerns identified from the pooled safety analysis.

The FDA's Assessment

FDA agrees with the Applicant's assessment.

Immunogenicity

The Applicant's Position

Immunogenicity was not assessed nor expected with small molecule therapy.

The FDA's Assessment

FDA agrees with the Applicant's assessment.

11.2.5 Analysis of Submission-Specific Safety Issues

The Applicant's Position

This section provides AESI summaries for the combination therapy pool, followed by a discussion of other important safety topics of interest in pediatric population including those identified in the nonclinical juvenile toxicity studies.

Adverse Events of Special Interest (AESI)

None of the pediatric patients receiving D+T had new primary or secondary malignancy events nor had pre-renal and intrinsic renal failure events; or died due to any AESI. Among the AESIs, skin toxicities (78.9%), pyrexia (67.3%), neutropenia (28.1%), bleeding events (27.5%), and hepatic disorders related events (20.5%) were reported in ≥ 20% of patients in the combination therapy pool. The majority of these AESIs were of grade ≤ 2, and none led to discontinuation of the study treatment. Neutropenia was the only AESI of grade ≥ 3 severity that was reported in more than 10% of patients; none of these events were fatal. Bleeding events and hepatic disorders, rarely resulted in study treatment modifications, and were mostly grade 1 or 2. Grade 4 events were reported for neutropenia AESIs and 1 patient with pancreatitis AESI. There were no grade 5 reported AESIs.

Table 11-49. Applicant - Overview of AESIs – Combination Therapy Pool (Safety Set)

	All Patients N=171	
Safety Topic	**All Grades n (%)**	**Grade ≥3 n (%)**
Number of patients with at least one AESI	162 (94.7)	54 (31.6)
Skin toxicity	135 (78.9)	4 (2.3)
Pyrexia	115 (67.3)	16 (9.4)
Bleeding events	47 (27.5)	2 (1.2)
Neutropenia	48 (28.1)	25 (14.6)
Hepatic disorders	35 (20.5)	12 (7.0)
Hypersensitivity	24 (14.0)	0
Ocular events	20 (11.7)	0
Hyperglycemia	14 (8.2)	1 (0.6)
Cardiac related events	11 (6.4)	2 (1.2)
Uveitis	5 (2.9)	1 (0.6)
Pancreatitis	4 (2.3)	2 (1.2)
Pneumonitis and interstitial lung disease*	1 (0.6)	0
Venous thromboembolism	1 (0.6)	0
Hypertension	4 (2.3)	2 (1.2)

Source: SCS-Table 2-12
Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.03, Case Retrieval Strategy version released 10-Oct-2021 (dabrafenib), 07-Oct-2021 (trametinib).
* No events of pneumonitis or ILD were reported, one event of bronchiolitis was retrieved in Study G2201 LGG cohort due to the broad search criteria used to identify possible cases of the AESI of pneumonitis/IDL. This event occurred 8.6 months after initiation of study drugs, it was a grade 1 non serious event, not suspected to be related to study drugs and resolved spontaneously and without discontinuation of study drugs.
Abbreviations: AESI, adverse event of special interest

AESI profile of D+T in Study G2201 LGG and HGG cohorts was consistent with that in the combination therapy pool. Pediatric patients with LGG treated with C+V reported more events of neutropenia (including grade ≥ 3 neutropenia) and fewer events of skin toxicities, pyrexia and bleeding events than patients treated with D+T in Study G2201. Grade ≥ 3 hypersensitivity

and hepatic disorders AESIs were more frequent with C+V treatment than with the D+T treatment.

11.2.5.1 Reproductive Toxicity and Renal Toxicity

Evidence of reproductive toxicity and renal toxicity were observed in nonclinical juvenile toxicity studies. Currently, there exists a knowledge gap on the effects of D+T on reproductive & renal toxicity in adult and pediatric human patients. No case of testicular toxicity was reported in the male pediatric patients from Study G2201. Renal toxicities that were only observed in juvenile rats (had not been observed in studies in adult animals) included partially reversible effects on kidneys (primary findings of tubular deposits, increased incidence of cortical cysts and tubular basophilia, increases in urea and/or creatinine concentrations). The observed preclinical findings occurred in rodent kidneys at a development stage corresponding to human kidney development under 1 year of age. Therefore, patients less than 1 year of age have been excluded from the clinical trials.

11.2.5.2 Skin Toxicity – Melanocytic Nevus

Treatment-emergent melanocytic nevi were reported at a higher frequency in pediatric patients treated with dabrafenib monotherapy (22/85 patients) than either in pediatric patients treated with trametinib monotherapy (3/91 in Study X2101) or D+T (7/171, in combination therapy pool). None of these events were serious and all of them were either grade 1 or 2 in severity. Across the pool of adult studies, melanocytic nevus was reported in 15/1076 patients treated with D+T. This higher incidence with dabrafenib monotherapy is consistent with the known paradoxical stimulation of MAPK pathway signaling by dabrafenib in the setting of wild-type BRAF (Hatzivassiliou et al 2010, Carnahan et al 2010). The lower incidence of melanocytic nevi observed in pediatric patients treated with the D+T are also consistent with the mitigating impact of trametinib on this paradoxical stimulation of wild type of BRAF kinase when added to dabrafenib treatment.

11.2.5.3 Growth and Development, Sexual Maturity, and Bone Age

The pediatric patients in clinical studies were also monitored for potential effects on growth and development (physical examination including routine monitoring of height and weight and bone age analysis) and effects on puberty (Tanner stage analysis). Overall, treatment of pediatric patients with D+T over 6 months did not significantly impact gain in height. However, weight gain was greater than expected based on age specific norms (i.e., positive weight velocity SDS). The median weight gain velocity SDS at 6 months ranged from +1.19 to +2.39 suggesting greater than expected weight gain for these patients, which is consistent with the shift from normal at baseline to high at post-baseline observed in the BMI SDS for 25.7% of the patients in the combined therapy pool.

From the 4 patients at risk of delayed puberty at the start of the study, none of the patients had delayed onset of puberty, though for one of the patients the status was 'unknown'. Tanner stage changes from lower at baseline to higher at post-baseline were very rare in the patients aged < 8 years. The growth plates were open at baseline and remained open throughout treatment for most patients, except when they closed at age-appropriate times. Results were similar in both cohorts of patients receiving D+T in Study G2201.

In Study G2201, the gain in weight for patients treated with D+T was generally greater than expected based on age specific norms (i.e., positive weight velocity SDS) and with about third of patients having notably high weight velocity. Clinically notable weight gain as reflected by ≥ 2 BMI-for-age percentile category change was markedly higher in the patients treated with D+T (35.6%) as compared to those treated with C+V (6.1%). One patient discontinued and another patient required dose modification, each for related grade 3 weight gain.

11.2.5.3.1 Palatability

Palatability for dabrafenib and trametinib liquid formulations was acceptable across both cohorts of Study G2201. The majority of patients or observers reported at least "neither good nor bad" or "good" for multiple domains. Considerable amount of data was missing for both dabrafenib and trametinib, therefore results should be interpreted with caution.

No palatability issues were reported by the patients in the supportive studies. Although, there were considerable amount of missing data, the majority of the patients who provided the responses liked the taste of the formulation, did not resist, or had no difficulty in taking the medication.

11.2.5.3.2 Other Laboratory Safety Assessments

Data from standard laboratory evaluations, i.e., hematology, biochemistry, ECG, and vital signs, were in line with the known safety knowledge with D+T and did not reveal any significant safety concern. The possible impact of combination of BRAF and MEK inhibitors on LVEF and visual acuity has been reported in published literature. Echocardiogram was performed across all pediatric studies, while change in visual acuity was assessed in pivotal Study G2201.

Echo assessment did not reveal any notable concern on LVEF in pediatric patients. Across the studies, the incidence of LVEF decrease ≥ 20% and below LLN was low in pediatric patients treated with D+T. Nine patients (5.3%) reported an AE of ejection fraction decreased, majority of these events were of grade ≤ 2. The event was considered as treatment related in 8 patients. For majority of patients, visual acuity was normal at baseline and was unchanged during the treatment. Although, ocular events AESIs were reported with D+T treatment, majority of these events were of grade ≤ 2, and none led to the discontinuation of treatment.

The FDA's Assessment

Based on the known safety profiles of dabrafenib and trametinib, FDA conducted analyses of cardiomyopathy, ocular toxicities, pancreatitis, and skin toxicity. Overall, these events were similar in incidence and degree of toxicity to that observed in the adult population.

FDA performed an analysis of patients in the pediatric pooled safety population who had cardiomyopathy defined as a decrease in LVEF ≥ 10% from baseline and below the institutional LLN; this definition of cardiomyopathy was previously used in Section 5 of the product label to describe the experience in adult patients. Of 161 patients who had available data to calculate change in LVEF, 14 (8.7%) had a qualifying LVEF measurement of ≥ 10% from baseline and below the institutional LLN. In reviewing the patient narratives, cardiac-related adverse event (AE) terms were reported in 4.1% of patients in the pooled safety population of whom two patients had ejection fraction decreased and one patient had ventricular enlargement. One event of ejection fraction decreased was grade 3, and the ventricular enlargement event was grade 3. This led to dose interruption of dabrafenib and trametinib; all three AEs resolved. An additional seven patients in the dabrafenib and trametinib group had decreased LVEF by at least 10% and resulting in less than LLN. Of these, LVEF decreased by at least 20% in three patients. Four of the seven patients had LVEF decrease resolved without any dose administration changes while remaining on study. None of the adverse events led to treatment dose modification or discontinuation.

In the D+T group, a serious AE (detachment of retinal pigment epithelium) was reported in one patient; no dose modifications were made, and the event did not resolve. There was also one event of grade 4 decreased visual acuity in a patient in the pooled safety population; additional information describing the event was requested. Based upon review of the narrative FDA agreed with the Applicant's assessment that this adverse event is not related to study drugs but most likely to of the effect of the tumor.

AEs concerning for pancreatitis events were reported in 4.1% of patients in the D+T group with PTs of amylase increased (two patients, grade 3 in one patient), lipase increased and pancreatitis (one patient each). One patient with an AE of pancreatitis had dose interruption of dabrafenib and subsequently resumed dabrafenib treatment.

Skin toxicity adverse events in the pooled safety population included seven cases of melanocytic nevus; none were ≥ Grade 3. New primary melanoma occurred in < 1% of patients. In the D+T group, skin toxicity adverse events were reported in 73% of the patients with the most frequently reported PTs of rash (51%) and dermatitis acneiform (22%). An SAE of erythema nodosum was reported in 1 patient. There was one patient with juvenile melanoma benign and no other patients with cutaneous malignancies. Most of the AEs were resolved with dose modifications and additional therapy.

11.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position

PRO data was collected in Study X2201; however, no analysis was performed for this submission.

The FDA's Assessment

The PROMIS Parent Proxy Global Health 7+2 was used to evaluate the quality of life of patients between the two treatment arms in the LGG cohort and was administered on weeks 1, 5, 8, followed by every 8 weeks thereafter. Global health scores and fatigue scores showed an improving trend in the dabrafenib and trametinib arm, while the pain scores between the 2 different arms showed no difference. Descriptive statistics were used to summarize the scored scales of PROMIS Parent Proxy Global Health 7+2. FDA agrees that overall, the global health scores showed an improvement for targeted therapy over standard chemotherapy.

11.2.7 Safety Analyses by Demographic Subgroups

The Applicant's Position

This section discusses the safety profile by age subgroups in pediatric patients aged < 2 years, 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years. The combination therapy pool included 4 children aged < 2 years, 40 children aged 2 to < 6 years, 55 children aged 6 to < 12 years, and 72 adolescents aged 12 to < 18 years treated with D+T. Safety data in < 6 years age subgroup can be considered as a surrogate for safety profile of the liquid formulations.

In the combination therapy pool, the incidence of AEs was generally comparable between the different age subgroups. In patients aged ≥ 2 years, AEs were most commonly reported in the SOCs of skin and subcutaneous tissue disorders at a comparable incidence across all age subgroups, primarily driven by dry skin, rash, rash maculo-papular, and dermatitis acneiform. There was no evidence of increased incidence of renal and urinary disorders AEs or ocular events (AEs in the eye disorders) in younger pediatric patients (< 6 years) relative to the older pediatric patients. Overall, the AE data in age groups below 6 years was consistent with the older age groups in the patients treated with D+T. No new safety signal was identified in patients below 6 years of age treated with D+T.

Excipient Safety

The excipients utilized in the liquid formulations of dabrafenib and trametinib are standard pharmacopeial excipients in common use in pharmaceutical formulations with the exception of the non-compendial flavors in both formulations - artificial berry flavor for the dabrafenib

formulation and artificial strawberry flavor for the trametinib formulation. Both flavors are commercially available combinations of ingredients established for use in medical products, are listed as GRAS (Generally Recognized As Safe) by the Flavor and Extract Manufacturers Association (FEMA) and are approved in accordance with the US Code of Federal Regulations, Title 21.

Safety analysis by age did not reveal any evidence of concern associated with (b) (4) in younger children. The incidences of vomiting and diarrhea were slightly higher in the younger patients (< 6 years) than in the older age subgroups, which is a common characteristic of oral treatment in these patients. The AE of blood creatinine increased was reported in 4/43 patient (9.1%) in the < 6 years age subgroup compared to 4/128 patients (3.1%) in the older age subgroups. Majority of these events were recovered/resolved while patients were on the study treatment.

The FDA's Assessment

The tables below provide an overview of adverse events by age category in the pooled safety population. The subgroups of pediatric patients include those ages 1 to < 2 years, 2 to < 6 years, 6 to < 12 years and 12 to < 18 years. The rates of AEs and SAEs were relatively similar across age groups. The rate of treatment discontinuation due to AEs was similar across age groups except for children 1 to < 2 years of age; however, given the extremely limited sample size in this age group, these results should be interpreted with caution.

Table 11-50. Analysis of Adverse Events by Age Group: 1 to <2 Years

	All Patients N=4	
Category	**All Grades n (%)**	**Grades 3-4 n (%)**
Adverse events	4(100)	2(50)
SAEs	2(50)	2(50)
Fatal SAEs	0 (0.0)	0 (0.0)
AEs leading to discontinuation	0 (0.0)	0 (0.0)
AEs leading to dose adjustment/interruption	3 (75)	2(50)

Source: Adapted from Novartis Analysis from Table HA1-Q14.1
Abbreviations: AE, adverse event; SAE, serious adverse event

Table 11-51. Analysis of Adverse Events by Age Group: 1 to <6 Years

	All Patients N=41	
Category	**All Grades n (%)**	**Grades 3-4 n (%)**
Adverse events	40 (98)	23 (56)
SAEs	23 (56)	18 (44)
Fatal SAEs	0 (0.0)	0 (0.0)
AEs leading to discontinuation	3 (7)	3 (7)
AEs leading to dose adjustment/interruption	33 (81)	15 (37)

Source: Adapted from Novartis Analysis from Table HA1-Q14.1
Abbreviations: AE, adverse event; SAE, serious adverse event

Table 11-52. Analysis of Adverse Events by Age Group: 6 to <12 Years

	All Patients N=53	
Category	**All Grades n (%)**	**Grades 3-4 n (%)**
Adverse events	53(100)	20(55)
SAEs	21 (40)	16(30)
Fatal SAEs	0 (0.0)	0 (0.0)
AEs leading to discontinuation	3 (6)	1 (2.0)
AEs leading to dose adjustment/interruption	40 (76)	22(42)

Source: Adapted from Novartis Analysis from Table HA1-Q14.1
Abbreviations: AE, adverse event; SAE, serious adverse event

Table 11-53. Overview of Adverse Events by Age Group: 12 to <18 Years

	All Patients N=72	
Category	**All Grades n (%)**	**Grades 3-4 n (%)**
Adverse events	71 (99)	43 (60)
SAEs	32 (44)	23 (32)
Fatal SAEs	3 (4)	3 (4)
AEs leading to discontinuation	7 (10)	2 (3)
AEs leading to dose adjustment/interruption	50 (70)	26 (36)

Source: Adapted from Novartis Analysis from Table HA1-Q14.1
Abbreviations: AE, adverse event; SAE, serious adverse event

11.2.8 Specific Safety Studies/Clinical Trials

The Applicant's Position

No specific safety studies were performed to support this submission.

The FDA's Assessment

FDA agrees with the Applicant's statement and has no further comments.

11.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position

No carcinogenicity studies were conducted for this submission.

The FDA's Assessment

FDA agrees with the Applicant's statement and has no further comments.

Human Reproduction and Pregnancy

The Applicant's Position

No new pregnancy cases have been reported from the pivotal Study G2201 and supportive Studies A2102 and X2101. The information on pregnancy and lactation is adequately described in the label.

The FDA's Assessment

FDA agrees with the Applicant's statement. In Study G2201, women who were known to be pregnant or breast-feeding were excluded from the study; birth control measures during treatment and ongoing pregnancy screening were enforced to ensure that no fetus was exposed to study drugs. Therefore, no information on the use of dabrafenib and trametinib in pregnancy or lactation are available.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position

The safety topic "Growth and development, sexual maturity, and bone age" is discussed in Section 11.2.5.3.

The FDA's Assessment

The FDA agrees with the Applicant in Section 11.2.5 and notes that none of the patients had delayed onset of puberty. Tanner stage changes from lower at baseline to higher at post-baseline were very rare in the patients aged < 8 years. The growth plates were open at baseline and remained open throughout treatment for most patients, except when they closed at age-appropriate times. Results were similar in both cohorts of patients receiving D+T in Study G2201. While on treatment, most patients had normal progression through the stages of sexual maturation except for one patient in the D+T and two patients in the C+V group who were

identified with premature puberty. Of note, none of the patients had delayed onset of puberty through Month 24 of treatment on study.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position

Overdose: No new information about overdose has been generated in support of this application; recommendations are described in the approved prescribing information.

Drug abuse: No new information about abuse/dependence potential has been generated in support of this application. There is no known potential for abuse for dabrafenib and trametinib and no abuse studies have been performed.

Withdrawal and rebound: No new information about withdrawal and rebound has been generated in support of this application. No studies have been conducted to assess withdrawal and rebound effects.

The FDA's Assessment

FDA agrees with the Applicant's statement and has no further comments.

11.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position

The most recent Periodic safety update report (PSUR) for dabrafenib covered the period from 27-Aug-2020 to 26-Aug-2021. The most recent PSUR for trametinib covered the period from 30-May-2020 to 29-May-2021. The cumulative worldwide patient exposures of dabrafenib and trametinib since their individual first approval are estimated to be (b) (4) and (b) (4) patient treatment years, respectively.

The review of all new safety data and information obtained during the reporting interval of Tafinlar PSUR 27-Aug-2020 to 26-Aug-2021 and Mekinist PSUR 30-May-2020 to 29-May-2021 revealed no new safety signals. In the most recent PSUR of dabrafenib covering the period from 27-Aug-2020 to 26-Aug-2021, the important identified risk of 'new primary/secondary malignancies' and the missing information topics 'safety in patients with severe renal impairment' and 'safety in patients with moderate to severe hepatic impairment' were removed from the Risk Management Plan (RMP) as per PRAC endorsement. In the most recent PSUR of trametinib covering the period from 30-May-2020 to 29-May-2021, 'safety in children < 18 years old' is considered as an important potential risk due to lack of data up to the cut-off date. A summary of post-authorization off-label use of dabrafenib and trametinib in pediatric

patients has been presented in respective PSURs. Based on the available information in the PSURs for pediatric off-label use, the safety profile is similar to the safety profile in adults and no new safety signal has emerged. Malignant neoplasm progression and pyrexia were the most frequently reported SAEs in pediatric patients.

The assessment of the corresponding safety topic of interest in the most recent PSUR is consistent with assessment of the clinical study data. Dabrafenib and trametinib as monotherapy and combination treatment have an established safety profile. Toxicities are predictable and manageable with standard medical treatments. Based on available data for post-marketing usage of D+T in pediatric patients, no new or changing safety signal has emerged that would substantially alter the known safety profile in the intended indication setting.

The FDA's Assessment

There is postmarket experience with both dabrafenib and trametinib. Dabrafenib and trametinib are expected to be administered by oncologists; management of and monitoring for adverse effects of anti-cancer medications including potentially serious adverse effects is standard practice in oncology. The safety profile of these drugs is not expected to change with use in the intended indication.

Expectations on Safety in the Postmarket Setting

The Applicant's Position

Not applicable since there is already substantial postmarket experience with both drugs.

The FDA's Assessment

FDA agrees with the Applicant's statement and has no further comments.

11.2.11 Integrated Assessment of Safety

The Applicant's Position

In conclusion, combination therapy with D+T in pediatric patients with BRAF V600 mutation-positive glioma had a predictable and manageable safety profile that is consistent with previous observations in the adult population in approved indications. Additionally, combination therapy with D+T demonstrated favorable safety profile in the treatment of patients with BRAF V600 mutation-positive LGG in comparison to the chemotherapy (C+V) treatment.

The median exposure to D+T (> 1 year) in pooled pediatric population corresponds to the long-term clinical use in glioma patients. Pyrexia was the most commonly occurring AEs (>50%

incidence) with D+T, which was mostly manageable with temporary dose adjustments and supportive therapy.

In the pediatric patients, melanocytic nevi were observed at a relatively higher rate with dabrafenib monotherapy (22/85) than with D+T (7/171). Evaluation of possible long-term effects in the pediatric patients on growth and development, renal system, and ocular system, did not reveal any untoward safety concern.

The side effects that were observed are both clinically manageable and amenable to risk reduction through routine pharmacovigilance, patient education, and labelling. Long-term dosing (> 6 months) with liquid formulations can be achieved and allows for dose adjustments as needed for patient's growth over time without the need for changing formulation and corresponding to the expected clinical use.

The ADR profile in pediatric patients was generally consistent with that in adult patients. Weight gain was included as an additional ADR in the pediatric population.

Subgroup analysis by age did not reveal any notable differences in the safety profile of D+T between different age categories. There was no evidence of increased incidence of renal and urinary disorders AEs or ocular events (AEs in the eye disorders) in younger pediatric patients (< 6 years) relative to the older pediatric patients. No new safety signal was identified in patients below 6 years of age treated with D+T.

The FDA's Assessment

FDA agrees with the description of the safety database provided by the Applicant and refers to product labeling and FDA's analysis for specific incidences of adverse events.

FDA also agrees that weight gain is a new safety signal in pediatric patients treated with dabrafenib and trametinib and that it should be identified as a new adverse drug reaction.

The Applicant agreed to conduct comprehensive and integrated safety analyses from clinical studies that further characterize the potential serious risk of long-term adverse effects of dabrafenib in combination with trametinib on growth and development and to further assess the serious risks of new primary malignancies (cutaneous and non-cutaneous), cardiomyopathy, and ocular toxicities, in pediatric patients with BRAF V600E mutant low-grade glioma over a sufficient period of follow-up time. This postmarketing requirement is intended to provide additional safety information that is needed to support the safety of the product. Please refer to Section 17 regarding postmarketing requirements.

12 SUMMARY AND CONCLUSIONS

12.1 Statistical Issues

The FDA's Assessment

There were no major statistical issues identified during the review of this application.

The efficacy evaluation was based on the primary analysis in the ITT population from the LGG cohort of Study G2201, with a data cutoff (DCO) date of August 23, 2021. Per FDA's request, the Applicant submitted additional follow-up data to better characterize the durability of response as well as to provide updated efficacy results with respect to ORR, PFS, and DOR in the same cohorts, with a new DCO date of April 5, 2022. At the updated DCO, DOR and PFS were more mature, allowing for a more stable characterization of summary statistics, while the OS results remained the same with only one death overall in the carboplatin with vincristine arm. Given the patient population and natural history of pLGG, long-term survival follow-up may be required to observe definitive differences in OS, if any.

Discordance of BOR between independent review and investigator assessment was observed during the review. The reason for assessment discordance was not clear, but likely relates to challenges in response assessment in this tumor type. However, it is unlikely to significantly impact interpretation of the study results, particularly taking the totality of data into account including consistency of ORR between independent and investigator assessment. Details regarding FDA's review of this issue are discussed in the Section 11.1.2.

Due to the single-arm design of the supportive studies, time-to-event endpoints such as PFS and OS observed in those studies are considered not interpretable as there is no comparative arm. The reported results are considered descriptive only. In addition, results from subgroup analyses are considered exploratory and should be interpreted with caution, particularly those with small sample sizes.

Efficacy results based on a limited number of patients, such as DOR in the chemotherapy arm of LGG cohort from Study G2201, should also be interpreted with caution.

12.2 Conclusions and Recommendations

The FDA's Assessment

Based on the evaluation of clinical data from G2201, the review team recommends regular approval of dabrafenib in combination with trametinib for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. The FDA's recommendation is based on the favorable benefit:risk assessment for dabrafenib in combination with trametinib based on review of data from the LGG cohort of

Study G2201, an open-label, global, randomized study evaluating the effect of dabrafenib in combination with trametinib compared with chemotherapy (carboplatin in combination with vincristine) in children and adolescent patients with BRAF V600 mutation positive LGG who require systemic therapy.

Pediatric LGGs represent 30% of all childhood brain tumors with approximately 1600 new cases per year in the United States. For pediatric patients with LGG, overall survival is generally > 90%, though presence of a BRAFV 600E mutation is associated with a poorer outcome compared to patients with tumors without BRAF V600E mutations. Several chemotherapeutic regimens are commonly used for pediatric patients with LGG who require systemic treatment. Despite the generally good survival outcomes, many patients receiving therapy for pLGGs experience sequelae of their disease or treatment, which can include cognitive impairment or delay, endocrine deficiencies, secondary malignancies, and growth abnormalities. There are currently no FDA-approved therapies for pediatric patients with LGG with BRAF V600E mutation eligible for first systemic therapy.

FDA considers the improvement in ORR with demonstration of durable responses and improvement in PFS in patients treated with dabrafenib and trametinib compared to those treated with carboplatin and vincristine observed in Study G2201 to be clinically meaningful. The ORR of 47% (95% CI: 34.8, 58.6) determined by BICR, median DOR of 23.7 months (95% CI, 14.5, NE) based on the updated DCO, and improvement in PFS (median PFS 20.1 months [95% CI: 12.8, NE] vs. 7.4 months [95% CI 3.6, 11.8], HR 0.31 [95% CI: 0.18, 0.55], $p < 0.001$), observed in G2201 are sufficient to establish substantial evidence of effectiveness. The Applicant will submit the results of the final analysis of PFS and OS in the LGG cohort of Study G2201, to be performed when all patients have been followed for at least 2 years, as a post-marketing commitment.

Supportive data for the combination therapy in pediatric patients with LGG was provided from children and adolescents with cancers harboring V600E mutation enrolled in Study CTMT212X2101, a dose-finding and activity-estimating trial of trametinib as a single agent or in combination with dabrafenib, and from Study CDRB436A2102, a study of dabrafenib as a single agent in pediatric patients with BRAF V600-positive tumors, including gliomas. Results from the respective single agent cohorts, demonstrating a lower ORR (trametinib as a single agent) and shorter DOR (dabrafenib as a single agent) in these studies are supportive of the need for dual BRAF/MEK inhibition in patients with BRAF V600E mutant LGG. Further strong mechanistic support for dual BRAF/MEK inhibition is derived from a substantial amount of prior scientific evidence in patients with BRAF V600E-driven tumors, including from clinical trials leading to multiple FDA approvals, notably in children 6 years and older and adults with BRAF V600E mutant advanced solid tumors (tissue agnostic indication).

The safety findings in G2201 are generally consistent with the known safety profile of dabrafenib in combination with trametinib observed in the oncology setting. A new safety signal for weight gain was observed in pediatric patients. Overall, dabrafenib in combination

with trametinib appears to have an acceptable safety profile in patients with pLGG. However, additional information including long-term data on growth and development in pediatric patients is needed given the anticipated need for long-term treatment; this information will be provided as a postmarketing requirement. Additional safety data from pediatric patients treated with dabrafenib and trametinib will also be submitted as a post-marketing requirement to further characterize the incidence of known serious risks of dabrafenib in combination with trametinib (including new primary malignancies, cardiomyopathy, and ocular toxicities) in pediatric patients. The Applicant agreed to a post-marketing commitment for the submission of a companion diagnostic to support selection of pediatric patients with LGG with BRAF V600E mutation for treatment with dabrafenib and trametinib.

In conclusion, the benefit:risk assessment for dabrafenib in combination with trametinib is favorable, and FDA recommends regular approval of dabrafenib in combination with trametinib for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

X X

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13 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. The application was discussed with international regulatory participants through Project ORBIS during the review period.

14 Pediatrics

The Applicant's Position

All relevant information from the pediatric population is presented in prior sections.

The FDA's Assessment

Evidence for the use of dabrafenib and trametinib in combination for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy is provided in this NDA. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients. The product for this application does not contain a new ingredient and is not subject to the provisions of FDARA. Given the product's orphan drug designation for this indication, the application is exempt from the requirements of PREA.

15 Labeling Recommendations

The Applicant's Position

Not applicable; refer to FDA assessment.

The FDA's Assessment

The proposed labeling submitted by the Applicant required extensive revision by FDA. 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 changes.

Table 15-1. Summary of Significant Labeling Changes for TAFINLAR

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Highlights	Section updated in alignment with the individual changes described below	Revised to reflect the text in the Full Prescribing Information.
1. Indication and Usage	New indication added: "BRAF V600E Mutation-Positive Low-Grade Glioma"	1.7 BRAF V600E Mutation-Positive Low-Grade Glioma TAFINLAR is indicated, in combination with trametinib, for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy *[see Dosage and Administration (2.1)].*
2. Dose and Administration	(b) (4)	Table 2 added recommended dosage for TAFINLAR for oral solution. Administration instructions for oral solution added to Section 2.3 Dosage Reductions for oral solution added to Section 2.4.
3. Dosage forms and Strengths	(b) (4)	Dosage form: TAFINLAR Tablets for Oral Suspension
5 Warnings and Precautions	No revisions proposed.	FDA separated the safety pools into Adult and Pediatric, and provided the incidences of each Warning by age group to best represent the safety for providers based on the indicated population.
6. Adverse Reactions	(b) (4)	The sponsor proposed to pool the safety of Study CDRB436G2201 (G2201) and Study CTMT212X2101 (X2101). Pooled adult and pediatric safety data was included in Section 5. Section 6 presents the safety data for each indication separately for clarity.

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
8. Use in Specific Populations	Pediatric Use section updated to include safety and efficacy data in pediatric patients from Study G2201	8.4 Pediatric Use section revised to state that safety and efficacy have been established for each approved pediatric indication, therefore the text was revised to specify the indication and the approved age group.
11. Description	Added liquid formulation description.	Inactive ingredients listed in alphabetical order.
12. Pharmacokinetics	Pharmacokinetic information on pediatric population added.	Section 12.3 was revised to remove ambiguous language and to include the median time to achieve peak plasma concentrations.
14. Clinical Studies	Efficacy results of adult studies G2201 added	New paragraph added to 14.6 BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors to provide the overall response rate from a single-arm cohort in Study CDRB436G2201 (G2201) – High-Grade Glioma Cohort. 14.7 Low-Grade Glioma Cohort text and table revised to remove (b) (4) [redacted] Section 14 is reserved for statistically tested and clinically relevant data.
Medication guide	Updated to reflect the new indication, age range and safety event of weight increase.	Text revised for consistency with Patient Labeling practice.
Instructions for Use	Added new instructions for use for dabrafenib 10 mg dispersible tablet for oral suspension (DT)	Text revised for consistency with Division of Medical Errors team practice and results of Human Factors study.

Table 15-2. Summary of Significant Labeling Changes for MEKINIST

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Highlights	Section updated in alignment with the individual changes described below	Revised to reflect the text in the Full Prescribing Information.
1 Indication and Usage	New indication added: "BRAF V600E Mutation-Positive Low-Grade Glioma"	1.6 BRAF V600E Mutation-Positive Low-Grade Glioma MEKINIST is indicated, in combination with dabrafenib, for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy *[see Dosage and Administration (2.1)].*
2. Dose and administration	(b) (4)	Table 2 added recommended dosage for MEKINIST for oral solution. Administration instructions for oral solution added to Section 2.3 Dosage Reductions for oral solution added to Section 2.4.
3. Dosage forms and Strengths		MEKINIST oral solution added.
5 Warnings and Precautions	No revisions proposed.	FDA separated the safety pools into Adult and Pediatric, and provided the incidences of each Warning by age group to best represent the safety for providers based on the indicated population.
6 Adverse reactions	(b) (4)	The sponsor proposed to pool the safety of Study CDRB436G2201 (G2201) and Study CTMT212X2101 (X2101). Pooled adult and pediatric safety data was included in Section 5. Section 6 presents the safety data for each indication separately for clarity.

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
8 Use in Specific population	Pediatric Use section updated to include safety and efficacy data in pediatric patients from Study G2201 (b) (4)	8.4 Pediatric Use section revised to state that safety and efficacy have been established for each approved pediatric indication, therefore the text was revised to specify the indication and the approved age group.
11. Description	Added liquid formulation description.	Inactive ingredients listed in alphabetical order.
12. Pharmacokinetics	Pharmacokinetic information on pediatric population added.	Section 12.3 was revised to remove ambiguous language and to include the median time to achieve peak plasma concentrations.
14 Clinical Studies	Efficacy results of adult studies G2201 added	New paragraph added to 14.6 BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors to provide the overall response rate from a single-arm cohort in Study CDRB436G2201 (G2201) – High-Grade Glioma Cohort. 14.7 Low-Grade Glioma Cohort text and table revised to remove (b) (4) ection 14 is reserved for statistically tested and clinically relevant data.
Medication guide	Updated to reflect the new indication, age range and safety event of weight.	Text revised for consistency with Patient Labeling practice.
Instructions for Use	Added new instructions for use for trametinib 4.7 mg powder for oral solution (PfOS)	Text revised for consistency with Division of Medical Errors team practice and results of Human Factors study.

Abbreviations: ADR, adverse drug reaction; BRAF, B-Raf proto-oncogene, serine/threonine kinase

The FDA's Assessment

After careful review and negotiation, the revised labeling has been agreed upon to convey adequate information for the safe and effective use of MEKINIST in combination with TAFINLAR.

16 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment

The risks of dabrafenib in combination with trametinib are acceptable in the indicated patient population with a serious and potentially life-threatening condition; the safe use of dabrafenib in combination with trametinib can be adequately implemented in the postmarketing setting through instructions contained in product labeling and routine pharmacovigilance. No additional risk management strategies are recommended.

17 Postmarketing Requirements and Commitment

The FDA's Assessment

NDAs 217513 and 217514 are intended to fulfill PMR 4298-2 for TAFINLAR (NDA 202806) and PMR 4297-2 for MEKINIST (NDA 204114), issued with the approval of the tissue agnostic indication, by providing an age-appropriate pediatric formulation. PMR 4297-3 and 4298-3, also issued with the approval of the tissue agnostic indication for dabrafenib and trametinib, required the conduct of Study G2201 to confirm safety and efficacy in pediatric patients with glioma one year of age and above. FDA considers that the applications adequately address PMRs 4298-2,4297-2, 4298-3 and 4297-3.

Two PMRs and three PMCs were deemed necessary for each product to ensure the safe and effective use of dabrafenib in combination with trametinib for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. The following post-marketing requirements/commitments, reviewed and agreed to by the Applicant, will be included in the action letter for NDAs 217513/217514:

FDA PMR #1 (TAFINLAR and MEKINIST)

Conduct an integrated safety analyses from clinical studies that further characterize the potential serious risk of long-term adverse effects including but not limited to growth plate abnormalities of dabrafenib in combination with trametinib on growth and development 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 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.

Draft Protocol Submission (Analysis Plan): 09/2023

Final Protocol Submission (Analysis Plan): 12/2023

Trial Completion: 11/2026

Final Report Submission: 05/2027

FDA PMR #2 (TAFINLAR and MEKINIST)

Conduct comprehensive safety analyses from ongoing trials to further assess the serious risks of dabrafenib in combination with trametinib, including but not limited to new primary malignancies (cutaneous and non-cutaneous), cardiomyopathy, and ocular toxicities, in pediatric patients with BRAFV600E mutant low-grade glioma over a sufficient period of follow-up time to further characterize these risks. The report should include appropriate monitoring and risk mitigation strategies.

Draft Protocol Submission (Analysis Plan): 09/2023

Final Protocol Submission (Analysis Plan): 12/2023

Study Completion: 11/2026
Final Report Submission: 05/2027

FDA PMC #1 (TAFINLAR and MEKINIST)

Complete Study CDRB436G2201, entitled “Phase II open-label global study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive Low Grade Glioma (LGG) or relapsed or refractory High Grade Glioma (HGG)”, and provide the final analysis for overall survival (OS) and progression free survival once all patients with LGG have been followed for at least 2 years. Include an analysis of change in visual acuity over the course of treatment with dabrafenib and trametinib for patients who enrolled on the study due to impaired vision.

Draft Protocol Submission (Analysis Plan): 03/2023

Final Protocol Submission (Analysis Plan): 04/2023

Study Completion: 04/2023

Final Report Submission: 10/2023

FDA PMC #2- MEKINIST

Conduct a food effect study to evaluate the impact of food on exposure of dabrafenib tablets for oral suspension per FDA food effect guidance titled “Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry.”

Draft Protocol Submission: 03/2023

Final Protocol Submission:	05/2023
Study Completion:	12/2023
Final Report Submission:	06/2024

FDA PMC #2- TAFINLAR

Conduct a food effect study to evaluate the impact of food on exposure of trametinib for oral solution per FDA food effect guidance titled "Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry."

Draft Protocol Submission:	03/2023
Final Protocol Submission:	05/2023
Study Completion:	12/2023
Final Report Submission:	06/2024

FDA PMC #3 (TAFINLAR and MEKINIST)

Commitment to support the availability of an in vitro diagnostic device, 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 dabrafenib in combination with trametinib (D+T) for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

Final Report Submission:	02/2025

18 Division Director (DHOT) (NME ONLY)

X

19 Division Director (OCP)

X

20 Division Director (OB)

X

21 Division Director (Clinical)

X

Nicole Drezner, MD

22 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 _____

23 Appendices

23.1 References

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23.2 Financial Disclosure

The Applicant's Position

As pre-agreed with FDA, studies G2201, A2102, and X2101 are considered covered by the "Financial Disclosure for Clinical Investigators" rule. All investigators were assessed for equity interest, significant payments, proprietary interest, and other compensation.

No investigators from studies had financial arrangements or interests to disclose.

The FDA's Assessment:

FDA agrees with the Applicant's position. No investigators from the studies supporting safety and effectiveness for this application had financial arrangements or interests to disclose that were significant conflicts with the study conduct.

Covered Clinical Study (Name and/or Number):* CDRB436G2201

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 578		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
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: NA Significant payments of other sorts: NA Proprietary interest in the product tested held by investigator: NA Significant equity interest held by investigator in study: NA Sponsor of covered study: NA		
Is an attachment provided with details of the disclosable financial interests/arrangements: NA	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: NA	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) NA		
Is an attachment provided with the reason: NA	Yes ☐	No ☐ (Request explanation from Applicant)

* The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number):* DRB436A2102

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 265		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
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: NA Significant payments of other sorts: NA Proprietary interest in the product tested held by investigator: NA Significant equity interest held by investigator in study: NA Sponsor of covered study: GSK and Novartis		
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) NA		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

* The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number):* CTMT212X2101

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 253		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

* The table above should be filled by the applicant, and confirmed/edited by the FDA.

23.3 Nonclinical Pharmacology/Toxicology

The Applicant's Position

No new information is provided in the current submission.

The FDA's Assessment

Not applicable

23.4 OCP Appendices (Technical Documents Supporting OCP Recommendations)

23.4.1 Population PK Analysis

Table 23-1. Population PK Summary Table for Dabrafenib

General Information		
Objectives of PPK analysis		Characterize the population pharmacokinetics of dabrafenib in pediatric patients. Support dose recommendation of liquid formulations of dabrafenib in combination with trametinib in pediatric patients.
Study included		CDRB436A2102 (BRF116013), CTMT212X2101 (MEK116540), CDRB436G2201 (Table 23-2)
Dose(s) included		Figure 23-1
Population included		243 Patients
Population characteristics	General	Age median: 11 (range: 1 – 17) year Weight median: 38.7 (range: 7.8 – 155.6) kg 122 (50.2%) male
	Organ impairment	NA
	Pediatrics (if any)	105 patients: 12 years or older 77 patients: 6-11 years of age 61 patients: <1 to 5 years of age
No. of patients, PK samples, and BLQ		243 Subjects, 2185 PK observations 31 (1.4%) BLQ samples
Covariates evaluated	Static	Body weight on apparent central volume, total apparent clearance, and apparent intercompartmental clearance. Combination with trametinib on apparent maximum inducible clearance at steady state. Liquid formulations on relative bioavailability, apparent maximum inducible clearance at steady state. Sex on total apparent clearance. Age on total apparent clearance and central volume of distribution.
	Time-varying	NA

Final Model	Summary	Acceptability [FDA's Comments]
Software and version	NONMEM (Version 7.3)	Acceptable
Model structure	A two-compartment model with a delayed 1st order absorption (Alag1, Ka) and an inducible elimination (CL/F) that consists of a base clearance (constant over time, CL_0/F) and a dose- and time-dependent inducible clearance (CL_{ind}/F).	Acceptable
Model parameter estimates	Table 23-3	Acceptable
Uncertainty and variability (RSE, IIV, shrinkage, bootstrap)	Table 23-3	Acceptable
BLQ for parameter accuracy	BLQ samples were ignored in population PK analysis	Acceptable due to low number of BLQ samples
GOF, VPC	The goodness-of-fit plots of the dabrafenib final population pharmacokinetic model for pediatric patients are shown in Figure 23-2 and Figure 23-3. VPCs for dabrafenib concentrations in pediatric patients show good agreement between simulated and observed data in Figure 23-4.	Acceptable
Significant covariates and clinical relevance	Sex and weight are significant covariates on the CL/F. Weight is also a significant covariate on the central volume (Vc/F) and intercompartmental clearance (Q/F). Combination of trametinib and formulations are significant covariates on $CL_{ind,ss}$/F. Figure 23-5 - Figure 23-7	Acceptable

Abbreviations: BLQ, below the limit of quantification; GOF, goodness-of-fit; NA, not applicable; PK, pharmacokinetics; PPK, population pharmacokinetics; VPC, visual predictive check

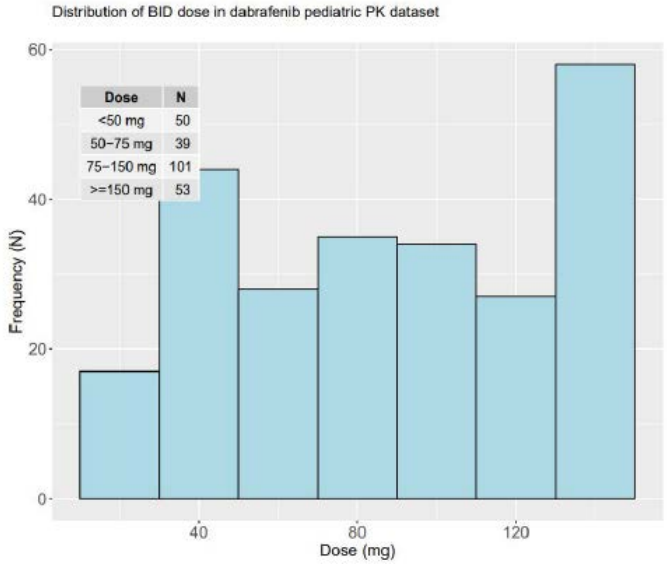
Table 23-2. Summary of Studies and Data Included in the Population Pharmacokinetic Analysis

Study	Design	Population (with available PK)	Analytes	PK sampling schedule*
CDRB436A2102 (BRF116013)	dabrafenib monotherapy Part 1: dose escalation N=27 Part 2: tumor specific expansion (N=58)	N=85 with 22 patients in the age range <1 to 5 years, 28 who are 6-11 years old, and 35 who are 12 years of age or older	Dabrafenib and its metabolites	D1: 0.5, 2, 4 h after dose D15: pre-dose, 0.5, 1, 2, 3, 4, 6, 8 h after dose
CTMT212X2101 (MEK116540)	Part A: trametinib dose escalation (N ~ 50) Part B: tumor specific expansion with trametinib alone (N ~ 40) Part C: limited dose escalation with dabrafenib+ trametinib combination (N ~ 18) Part D: expansion with dabrafenib+ trametinib combination (N ~ 20 with LGG and 10 with LCH)	N=133, with 21 subjects who are 12 years of age or older receiving trametinib alone, 28 subjects between 6 and 11 years old receiving trametinib alone, and 37 subjects in the age range <1 to 5 receiving trametinib alone; 17 who are 12 years or older receiving combination, 15 between 6 and 11 years old receiving combination, and 15 in the age range <1 to 5 receiving combination	dabrafenib and its metabolites, trametinib	D1: 0.5, 2, 4 h after dose D15: pre-dose, 0.5, 1, 2, 3, 4, 6, 8 h after dose D22: pre-dose
CDRB436G2201	dabrafenib+trametinib combination (LGG ~ 73, HGG~41);	N=111; 53 older than 12 years, N=34 between 6 and 11 years old, and N=24 between 1 and 5 years old	dabrafenib and its metabolites, trametinib	D1: 0.5, 2, 4 h after dose D15: pre-dose, 0.5, 1, 2, 3, 4, 6, 8 h after dose D22: pre-dose

*: The most detailed schedule is listed when multiple schedules were present in the design.

Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 17, Table 5-2
Abbreviations: h, hour(s); LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; PK, pharmacokinetics

Figure 23-1. Distribution of BID Doses in Pediatric Patients Treated With Dabrafenib



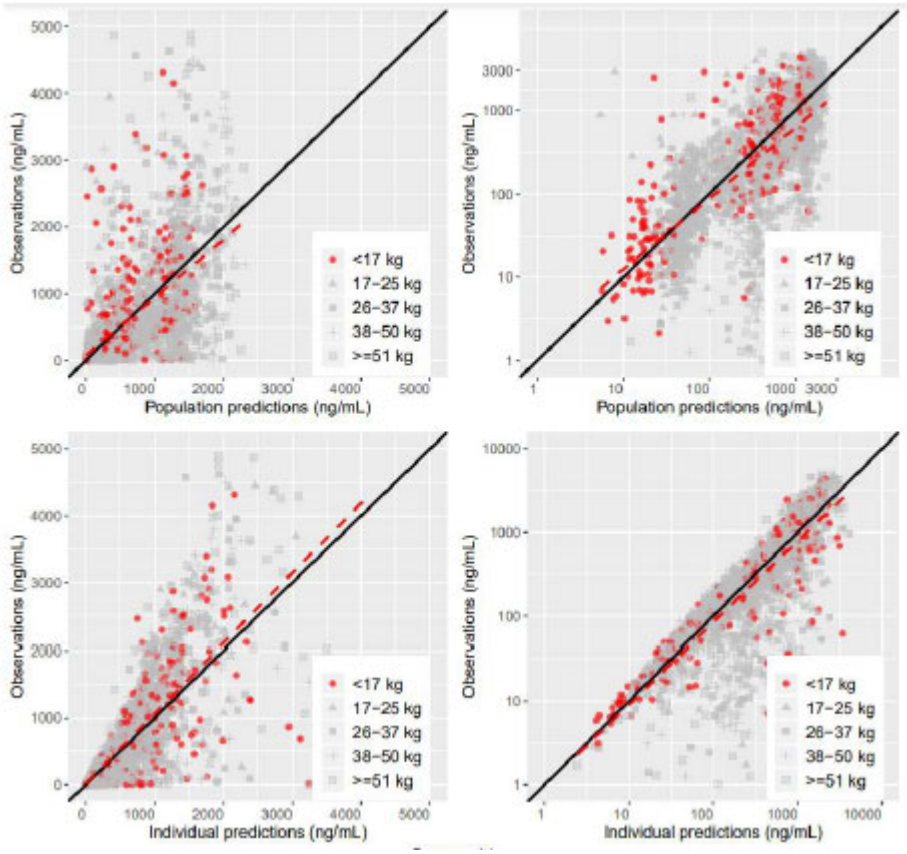
Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 38, Figure 7-4.
Abbreviations: BID, twice a day

Table 23-3. Dabrafenib Parameter Posteriors Updated by the Final Population PK *M*odel

Parameter Name	Mean	SD	Naive SE	Time-series SE	2.5%	25%	50%	75%	97.5%	Effective N	95% Confidence Interval	Null value
Vp (L)	190.57	Fixed	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CLbase (L/h)	11.022	0.921	0.004	0.032	9.244	10.399	11.006	11.631	12.84	827	(9.244 - 12.84)	NA
Vc (L)	57.463	4.02	0.019	0.114	49.784	54.727	57.39	60.104	65.657	1257	(49.784 - 65.657)	NA
Q (L/h)	5.175	0.652	0.003	0.018	4.013	4.721	5.132	5.589	6.559	1379	(4.013 - 6.559)	NA
KA (1/h)	1.312	0.091	0	0.003	1.145	1.249	1.308	1.373	1.501	1140	(1.145 - 1.501)	NA
ALAG1 (h)	0.412	0.002	0	0	0.408	0.411	0.412	0.413	0.415	2269	(0.408 - 0.415)	NA
CLindmax (L/h)	26.177	1.579	0.007	0.039	23.197	25.095	26.14	27.199	29.446	1634	(23.197 - 29.446)	NA
Alpha (-)	1.014	0.01	0	0	0.994	1.007	1.014	1.021	1.033	6726	(0.994 - 1.033)	NA
T50 (h)	97.858	17.319	0.082	0.383	65.999	85.662	97.015	109.181	133.576	2051	(65.999 - 133.576)	NA
WT_CL (-)	0.307	0.047	0	0.001	0.215	0.275	0.306	0.338	0.398	1200	(0.215 - 0.398)	0
WT_Q (-)	1.185	0.118	0.001	0.003	0.954	1.105	1.184	1.265	1.414	1342	(0.954 - 1.414)	0
WT_Vc (-)	0.917	0.073	0	0.002	0.771	0.868	0.918	0.967	1.059	1286	(0.771 - 1.059)	0
SEX_CL (-)	0.935	0.029	0	0.001	0.878	0.916	0.935	0.955	0.993	1466	(0.878 - 0.993)	1
Combo_CLind (-)	0.855	0.047	0	0.001	0.768	0.822	0.854	0.886	0.952	1562	(0.768 - 0.952)	1
Form1_CLind (-)	0.992	0.075	0	0.002	0.853	0.94	0.989	1.041	1.148	2056	(0.853 - 1.148) #	1
Form2_CLind (-)	0.934	0.068	0	0.002	0.809	0.886	0.931	0.978	1.075	1669	(0.809 - 1.075) #	1
ω^2_{CL}	0.545	0.076	0	0.001	0.413	0.492	0.539	0.592	0.709	2833	(0.413 - 0.709)	NA
ω^2_{Vc}	0.287	0.046	0	0.001	0.205	0.255	0.284	0.316	0.384	2012	(0.205 - 0.384)	NA
$\omega_{CL}\omega_{Vc}$	0.184	0.035	0	0.001	0.123	0.159	0.182	0.206	0.262	1302	(0.123 - 0.262)	NA
ω^2_{Q}	0.597	0.096	0	0.001	0.429	0.528	0.59	0.656	0.804	4807	(0.429 - 0.804)	NA
ω^2_{Ka}	1.269	0.17	0.001	0.002	0.974	1.149	1.256	1.375	1.638	6783	(0.974 - 1.638)	NA
SIGMA.1.1.	0.327	0.014	0	0	0.301	0.318	0.327	0.337	0.356	10979	(0.301 - 0.356)	NA
MCMCOBJ	24754.226	89.224	0.421	2.368	24580.471	24693.792	24753.692	24814.144	24930.592	1467	(24580.471 - 24930.592)	NA
Model#	runA2_2											

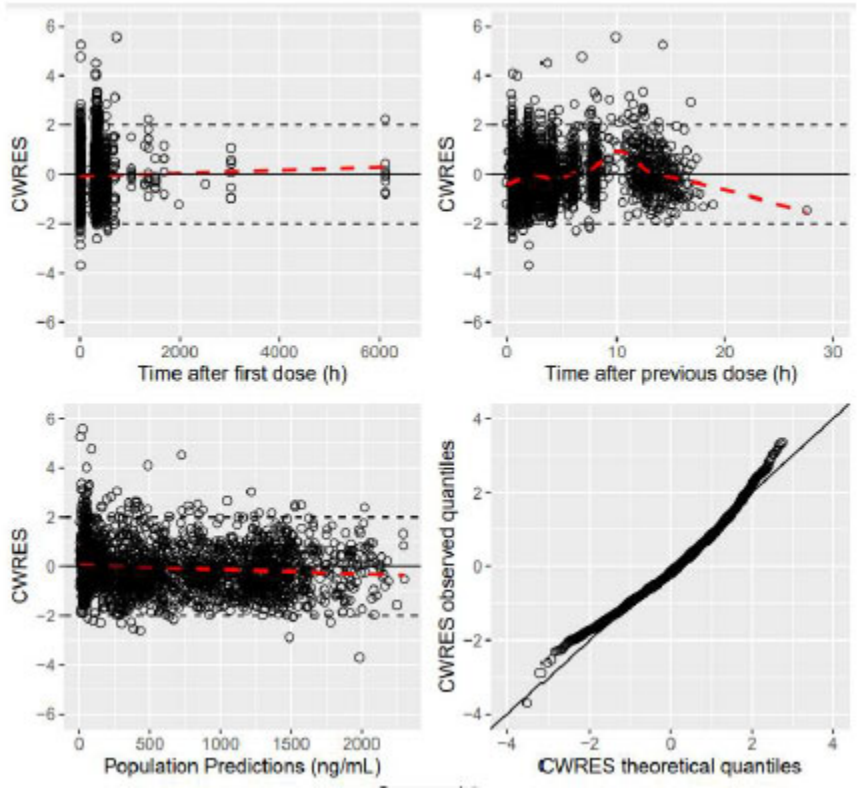
Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 52-53, Table 7-10.
Abbreviations: ALAG1, absorption lag-time; CL, clearance; KA, absorption rate constant; NA, not applicable; PK, pharmacokinetics; Q, organ blood flow; SD, standard deviation; SE, standard error; T50, time required to release 50% of drug; Vc, volume of the central compartment; Vp, volume of the peripheral compartment; WT, weight

Figure 23-2. Observed vs. Population Prediction and Individual Prediction of Dabrafenib PK With Weight Distributions Overlaid



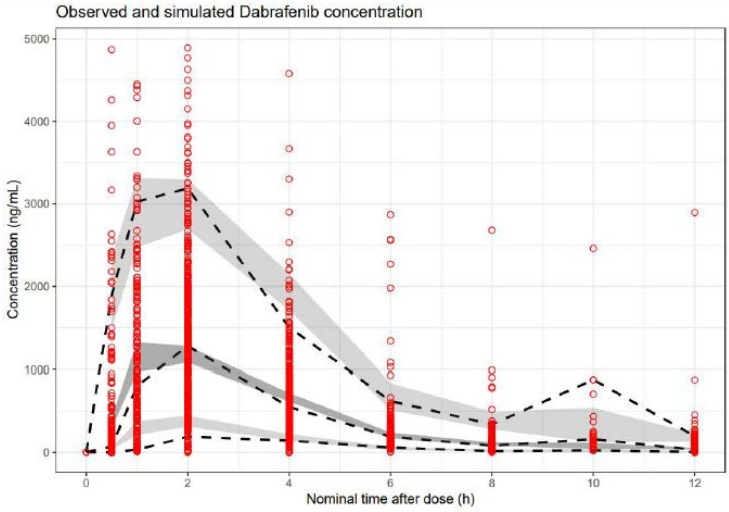
Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 61, Figure 7-16.
Abbreviations: PK, pharmacokinetics

Figure 23-3. Residual Based Diagnostics of Dabrafenib Population PK Model



Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 61, Figure 7-17.
Abbreviations: CWRES, conditional weighted residuals; h, hour; PK, pharmacokinetics

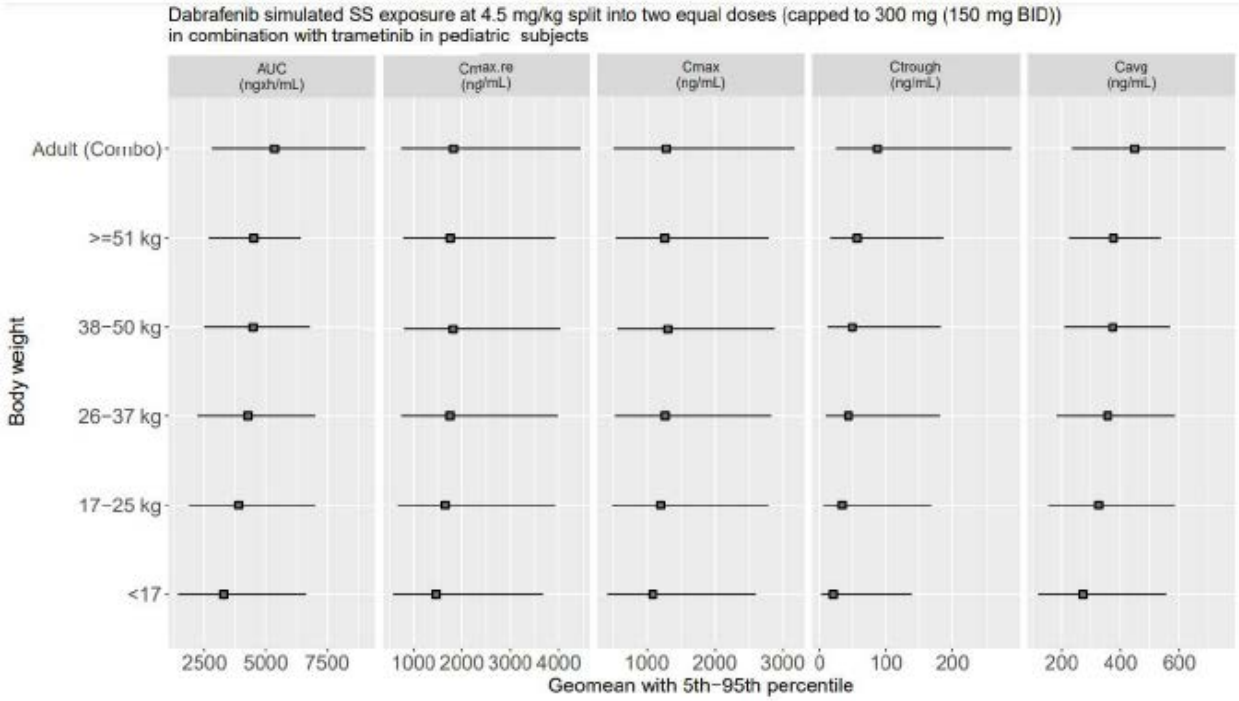
Figure 23-4. Visual Predictive Checks of Dabrafenib Concentration in Pediatric Patients



Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 62, Figure 7-18.

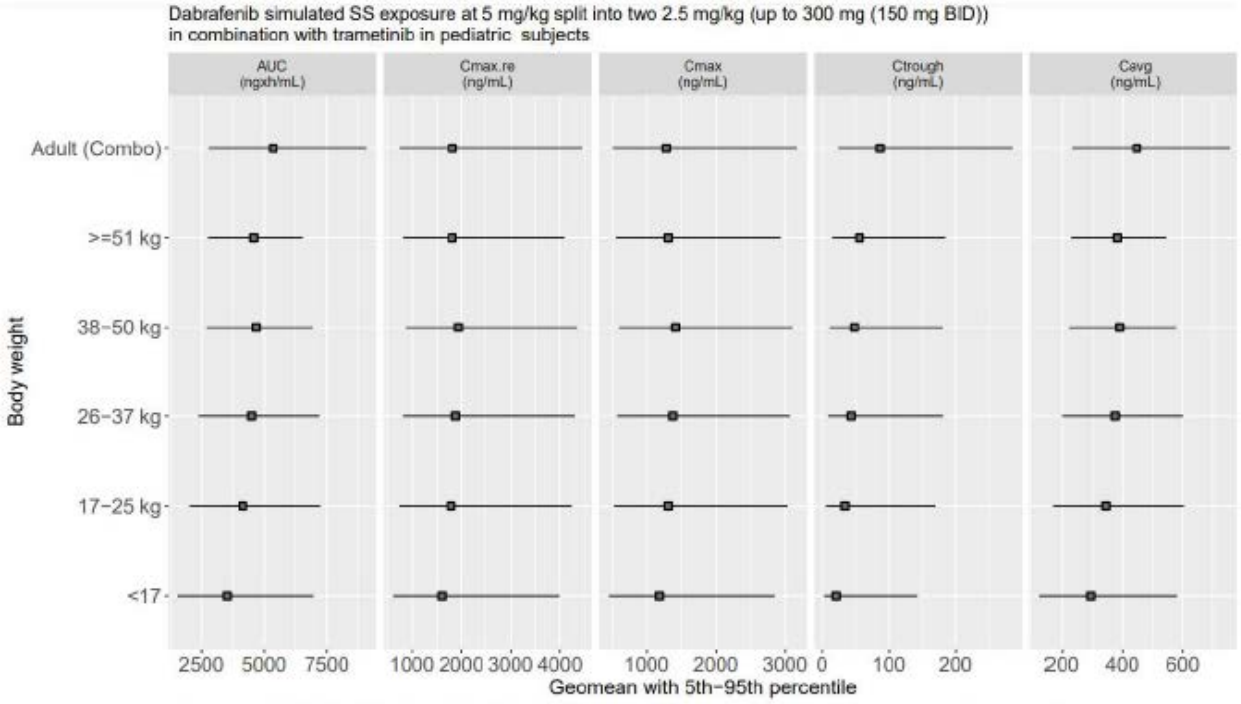
Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Figure 23-5. Model-Predicted Dabrafenib Exposure at 4.5 mg/kg Capped at 300 mg QD in Combination With Trametinib



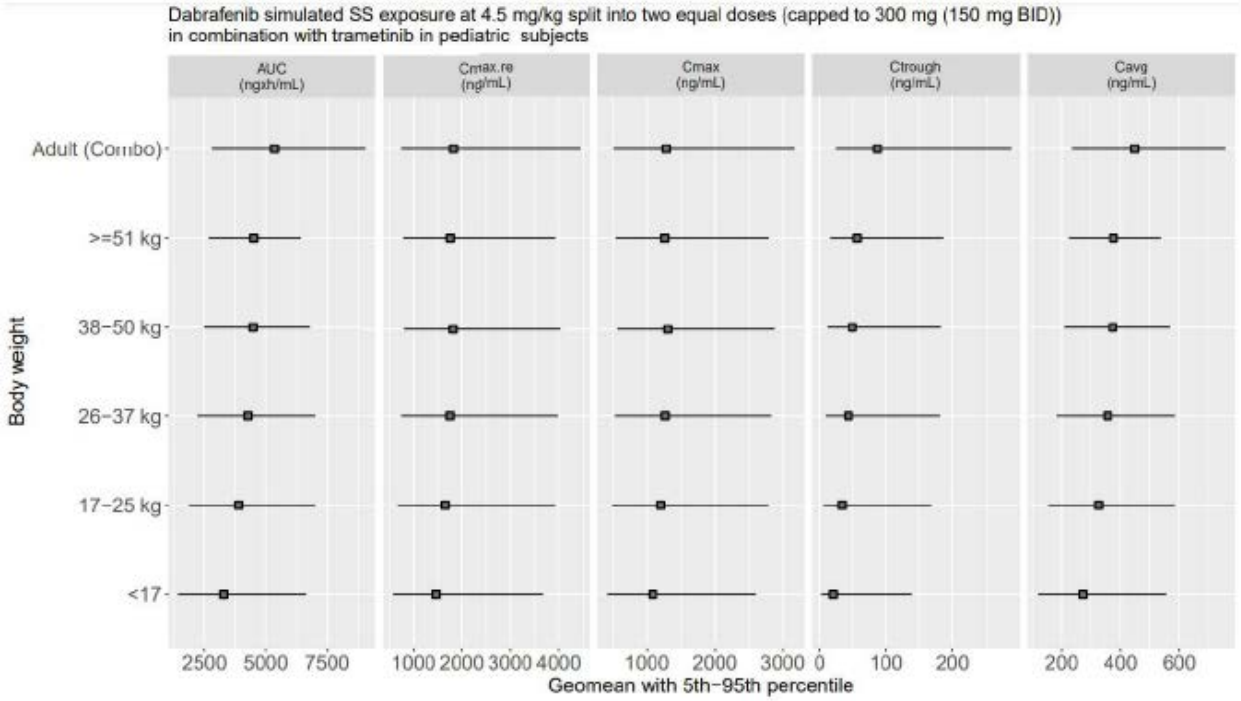
Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 83, Figure 7-29.
Abbreviations: BID, twice a day; QD, once a day; SS, steady state

Figure 23-6. Model-Predicted Dabrafenib Exposure at 5 mg/kg Capped at 300 mg QD in Combination With Trametinib



Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 85, Figure 7-30.
Abbreviations: BID, twice a day; QD, once a day

Figure 23-7. Model-Predicted Dabrafenib Exposure at 5.25 mg/kg Capped at 300 mg QD in Combination With Trametinib



Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 86, Figure 7-31.
Abbreviations: BID, twice a day; QD, once a day

Table 23-4. Population PK Summary Table for Trametinib

General Information		
Objectives of PPK analysis		Characterize the population pharmacokinetics of trametinib in <1-17-year-old patients. Support dose recommendation of liquid formulations of trametinib in combination with dabrafenib in <1-17-year-old patients.
Study included		CTMT212X2101 (MEK116540), CDRB436G2201 (Table 23-5)
Dose(s) included		Figure 23-8
Population included		244 patients
Population characteristics	General	Age median: 9 (range: 1 – 17) year Weight median: 32.9 (range: 6.1 – 155.6) kg 119 (48.8%) male
	Organ impairment	NA
	Pediatrics (if any)	91 patients: 12 years or older 77 patients: 6-11 years of age 76 patients: <1 to 5 years of age

General Information		
No. of patients, PK samples, and BLQ		244 Patients, 1943 PK observations 16 (0.8%) BLQ samples
Covariates evaluated	Static	Body weight on apparent central and peripheral volume, total apparent clearance, and apparent intercompartmental Clearance. Combination with dabrafenib on relative bioavailability Sex on apparent clearance Formulation on relatively bioavailability, absorption rate constant Ka2.
	Time-varying	NA

Final Model	**Summary**	**Acceptability [FDA's Comments]**
Software and version	NONMEM (Version 7.3)	Acceptable
Model structure	Two-compartment model with dual sequential 1st order absorption (Ka1, Ka2) and 1st order elimination (CL/F).	Acceptable
Model parameter estimates	Table 23-6	Acceptable
Uncertainty and variability (RSE, IIV, shrinkage, bootstrap)	Table 23-6	Acceptable
BLQ for parameter accuracy	BLQ samples were ignored in population PK analysis	Acceptable due to low of BLQ samples
GOF, VPC	The goodness-of-fit plots of the dabrafenib final population pharmacokinetic model for pediatric patients are shown in Figure 23-9 and Figure 23-10. VPCs for dabrafenib concentrations in pediatric patients show good agreement between simulated and observed data in Figure 23-11.	Acceptable
Significant covariates and clinical relevance	Sex and weight are significant covariates on CL/F, and weight is also a significant covariate on Q/F. Combination of dabrafenib, is a covariate on the relative bioavailability of trametinib. Formulation is a covariate on Ka2. Figure 23-12- Figure 23-15	Acceptable

Abbreviations: BLQ, below the limit of quantification; GOF, goodness-of-fit; IIV, interindividual variability; PK, pharmacokinetics; RSE, relative standard error; VPC, visual predictive check

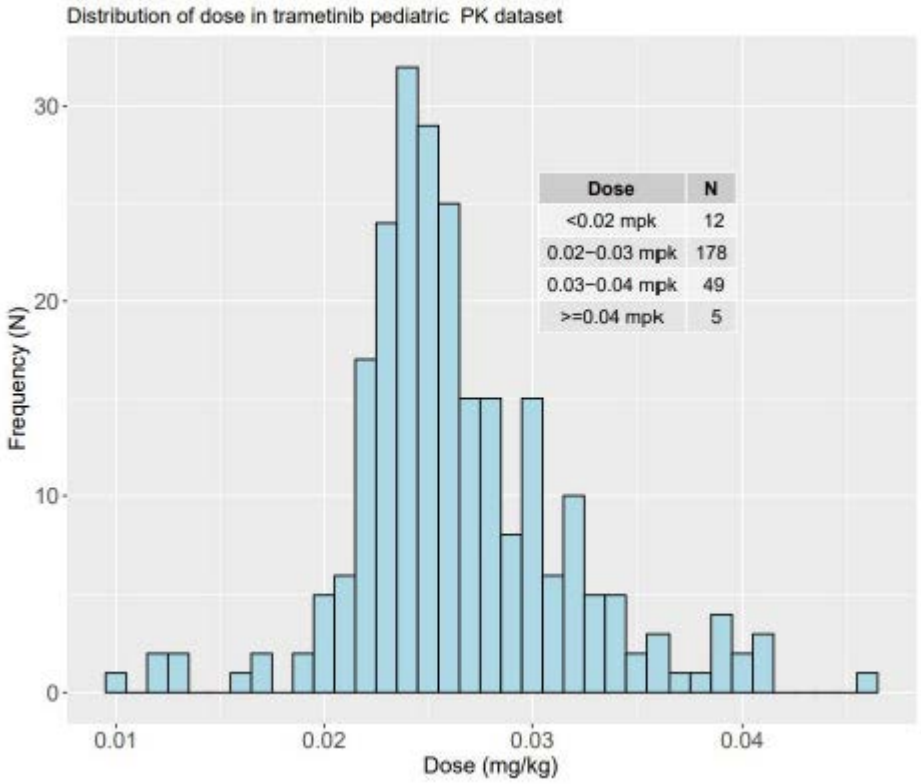
Table 23-5. Summary of Studies and Data Included in the Population Pharmacokinetic Analysis

Study	Design	Population (with available PK)	Analytes	PK sampling schedule*
CDRB436A2102 (BRF116013)	dabrafenib monotherapy Part 1: dose escalation N=27 Part 2: tumor specific expansion (N=58)	N=85 with 22 patients in the age range <1 to 5 years, 28 who are 6-11 years old, and 35 who are 12 years of age or older	Dabrafenib and its metabolites	D1: 0.5, 2, 4 h after dose D15: pre-dose, 0.5, 1, 2, 3, 4, 6, 8 h after dose
CTMT212X2101 (MEK116540)	Part A: trametinib dose escalation (N ~ 50) Part B: tumor specific expansion with trametinib alone (N ~ 40) Part C: limited dose escalation with dabrafenib+ trametinib combination (N ~ 18) Part D: expansion with dabrafenib+ trametinib combination (N ~ 20 with LGG and 10 with LCH)	N=133, with 21 subjects who are 12 years of age or older receiving trametinib alone, 28 subjects between 6 and 11 years old receiving trametinib alone, and 37 subjects in the age range <1 to 5 receiving trametinib alone; 17 who are 12 years or older receiving combination, 15 between 6 and 11 years old receiving combination, and 15 in the age range <1 to 5 receiving combination	dabrafenib and its metabolites, trametinib	D1: 0.5, 2, 4 h after dose D15: pre-dose, 0.5, 1, 2, 3, 4, 6, 8 h after dose D22: pre-dose
CDRB436G2201	dabrafenib+trametinib combination (LGG ~ 73, HGG~41);	N=111; 53 older than 12 years, N=34 between 6 and 11 years old, and N=24 between 1 and 5 years old	dabrafenib and its metabolites, trametinib	D1: 0.5, 2, 4 h after dose D15: pre-dose, 0.5, 1, 2, 3, 4, 6, 8 h after dose D22: pre-dose

*: The most detailed schedule is listed when multiple schedules were present in the design.

Source: PopPK of trametinib and dabrafenib in pediatric patients modeling report, Page 17, Table 5-2.
Abbreviations: HGG, high-grade glioma; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; PK, pharmacokinetics

Figure 23-8. Distribution of Dose in Pediatric Patients Treated With Trametinib



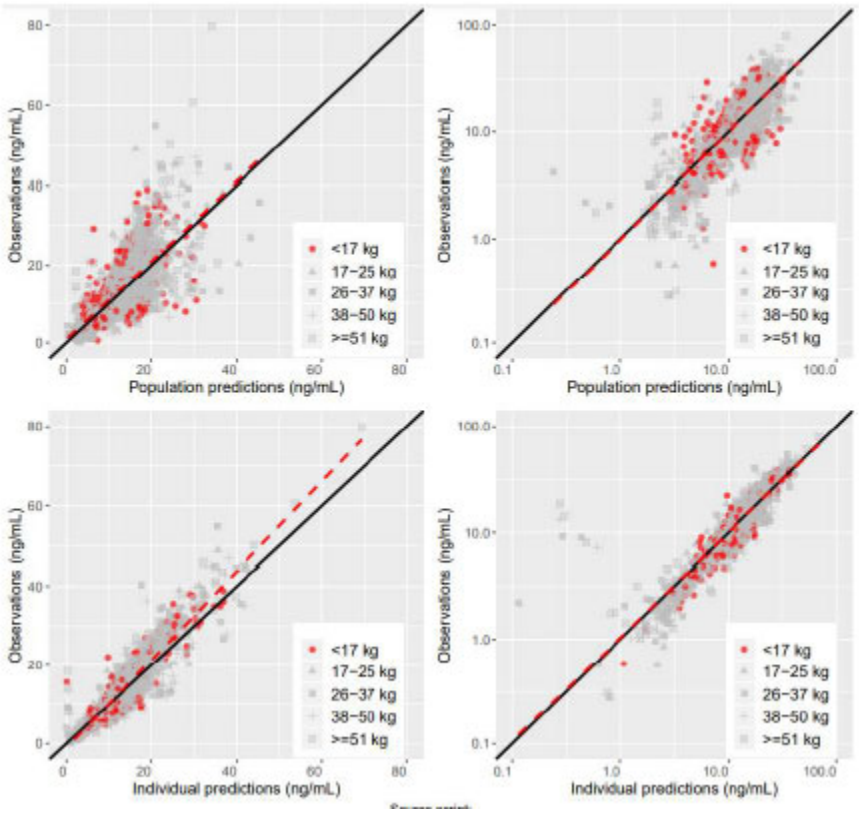
Source: PopPK of trametinib and dabrafenib in pediatric patients modeling report, Page 42, Figure 7-8.
Abbreviations: PK, pharmacokinetics

Table 23-6. Trametinib Parameter Posteriors Updated by the Final Population PK Model

Parameter Name	Mean	SD	Naive SE	Time-series SE	2.5%	25%	50%	75%	97.5%	Effective N	95% Confidence Interval	Null value
Q (L/h)	60	Fixed	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
M (-)	0.1	Fixed	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CL (L/h)	5.212	0.288	0.001	0.009	4.661	5.016	5.205	5.401	5.788	947	(4.661 - 5.788)	NA
VC (L)	118.285	19.676	0.093	0.655	81.746	104.519	117.485	131.601	158.281	918	(81.746 - 158.281)	NA
VP (L)	371.939	41.173	0.194	1.192	294.231	343.535	370.634	398.929	455.501	1198	(294.231 - 455.501)	NA
KA1 (1/h)	0.026	0.005	0	0	0.018	0.022	0.025	0.028	0.037	584	(0.018 - 0.037)	NA
KA2 (1/h)	1.432	0.251	0.001	0.008	0.993	1.255	1.414	1.59	1.96	1019	(0.993 - 1.96)	NA
MTIME (h)	0.372	0.028	0	0.001	0.316	0.353	0.373	0.391	0.425	447	(0.316 - 0.425)	NA
WT_CL (-)	0.472	0.039	0	0.001	0.393	0.446	0.472	0.498	0.548	1014	(0.393 - 0.548)	0
WT_Q (-)	0.586	0.113	0.001	0.004	0.366	0.511	0.585	0.662	0.807	1059	(0.366 - 0.807)	0
SEX_CL (-)	0.862	0.033	0	0.001	0.798	0.84	0.862	0.885	0.929	1258	(0.798 - 0.929)	1
Combo_F1 (-)	0.721	0.028	0	0.001	0.666	0.702	0.721	0.74	0.778	961	(0.666 - 0.778)	1
Form1_F1(-)	1.234	0.052	0	0.002	1.135	1.198	1.232	1.269	1.338	1066	(1.135 - 1.338)	1
WT_VC (-)	0.966	0.137	0.001	0.004	0.704	0.873	0.963	1.055	1.248	947	(0.704 - 1.248)	0
WT_VP (-)	0.995	0.093	0	0.003	0.809	0.932	0.996	1.059	1.17	1191	(0.809 - 1.17)	0
Form1_KA2 (-)	2.232	0.3	0.001	0.007	1.67	2.023	2.223	2.434	2.837	1858	(1.67 - 2.837)	1
ω^2_{CL}	0.038	0.008	0	0	0.023	0.032	0.037	0.043	0.056	1182	(0.023 - 0.056)	NA
$\omega_{CL}\omega_{Vc}$	0.095	0.023	0	0.001	0.054	0.079	0.093	0.109	0.144	1321	(0.054 - 0.144)	NA
ω^2_{Vc}	0.522	0.109	0.001	0.003	0.347	0.446	0.51	0.585	0.772	1465	(0.347 - 0.772)	NA
ω^2_Q	0.54	0.147	0.001	0.004	0.306	0.434	0.522	0.625	0.875	1548	(0.306 - 0.875)	NA
$\omega^2_{V_p}$	0.059	0.037	0	0.002	0.011	0.029	0.051	0.082	0.145	260	(0.011 - 0.145)	NA
$\omega^2_{K_{A_1}}$	0.618	0.196	0.001	0.008	0.33	0.48	0.586	0.723	1.084	572	(0.33 - 1.084)	NA
$\omega^2_{K_{A_2}}$	0.04	0.034	0	0.002	0.009	0.019	0.03	0.049	0.137	249	(0.009 - 0.137)	NA
ω^2_{MTIME}	0.146	0.056	0	0.002	0.063	0.106	0.137	0.176	0.28	813	(0.063 - 0.28)	NA
SIGMA.1.1.	0.049	0.002	0	0	0.044	0.047	0.049	0.05	0.053	3722	(0.044 - 0.053)	NA
MCMCOBJ	-5007.743	242.911	1.145	12.184	-5478.655	-5173.792	-5009.893	-4845.836	-4520.511	398	(-5478.655 - -4520.511)	NA
Model# runA13												

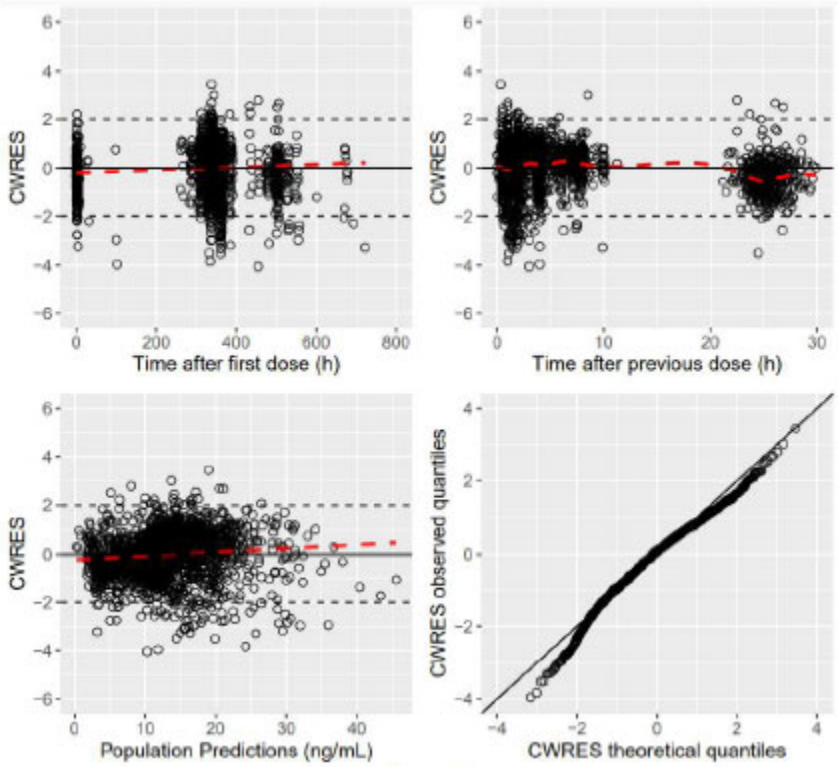
Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 71-72, Table 7-15.
Abbreviations: PK, pharmacokinetics; SD, standard deviation; SE, standard error

Figure 23-9. Observed vs. Population Prediction and Individual Prediction of Trametinib PK With Weight Distributions Overlaid



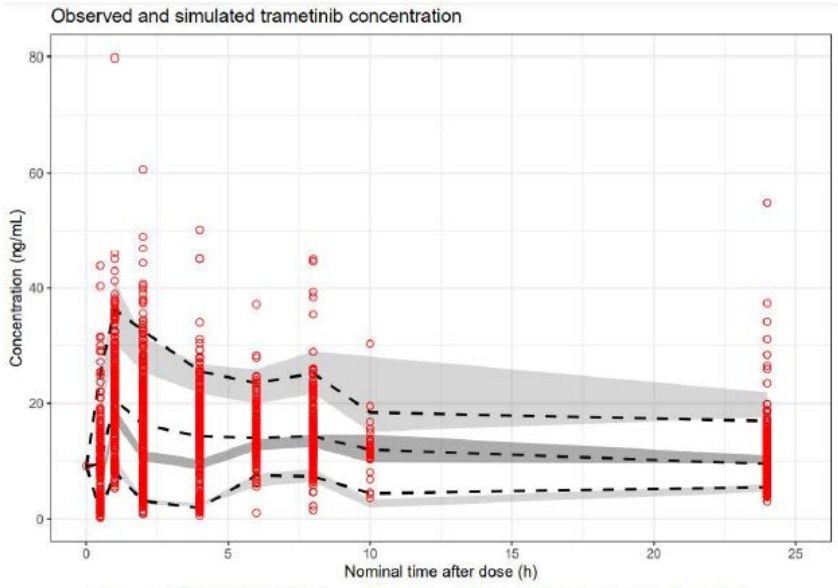
Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 80, Figure 7-26.
Abbreviations: PK, pharmacokinetics

Figure 23-10. Residual Based Diagnostics of Trametinib Population PK *M*odel



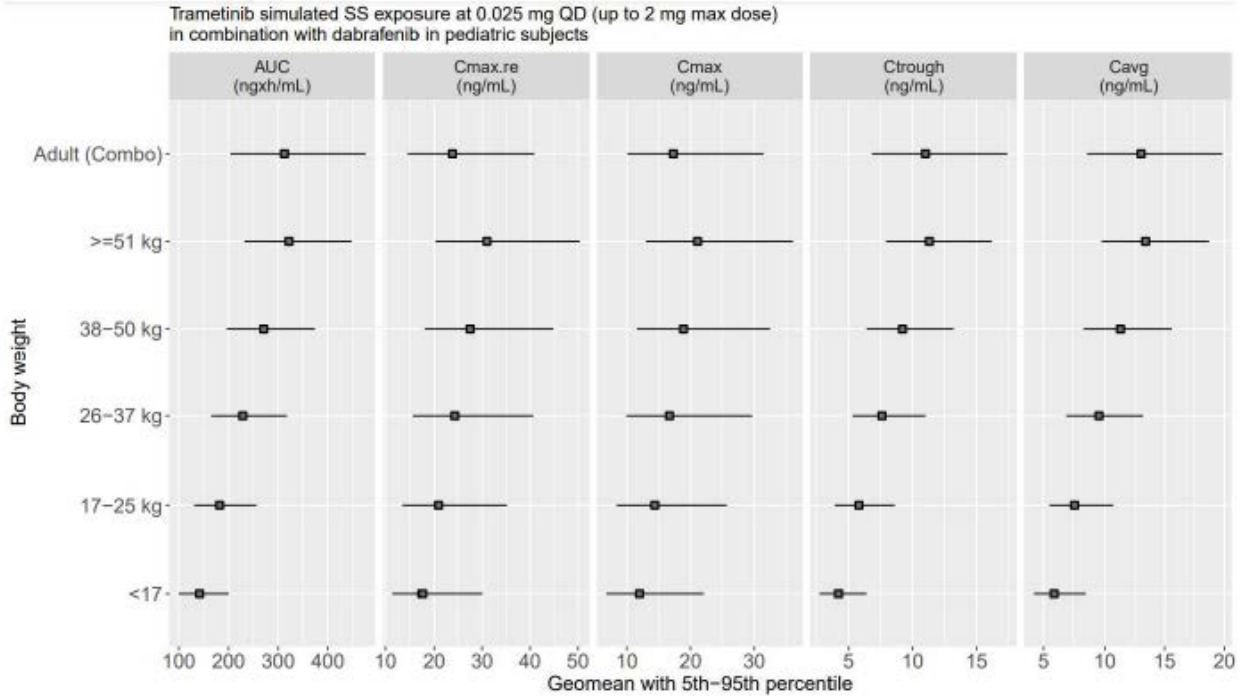
Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 80, Figure 7-27.
Abbreviations: PK, pharmacokinetics

Figure 23-11. Visual Predictive Checks of Trametinib Concentration in Pediatric Patients



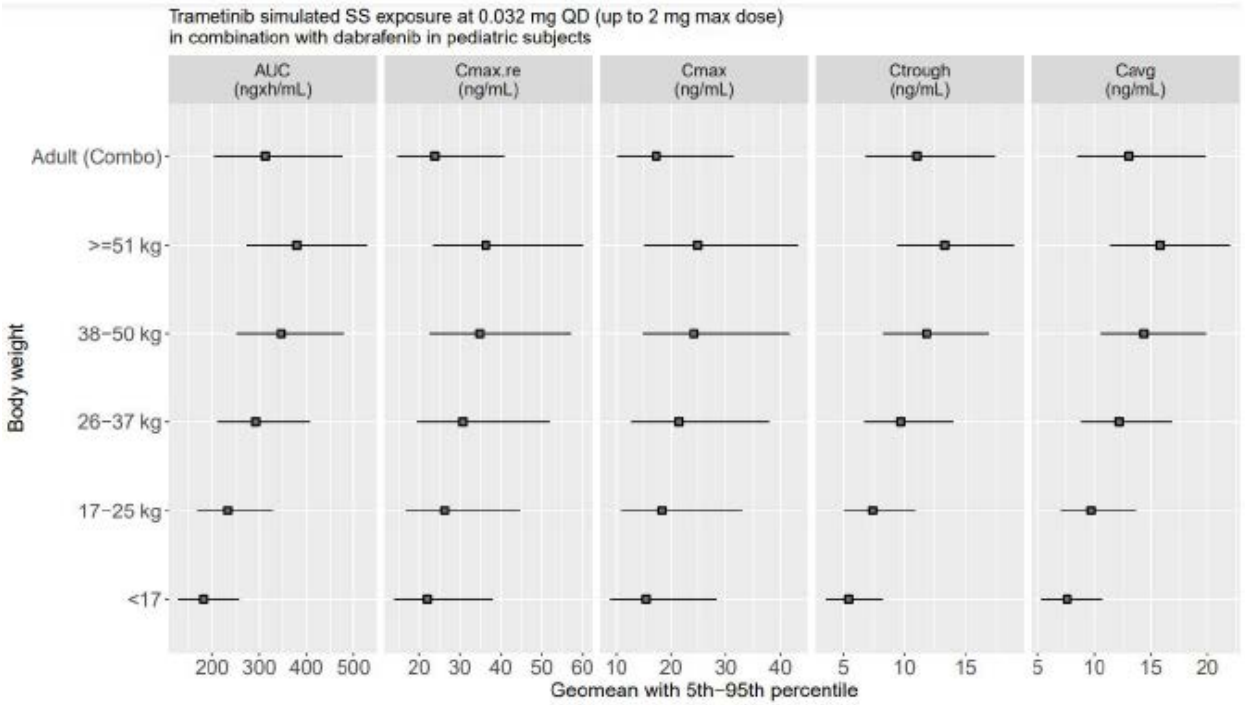
Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 81, Figure 7-28.

Figure 23-12. Model-Predicted Trametinib Exposure at 0.025 mg/kg Capped at 2 mg QD in Combination With Dabrafenib



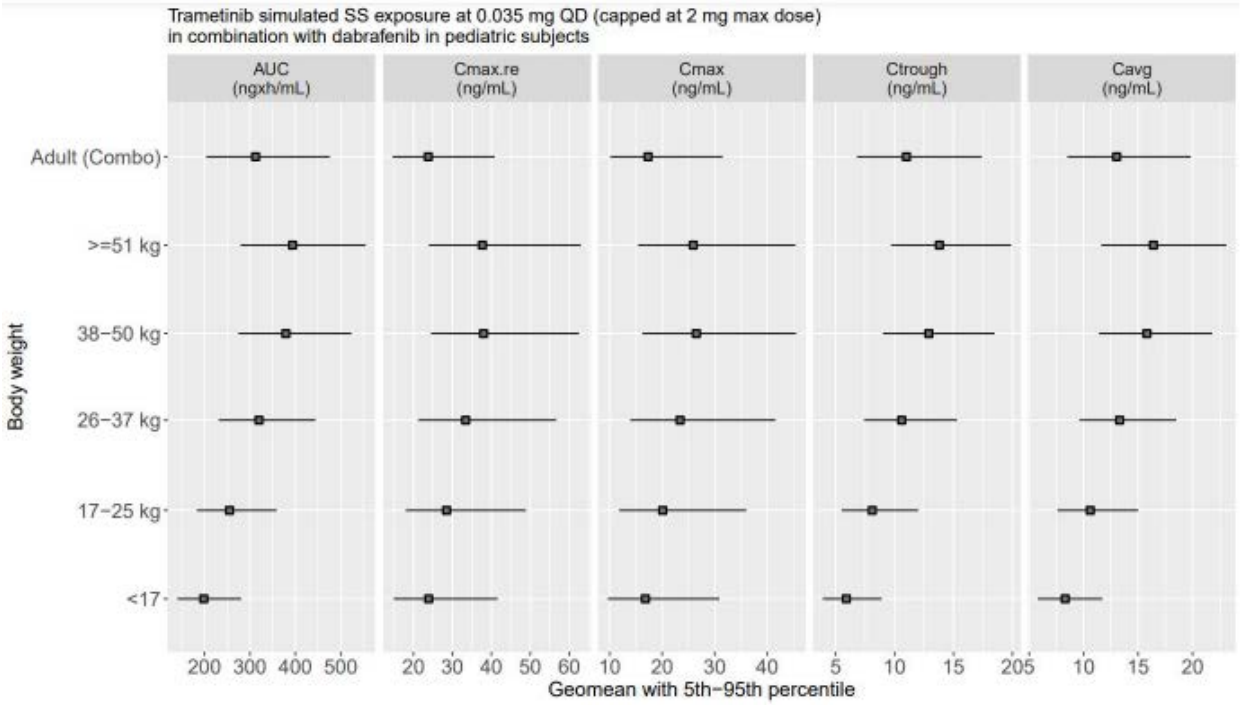
Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 88, Figure 7-32.
Abbreviations: QD, once a day

Figure 23-13. Model-Predicted Trametinib Exposure at 0.032 mg/kg Capped at 2 mg QD in Combination With Dabrafenib



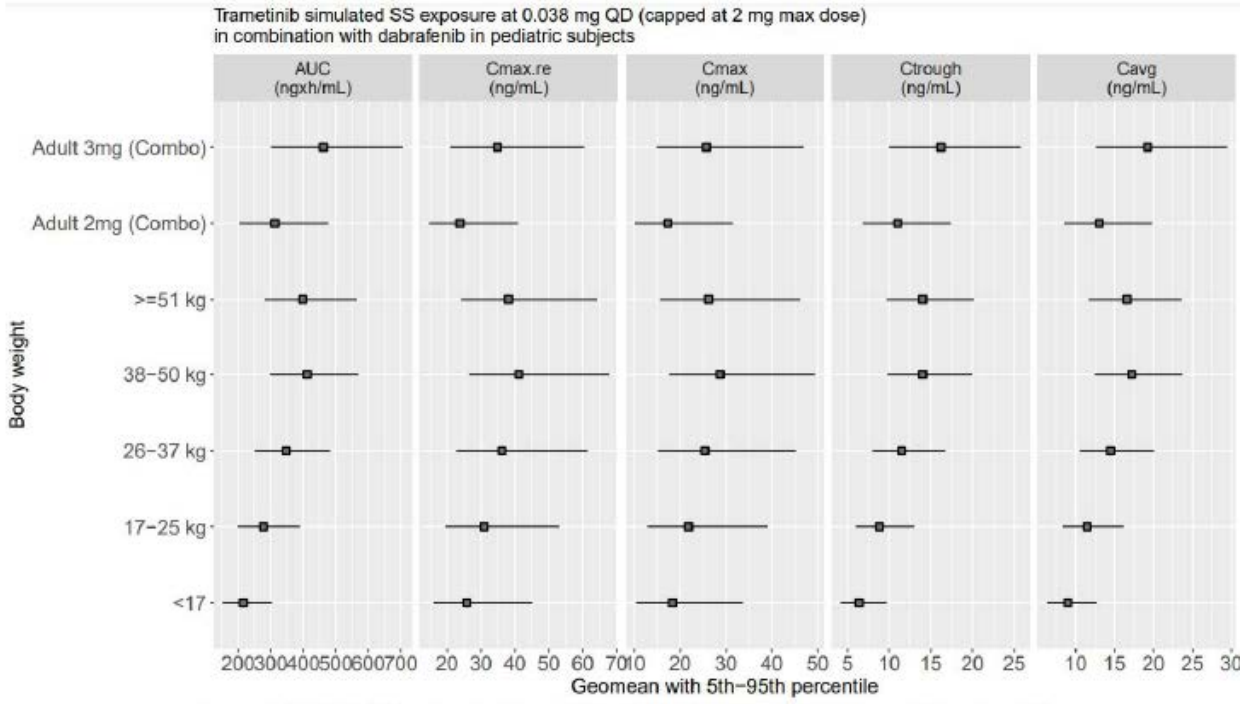
Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 89, Figure 7-33.
Abbreviations: QD, once a day

Figure 23-14. Model-Predicted Trametinib Exposure at 0.035 mg/kg Capped at 2 mg QD in Combination With Dabrafenib



Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 90, Figure 7-34.
Abbreviations: QD, once a day

Figure 23-15. Model-Predicted Trametinib Exposure at 0.038 mg/kg Capped at 2 mg QD in Combination With Dabrafenib

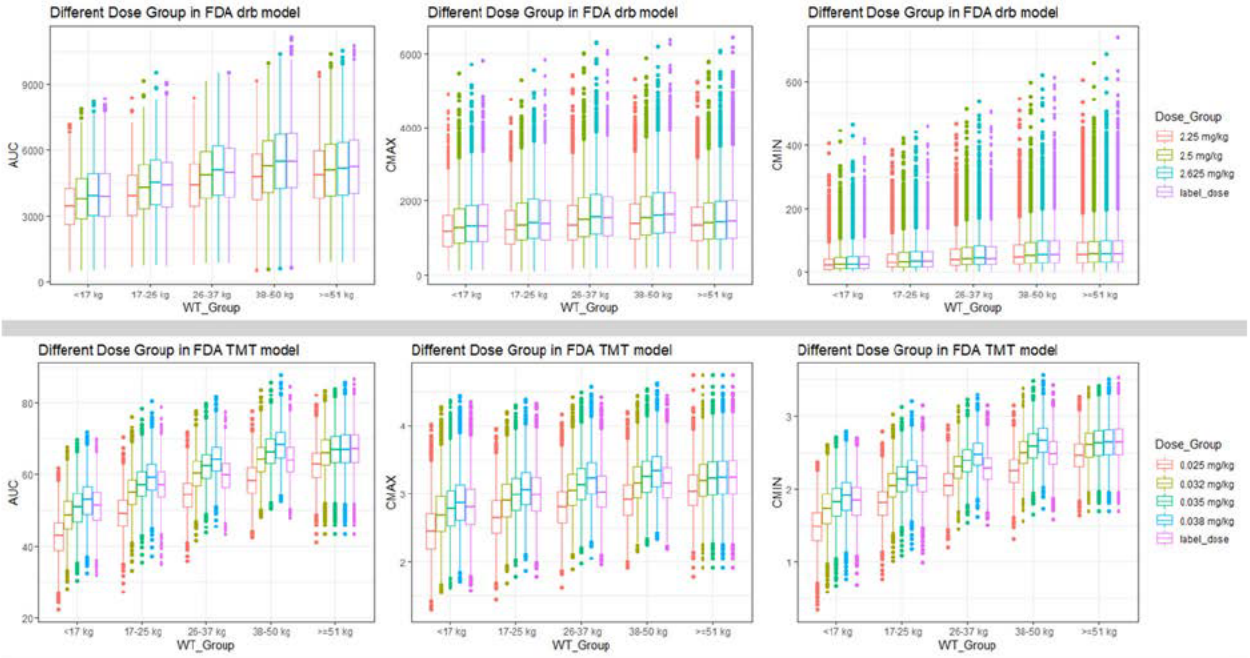


Source: PopPK of dabrafenib and trametinib in pediatric patients modeling report, Page 91, Figure 7-35.
Abbreviations: QD, once a day

The FDA's Assessment

The result of population PK analysis for dabrafenib and trametinib in pediatric patients were checked by the reviewer. The results were generally acceptable based on the agreement between prediction and observation. The dabrafenib and trametinib exposures with proposed dose in label were simulated with their final population PK model by the reviewer to compare with the simulated exposure under body weight-based dosing regimen in pediatric patients. The results were presented in Figure 23-16 which showed that the steady state exposures of dabrafenib and trametinib in combination at proposed pediatric dosages were consistent with applicant's simulation results and generally within the range of the adults' exposures at the recommended flat dosages. Slightly lower exposures were observed in pediatric patients with body weight lower than 17 kg.

Figure 23-16. Model-Predicted Dabrafenib and Trametinib With Different Doses



Source: Reviewer's analysis

23.4.2 Exposure-Response Analysis for Efficacy

Table 23-7. ER Efficacy Summary Table

General Information			
Goal of ER analysis		Explore the relationships between dabrafenib and trametinib plasma exposures and efficacy in pediatric patients	
Study Included		CDRB436G2201	
Endpoint		Primary: ORR Secondary: PFS	
No. of patients		111	
Population Characteristics (Table 23-8)	General	Age median: 11 (range: 1 - 17) years Weight median: 40.5 (range: 8 -156) kg 47 (42.3%) male Race: 77 (69.4%) White 16 (14.4%) Asian 9 (8.1%) Other or unknown	
	Pediatrics (if any)	111 patients	
Exposure metrics explored (range)		Dabrafenib: $C_{predose}$: 4.44 – 876 ng/mL C_{avg}: 73.5 – 715 ng/mL Trametinib: $C_{predose}$: 4.22 – 19.5 ng/mL C_{avg}: 2.3 -16.8 ng/mL	
Covariates Evaluated		NA	
Final Model Parameters		**Summary**	**Acceptability [FDA's Comments]**
Model structure		ORR: Logistic regression models PFS: Cox regression	**Acceptable**
Model parameter estimates		Table 23-9 and Table 23-10	Acceptable
Covariates and clinical relevance		NA	
Visualization of E-R relationships		Figure 23-17 and Figure 23-18	Acceptable

Abbreviations: ER, exposure-response; ORR, overall response rate; PFS, progression-free survival

Table 23-8. Demographics and Baseline Characteristics in Exposure Response Analysis Dataset

Demographic variable	All subjects N=150	PK/Efficacy set N=111	PK/Safety set N=147
Study -n (%)			
CDRB436G2201	114 (76.0)	111 (100)	111 (75.5)
CTMT212X2101	36 (24.0)	0	36 (24.5)
Age (years)			
n	150	111	147
Mean (SD)	10.3 (4.85)	10.3 (4.95)	10.3 (4.85)
Median	11.0	11.0	11.0
Min-Max	1-17	1-17	1-17
Age category -n (%)			
<6 years	32 (21.3)	24 (21.6)	31 (21.1)
>=6 years	118 (78.7)	87 (78.4)	116 (78.9)
Sex -n (%)			
Female	85 (56.7)	64 (57.7)	82 (55.8)
Male	65 (43.3)	47 (42.3)	65 (44.2)
Race -n (%)			
White	107 (71.3)	77 (69.4)	104 (70.7)
Asian	19 (12.7)	16 (14.4)	19 (12.9)
Unknown	9 (6.0)	9 (8.1)	9 (6.1)
Not Collected	5 (3.3)	0	5 (3.4)
Black or African American	4 (2.7)	3 (2.7)	4 (2.7)
Other	3 (2.0)	3 (2.7)	3 (2.0)
Missing	3 (2.0)	3 (2.7)	3 (2.0)
Weight (kg)			
n	150	111	147
Mean (SD)	45.7 (26.55)	45.9 (26.96)	46.0 (26.65)
Median	41.4	40.5	41.4
Min-Max	8-156	8-156	8-156
Karnofsky/Lansky Performance Score -n (%)			
< 80	12 (8.0)	11 (9.9)	12 (8.2)
>= 80	137 (91.3)	99 (89.2)	134 (91.2)
Missing	1 (0.7)	1 (0.9)	1 (0.7)
Baseline sum of products of lesion diameters (mm^2)			
n	147	111	144
Mean (SD)	1308.3 (1140.29)	1128.3 (1008.94)	1313.6 (1149.44)
Median	936.0	780.0	935.5
Min-Max	54-5298	54-5040	54-5298
Glioma grade -n (%)			
LGG	109 (72.7)	70 (63.1)	106 (72.1)
HGG	41 (27.3)	41 (36.9)	41 (27.9)
Tumor enhancement at baseline -n (%)			
Yes	81 (54.0)	79 (71.2)	79 (53.7)
No	33 (22.0)	32 (28.8)	32 (21.8)
Missing	36 (24.0)	0	36 (24.5)

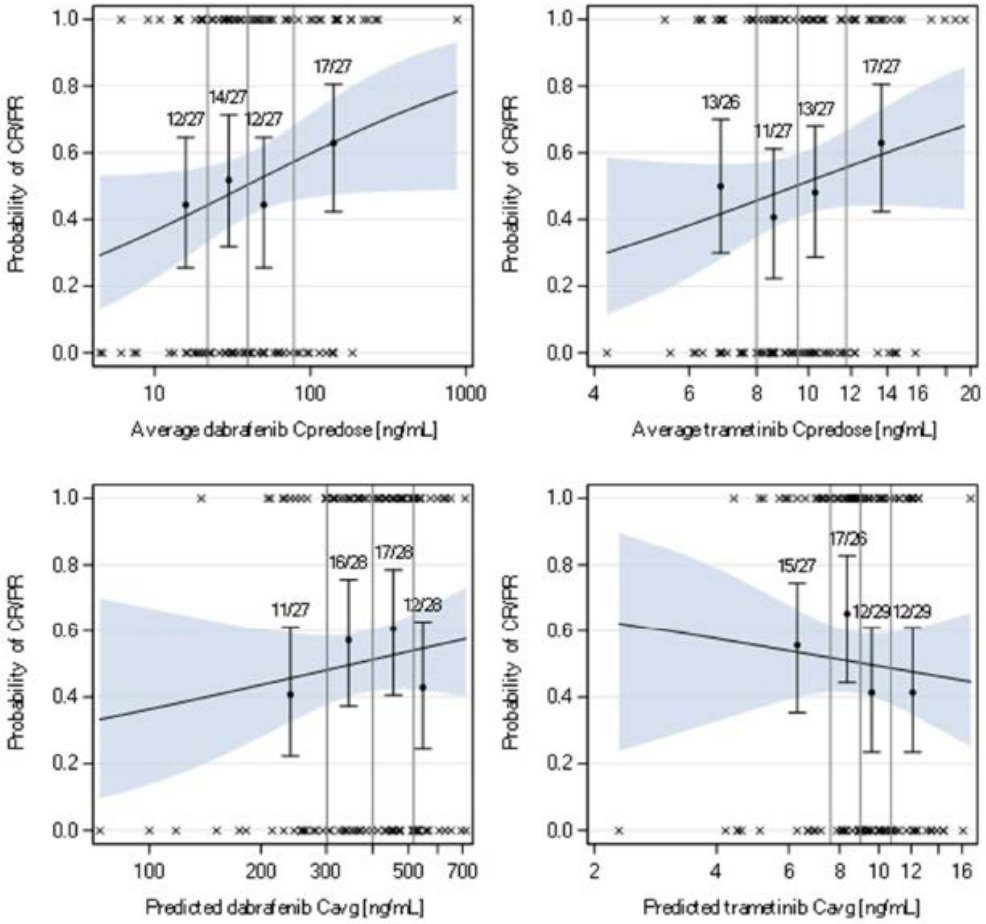
Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 24-25, Table 7-1.
Abbreviations: HGG, high-grade glioma; LGG, low-grade glioma; PK, pharmacokinetics; SD, standard error

Table 23-9. Logistic *R*egression for BOR vs. *E*xposure in Patients With HGG and LGG

Observed CR/PR rate (n/N)	Model parameter	Estimate (SE)	p-value	Odds ratio estimate (95% CI)
55/108	Intercept	-1.49 (0.82)	0.068	
	Log of average dabrafenib Cpredose	0.41 (0.21)	0.054	
	75th vs 50th percentile of Cpredose (78.3 vs 39.5)			1.32 (0.99, 1.76)
	25th vs 50th percentile of Cpredose (21.9 vs 39.5)			0.78 (0.61, 1.00)
56/111	Intercept	-2.58 (2.78)	0.354	
	Log of predicted dabrafenib Cavg	0.44 (0.47)	0.349	
	75th vs 50th percentile of Cavg (516.3 vs 399.9)			1.12 (0.88, 1.41)
	25th vs 50th percentile of Cavg (301.4 vs 399.9)			0.88 (0.68, 1.15)
54/107	Intercept	-2.35 (1.60)	0.140	
	Log of average trametinib Cpredose	1.05 (0.70)	0.134	
	75th vs 50th percentile of Cpredose (11.8 vs 9.5)			1.24 (0.93, 1.65)
	25th vs 50th percentile of Cpredose (8.0 vs 9.5)			0.83 (0.65, 1.06)
56/111	Intercept	0.81 (1.36)	0.551	
	Log of predicted trametinib Cavg	-0.36 (0.62)	0.556	
	75th vs 50th percentile of Cavg (10.7 vs 9.0)			0.94 (0.76, 1.16)
	25th vs 50th percentile of Cavg (7.6 vs 9.0)			1.06 (0.87, 1.30)

Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 24-27, Table 7-2.
Abbreviations: BOR, best overall response; CI, confidence interval; HGG, high-grade glioma; LGG, low-grade glioma; SE, standard error

Figure 23-17. Predicted Probability of BOR vs. Exposure in Patients With HGG and LGG



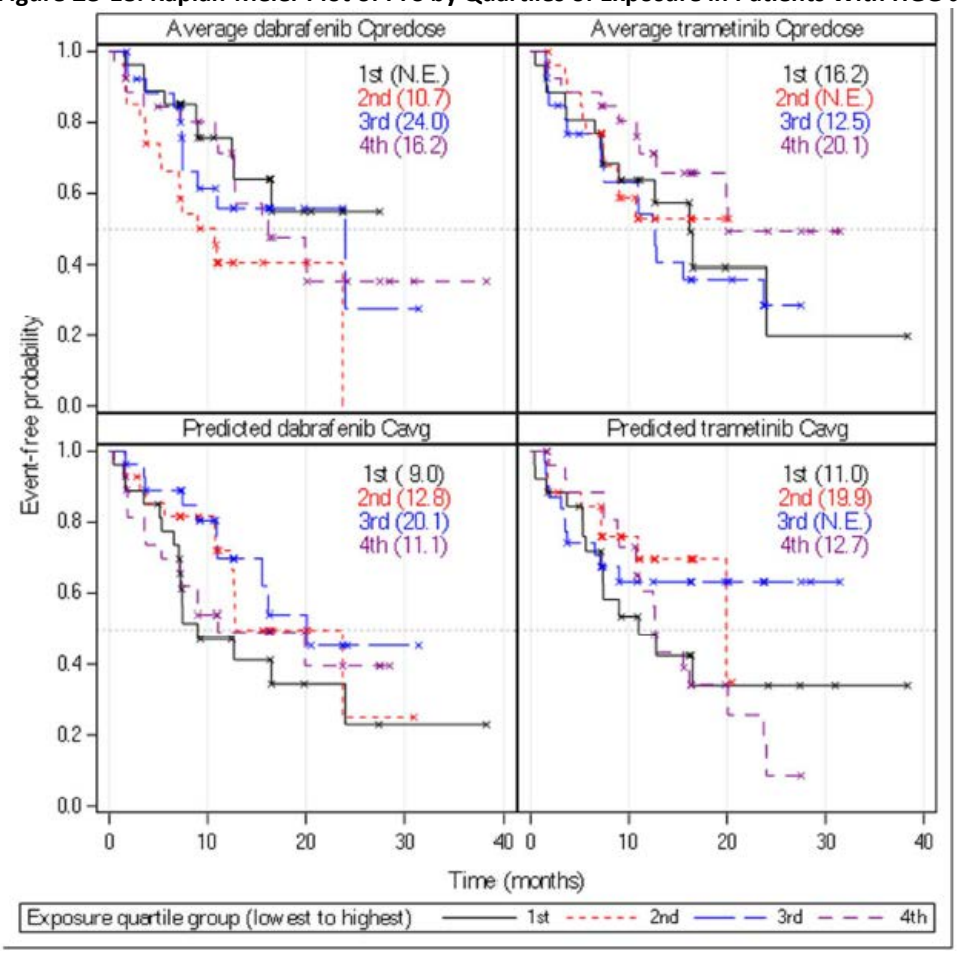
Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 28, Figure 7-2.
Abbreviations: BOR, best overall response; HGG, high-grade glioma; LGG, low-grade glioma

Table 23-10. Cox Regression Model of PFS vs. Exposure in Patients With HGG and LGG

Observed event rate (n/N)	Model parameter	Estimate (SE)	p-value	Hazard ratio estimate (95% CI)
50/108	Log of average dabrafenib Cpredose	-0.09 (0.14)	0.512	
	75th vs 50th percentile of Cpredose (78.3 vs 39.5)			0.94 (0.78, 1.13)
	25th vs 50th percentile of Cpredose (21.9 vs 39.5)			1.06 (0.90, 1.24)
52/111	Log of predicted dabrafenib Cavg	-0.66 (0.35)	0.061	
	75th vs 50th percentile of Cavg (500.6 vs 412.8)			0.88 (0.77, 1.01)
	25th vs 50th percentile of Cavg (300.9 vs 412.8)			1.23 (0.99, 1.54)
50/107	Log of average trametinib Cpredose	-0.57 (0.48)	0.232	
	75th vs 50th percentile of Cpredose (11.8 vs 9.5)			0.89 (0.73, 1.08)
	25th vs 50th percentile of Cpredose (8.0 vs 9.5)			1.11 (0.94, 1.30)
52/111	Log of predicted trametinib Cavg	-0.04 (0.49)	0.933	
	75th vs 50th percentile of Cavg (11.3 vs 9.4)			0.99 (0.83, 1.18)
	25th vs 50th percentile of Cavg (8.1 vs 9.4)			1.01 (0.87, 1.16)

Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 30, Table 7-3.
Abbreviations: CI, confidence interval; HGG, high-grade glioma; LGG, low-grade glioma; PFS, progression-free survival; SE, standard error

Figure 23-18. Kaplan-Meier Plot of PFS by Quartiles of Exposure in Patients With HGG and LGG

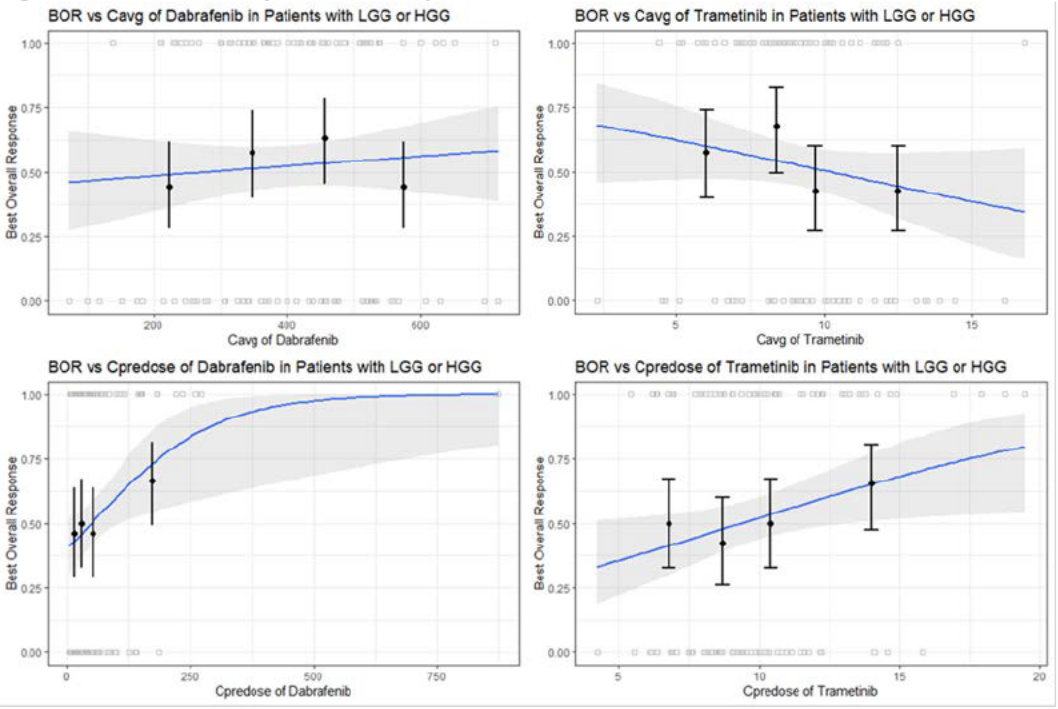


Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 29, Figure 7-3.
Abbreviations: HGG, high-grade glioma; LGG, low-grade glioma; PFS, progression-free survival

The FDA's Assessment

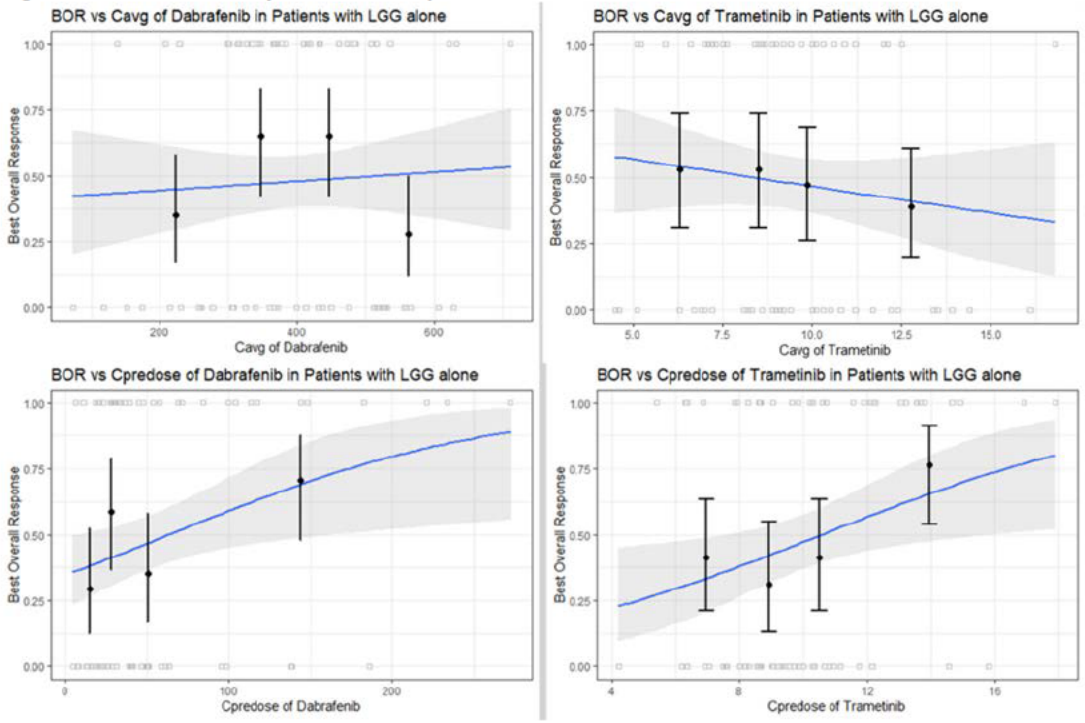
The exposure-response analysis was checked by the reviewer. No clear relationships for exposure-ORR or exposure-PFS were observed with either log of $C_{predose}$ or C_{avg} for dabrafenib or trametinib in patients with LGG and HGG or LGG alone. (Figure 23-19 - Figure 23-21) Slightly positive trends were observed between BOR and $C_{predose}$ of dabrafenib or trametinib in patients with LGG. However, the results were inconclusive due to limited number of pediatric patients included in the analysis.

Figure 23-19. Probability of BOR vs. Exposure in Patients With HGG and LGG



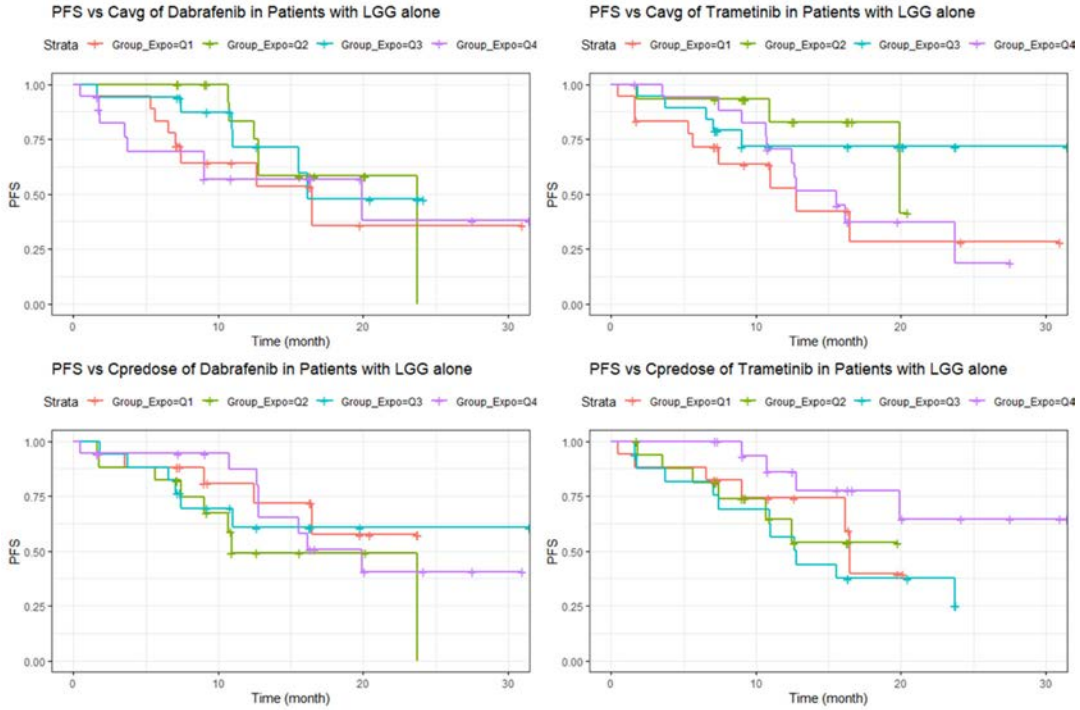
Source: Reviewer's analysis
Abbreviations: OBR, best overall response; HGG, high-grade glioma; LGG, low-grade glioma

Figure 23-20. Probability of BOR vs. Exposure in Patients With LGG



Source: Reviewer's analysis
Abbreviations: BOR, best overall response; LGG, low-grade glioma

Figure 23-21. Kaplan-Meier Plot of PFS by Quartiles of Exposure in Patients With LGG



Source: Reviewer's analysis
Abbreviations: LGG, low-grade glioma; PFS, progression-free survival

23.4.3 Exposure-Response Analysis for Safety

Table 23-11. ER Safety Summary Table

General Information		
Goal of ER analysis		Explore the relationships between dabrafenib and trametinib plasma exposures and selected safety endpoints in pediatric patients.
Study Included		CTMT212X2101 (MEK116540) and CDRB436G2201
Population Included		Pediatric patients
Endpoint		AE (grade ≥3), pyrexia, rash (any grade), paronychia (any grade), maximum change in ALT, maximum change in AST
No. of patients		147
Population Characteristics (Table 23-8)	General	Age median: 11 (range: 1 - 17) years Weight median: 40.5 (range: 8 -156) kg 47 (42.3%) male Race: 77 (69.4%) White 16 (14.4%) Asian 9 (8.1%) Other or unknown
	Pediatrics (if any)	147 patients
	Geriatrics (if any)	NA

General Information		
Exposure metrics explored (range)	Dabrafenib: $C_{predose}$: 4.44 – 876 ng/mL C_{avg}: 73.2 – 1920 ng/mL Trametinib: $C_{predose}$: 4.22 – 19.5 ng/mL C_{avg}: 1.6 -18.5 ng/mL	
Covariates evaluated	NA	
Final Model Parameters	**Summary**	**Acceptability [FDA's Comments]**
Model structure	Logistic regression: AE (grade ≥3), pyrexia, rash (any grade), paronychia (any grade) Linear regression: maximum change in ALT, maximum change in AST	**Acceptable**
Model parameter estimates	Table 23-12- Table 23-16	Acceptable
Covariates and clinical relevance	NA	
Visualization of E-R relationships	Figure 23-22 - Figure 23-26	Acceptable

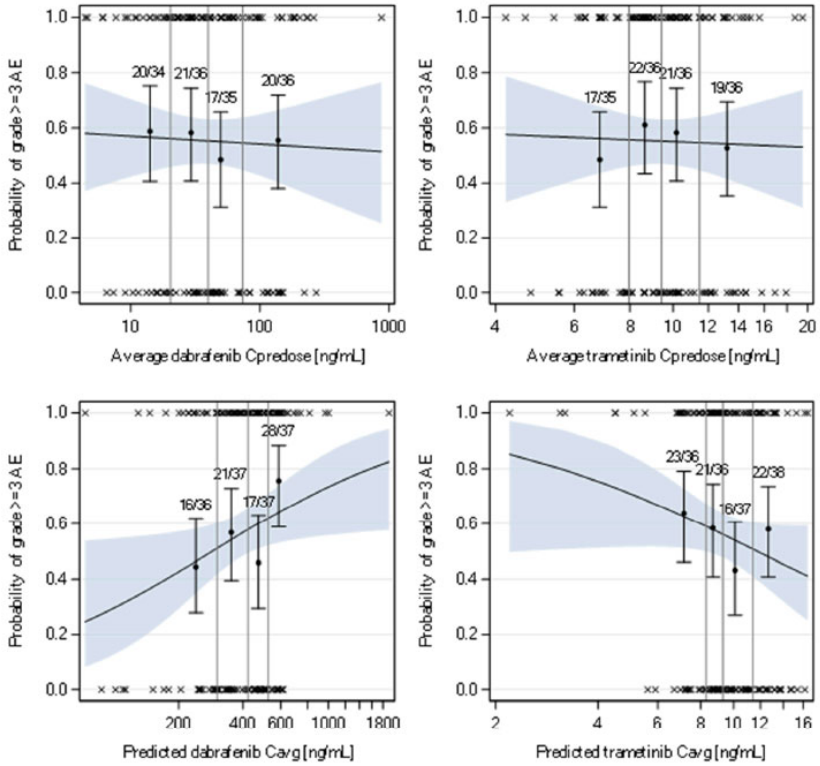
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ER, exposure-response; NA, not applicable

Table 23-12. Logistic Regression of AEs (Grade ≥3) vs. Exposures

Observed event rate (n/N)	Model parameter	Estimate (SE)	p-value	Odds ratio estimate (95% CI)
78/141	Intercept	0.40 (0.68)	0.559	
	Log of average dabrafenib Cpredose	-0.05 (0.18)	0.779	
	75th vs 50th percentile of Cpredose (73.8 vs 39.8)			0.97 (0.78, 1.20)
	25th vs 50th percentile of Cpredose (20.3 vs 39.8)			1.03 (0.82, 1.31)
82/147	Intercept	-4.62 (2.25)	0.040	
	Log of predicted dabrafenib Cavg	0.82 (0.38)	0.031	
	75th vs 50th percentile of Cavg (524.0 vs 421.5)			1.19 (1.02, 1.40)
	25th vs 50th percentile of Cavg (302.4 vs 421.5)			0.76 (0.60, 0.98)
79/143	Intercept	0.48 (1.35)	0.724	
	Log of average trametinib Cpredose	-0.12 (0.60)	0.842	
	75th vs 50th percentile of Cpredose (11.5 vs 9.4)			0.98 (0.78, 1.23)
	25th vs 50th percentile of Cpredose (8.0 vs 9.4)			1.02 (0.84, 1.24)
82/147	Intercept	2.58 (1.37)	0.060	
	Log of predicted trametinib Cavg	-1.05 (0.60)	0.083	
	75th vs 50th percentile of Cavg (11.4 vs 9.3)			0.81 (0.63, 1.03)
	25th vs 50th percentile of Cavg (8.3 vs 9.3)			1.13 (0.98, 1.29)

Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 32, Table 7-4.
Abbreviations: AE, adverse event; CI, confidence interval; SE, standard error

Figure 23-22. Predicted Probability of AEs (Grade ≥3) vs. Exposures



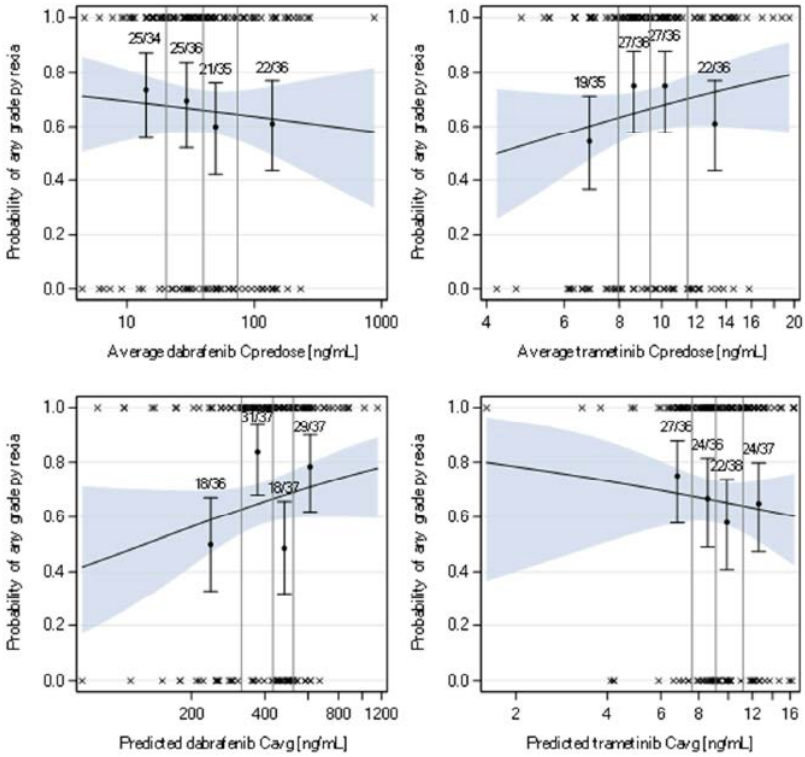
Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 33, Figure 7-5.
Abbreviations: AE, adverse event

Table 23-13. Logistic Regression of Any Grade Pyrexia vs. Exposures

Observed event rate (n/N)	Model parameter	Estimate (SE)	p-value	Odds ratio estimate (95% CI)
93/141	Intercept	1.07 (0.72)	0.138	
	Log of average dabrafenib Cpredose	-0.11 (0.19)	0.557	
	75th vs 50th percentile of Cpredose (73.8 vs 39.8)			0.93 (0.74, 1.17)
	25th vs 50th percentile of Cpredose (20.3 vs 39.8)			1.08 (0.84, 1.38)
96/147	Intercept	-2.77 (2.16)	0.200	
	Log of predicted dabrafenib Cavg	0.57 (0.36)	0.115	
	75th vs 50th percentile of Cavg (522.1 vs 431.2)			1.12 (0.97, 1.28)
	25th vs 50th percentile of Cavg (320.0 vs 431.2)			0.84 (0.68, 1.04)
95/143	Intercept	-1.26 (1.44)	0.379	
	Log of average trametinib Cpredose	0.87 (0.64)	0.175	
	75th vs 50th percentile of Cpredose (11.5 vs 9.4)			1.19 (0.93, 1.52)
	25th vs 50th percentile of Cpredose (8.0 vs 9.4)			0.87 (0.70, 1.07)
97/147	Intercept	1.58 (1.24)	0.204	
	Log of predicted trametinib Cavg	-0.41 (0.56)	0.456	
	75th vs 50th percentile of Cavg (11.2 vs 9.1)			0.92 (0.73, 1.15)
	25th vs 50th percentile of Cavg (7.6 vs 9.1)			1.08 (0.89, 1.31)

Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 35, Table 7-5.
Abbreviations: CI, confidence interval; SE, standard error

Figure 23-23. Predicted Probability of Any Grade Pyrexia vs. Exposures



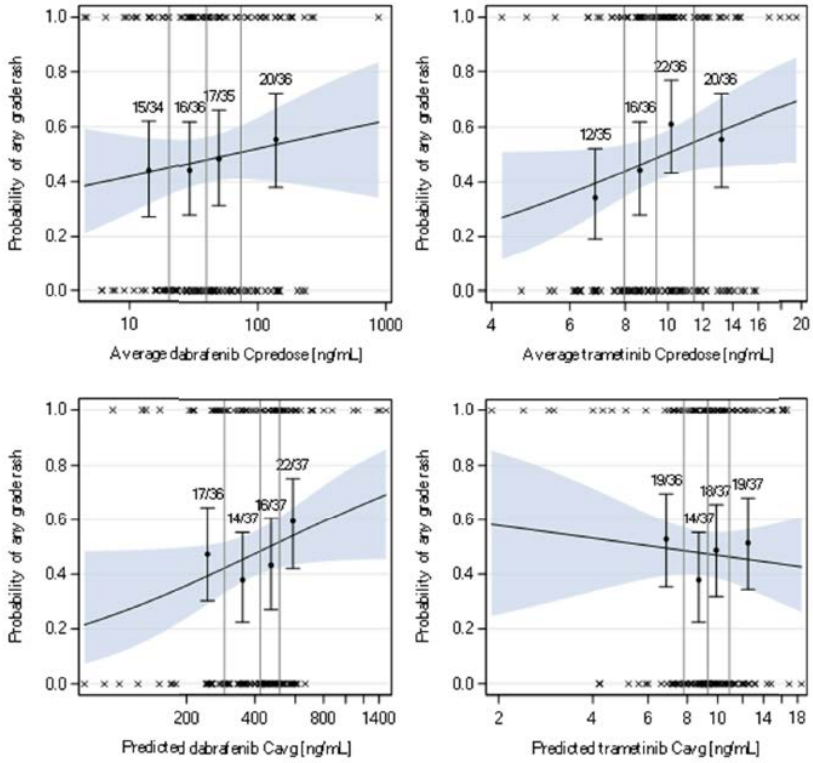
Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 36, Figure 7-7.

Table 23-14. Logistic Regression of Any Grade Rash vs. Exposures

Observed event rate (n/N)	Model parameter	Estimate (SE)	p-value	Odds ratio estimate (95% CI)
68/141	Intercept	-0.73 (0.69)	0.283	
	Log of average dabrafenib Cpredose	0.18 (0.18)	0.317	
	75th vs 50th percentile of Cpredose (73.8 vs 39.8)			1.12 (0.90, 1.39)
	25th vs 50th percentile of Cpredose (20.3 vs 39.8)			0.89 (0.70, 1.12)
69/147	Intercept	-4.24 (2.13)	0.046	
	Log of predicted dabrafenib Cavg	0.69 (0.36)	0.052	
	75th vs 50th percentile of Cavg (512.1 vs 421.9)			1.14 (1.00, 1.31)
	25th vs 50th percentile of Cavg (293.9 vs 421.9)			0.78 (0.61, 1.00)
70/143	Intercept	-2.70 (1.40)	0.055	
	Log of average trametinib Cpredose	1.18 (0.62)	0.057	
	75th vs 50th percentile of Cpredose (11.5 vs 9.4)			1.26 (0.99, 1.60)
	25th vs 50th percentile of Cpredose (8.0 vs 9.4)			0.82 (0.67, 1.01)
70/147	Intercept	0.51 (1.03)	0.624	
	Log of predicted trametinib Cavg	-0.27 (0.46)	0.555	
	75th vs 50th percentile of Cavg (10.9 vs 9.3)			0.96 (0.83, 1.11)
	25th vs 50th percentile of Cavg (7.8 vs 9.3)			1.05 (0.89, 1.23)

Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 38, Table 7-6.
Abbreviations: CI, confidence interval; SE, standard error

Figure 23-24. Predicted Probability of Any Grade Rash vs. Exposures



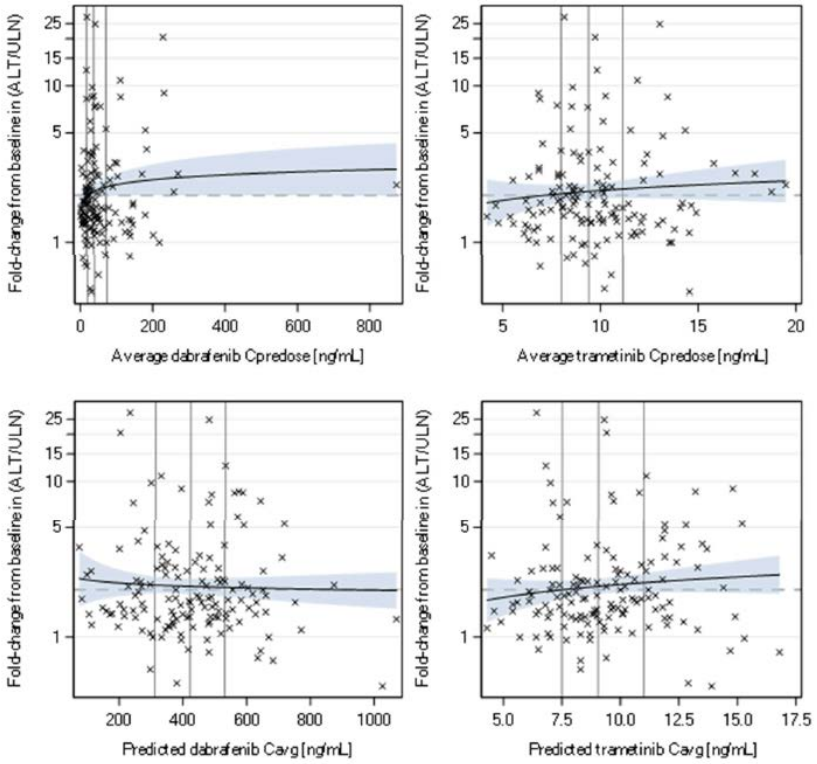
Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 39, Figure 7-9.

Table 23-15. Linear Regression of Maximum ULN-Normalized Change from Baseline in ALT vs. Exposures

N	Model parameter	Estimate (SE)	p-value	Fold change ratio estimate (95% CI)
139	Intercept	-0.08 (0.25)	0.764	
	Log of baseline ULN-normalized ALT	-0.53 (0.11)	<.001	
	Log of average dabrafenib Cpredose	0.11 (0.06)	0.084	
	75th vs 50th percentile of Cpredose (73.8 vs 39.8)			1.07 (0.99, 1.15)
	25th vs 50th percentile of Cpredose (20.3 vs 39.8)			0.93 (0.86, 1.01)
144	Intercept	0.75 (0.73)	0.307	
	Log of baseline ULN-normalized ALT	-0.47 (0.11)	<.001	
	Log of predicted dabrafenib Cavg	-0.07 (0.12)	0.586	
	75th vs 50th percentile of Cavg (531.6 vs 422.3)			0.98 (0.93, 1.04)
	25th vs 50th percentile of Cavg (311.6 vs 422.3)			1.02 (0.95, 1.10)
141	Intercept	-0.16 (0.47)	0.735	
	Log of baseline ULN-normalized ALT	-0.54 (0.11)	<.001	
	Log of average trametinib Cpredose	0.21 (0.20)	0.304	
	75th vs 50th percentile of Cpredose (11.2 vs 9.4)			1.04 (0.97, 1.11)
	25th vs 50th percentile of Cpredose (8.0 vs 9.4)			0.97 (0.91, 1.03)
144	Intercept	-0.27 (0.48)	0.573	
	Log of baseline ULN-normalized ALT	-0.49 (0.11)	<.001	
	Log of predicted trametinib Cavg	0.27 (0.21)	0.189	
	75th vs 50th percentile of Cavg (11.0 vs 9.1)			1.05 (0.97, 1.14)
	25th vs 50th percentile of Cavg (7.5 vs 9.1)			0.95 (0.88, 1.03)

Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 41, Table 7-7.
Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; SE, standard error; ULN, upper limit of normal

Figure 23-25. Predicted Maximum ULN-Normalized Change from Baseline in ALT vs. Exposures



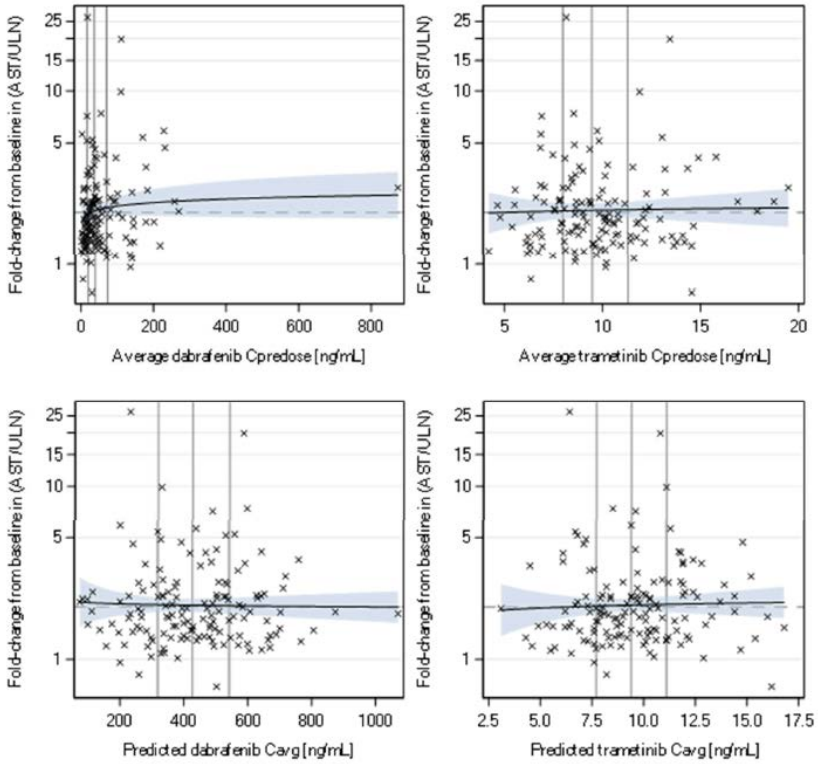
Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 42, Figure 7-11.
Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal

Table 23-16. Linear Regression of Maximum ULN-Normalized Change From Baseline in AST vs. Exposures

N	Model parameter	Estimate (SE)	p-value	Fold change ratio estimate (95% CI)
138	Intercept	0.16 (0.19)	0.400	
	Log of baseline ULN-normalized AST	-0.47 (0.13)	<.001	
	Log of average dabrafenib Cpredose	0.07 (0.05)	0.159	
	75th vs 50th percentile of Cpredose (73.8 vs 39.9)			1.04 (0.98, 1.11)
	75th vs 50th percentile of Cpredose (20.3 vs 39.9)			0.95 (0.90, 1.02)
143	Intercept	0.56 (0.56)	0.315	
	Log of baseline ULN-normalized AST	-0.46 (0.13)	<.001	
	Log of predicted dabrafenib Cavg	-0.02 (0.09)	0.792	
	75th vs 50th percentile of Cavg (541.6 vs 426.5)			0.99 (0.95, 1.04)
	75th vs 50th percentile of Cavg (318.4 vs 426.5)			1.01 (0.95, 1.06)
140	Intercept	0.32 (0.36)	0.382	
	Log of baseline ULN-normalized AST	-0.47 (0.13)	<.001	
	Log of average trametinib Cpredose	0.04 (0.16)	0.784	
	75th vs 50th percentile of Cpredose (11.3 vs 9.5)			1.01 (0.95, 1.07)
	75th vs 50th percentile of Cpredose (8.0 vs 9.5)			0.99 (0.94, 1.05)
143	Intercept	0.29 (0.36)	0.410	
	Log of baseline ULN-normalized AST	-0.44 (0.13)	<.001	
	Log of predicted trametinib Cavg	0.06 (0.15)	0.699	
	75th vs 50th percentile of Cavg (11.1 vs 9.4)			1.01 (0.96, 1.06)
	75th vs 50th percentile of Cavg (7.7 vs 9.4)			0.99 (0.93, 1.05)

Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 43., Table 7-8.
Abbreviations: AST, aspartate aminotransferase; CI, confidence interval; SE, standard error; ULN, upper limit of normal

Figure 23-26. Predicted Maximum ULN-Normalized Change From Baseline in AST vs. Exposures



Source: Exposure Response of dabrafenib and trametinib in pediatric patients modeling report, Page 44, Figure 7-12.
Abbreviations: AST, aspartate aminotransferase; ULN, upper limit of normal

The FDA's Assessment

The exposure-response analysis for safety was checked by the reviewer. Relatively flat ER relationships were observed for the safety endpoints including any grade pyrexia, any grade paronychia, increases from baseline in ULN-normalized ALT and AST with either log of Cpredose or Cavg for dabrafenib or trametinib. Slightly positive ER trends were observed for Grade ≥3 AEs with Cavg of dabrafenib; any grade rash with Cpredose of trametinib and Cavg of dabrafenib. The results were broadly consistent with previous exposure-response analyses in adults with melanoma.

23.4.4 Additional Safety Analyses Conducted by FDA

The FDA's Assessment

Refer to Section 11.2 for FDA's review of safety.

NDA 217513
NDA 217514

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Jeannette Nashed, M.D.	CDER/OOD/DO2	**Sections:** 1, 4.3, 11.2	**Select one:** _x__ Authored ___ Approved
	Signature: Jeannette C. Nashed -S Digitally signed by Jeannette C. Nashed -S Date: 2023.03.14 16:15:19 -04'00'			
Clinical Reviewer	Michael Barbato, M.D.	CDER/OOD/DO2	**Sections:** 1, 2, 4, 5, 6, 7, 10, 11.1-11.1.9, 12, 13, 14 ,16, 17, 23.1-23.2	**Select one:** _**x**__ Authored Approved
	Signature: Michael I. Barbato -S Digitally signed by Michael I. Barbato -S Date: 2023.03.15 09:05:25 -04'00'			
Clinical Team Leader	Diana Bradford, M.D.	CDER/OOD/DO2	Sections: All	**Select one:** _X__ Authored __X_ Approved
	Signature: See Cross-Disciplinary Team Lead			
Statistical Reviewer	Yi Ren, Ph.D.	CDER/OTS/DBV	Sections: 11.1, 12.1	**Select one:** _X_ Authored ___ Approved
	Signature: Yi Ren -S Digitally signed by Yi Ren -S Date: 2023.03.15 09:48:59 -04'00'			
Statistical Team Leader	Anup Amatya, Ph.D.	CDER/OTS/DBV	Sections: 11.1, 12.1	**Select one:** ___ Authored __x___ Approved
	Signature: Anup K. Amatya -S Digitally signed by Anup K. Amatya -S Date: 2023.03.14 17:04:12 -04'00'			
Supervisory Mathematical Statistician (OB/DBV)	Pallavi Mishra-Kalyani, Ph.D.	CDER/OTS/DBV	Sections: 1, 11.1, 12.1	**Select one:** ___ Authored _x_ Approved
	Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S Date: 2023.03.14 18:42:51 -04'00'			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Sachia Khasar, Ph.D.	CDER/OND/OOD/DHOT	Sections:7.2, 8	**Select one:** _X__Authored ___ Approved
	Signature: Gabriel S. Khasar -S Digitally signed by Gabriel S. Khasar -S Date: 2023.03.14 17:18:00 -04'00'			
Acting Nonclinical Team leader	Claudia P. Miller, Ph.D.	CDER/OND/OOD/DHOT	**Sections:**7.2, 8	**Select one:** X__ Authored _X_Approved
	Signature: Claudia Miller -S Digitally signed by Claudia Miller -S Date: 2023.03.14 18:10:01 -04'00'			
Clinical Pharmacology Reviewer	Banu Zolnik, Ph.D.	CDER/OTS/OCP/DCPII	Sections: 6	**Select one:** X__ Authored ___Approved
	Signature: Banu S. Zolnik -S Digitally signed by Banu S. Zolnik -S Date: 2023.03.15 06:04:37 -04'00'			
Clinical Pharmacology Team Leader	Hong Zhao, Ph.D.	CDER/OTS/OCP/DCPII	Sections:6, 19.4	**Select one:** X__ Authored __X_Approved
	Signature: Hong Zhao -S Digitally signed by Hong Zhao -S Date: 2023.03.14 16:57:47 -04'00'			
Pharmacometrics Reviewer	Yangbing Li, Ph.D.	CDER/OTS/OCP/DTPM	Sections:6, 19.4	**Select one:** X__ Authored __Approved
	Signature: Yangbing Li -S (Affiliate) Digitally signed by Yangbing Li -S (Affiliate) Date: 2023.03.15 09:08:24 -04'00'			
Pharmacometrics Team Leader	Youwei Bi, Ph.D.	CDER/OTS/OCP/DTPM	Sections:6, 19.4	**Select one:** ___ Authored _X__Approve
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2023.03.14 21:41:53 -04'00'			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Deputy Division Director	Stacy Shord, PharmD	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: 2023.03.15 08:42:15 -04'00'			
Associate Director for Labeling (ADL)	Barbara Scepura	CDER/OND/OOD/DOII	Sections: 15	**Select one:** ___x Authored ___ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2023.03.15 09:15:16 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Diana Bradford, M.D.	CDER/OOD/DO2	Sections: All	**Select one:** __X__Authored __X__Approved
	Signature: Diana L. Bradford -S Digitally signed by Diana L. Bradford -S Date: 2023.03.14 16:42:07 -04'00'			
Deputy Director (Signatory)	Nicole Drezner, M.D.	CDER/OOD/DO2	Sections: All	**Select one:** ____ Authored __x_ Approved
	Signature: Nicole L. Drezner -S Digitally signed by Nicole L. Drezner -S Date: 2023.03.15 09:57:54 -04'00'			

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
03/16/2023 06:15:10 AM

NICOLE L DREZNER
03/16/2023 08:04:14 AM