NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: 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	SE-1 Efficacy Supplements with Major Amendment
Application Number(s)	202806_S-22 and 204114_S-24
Priority or Standard	Priority
Submit Date(s)	September 22, 2021 (both)
Received Date(s)	September 22, 2021 (both)
PDUFA Goal Date	June 22, 2022 (3-month extension due to Major Amendment)
Division/Office	DO3/OOD
Review Completion Date	June 22, 2022
Established Name	Dabrafenib and trametinib
(Proposed) Trade Name	TAFINLAR and MEKINIST
Pharmacologic Class	BRAF inhibitor and MEK inhibitor
Code name	GSK2118436 and GSK1120212
Applicant	Novartis Pharmaceuticals Corporation
Formulation(s)	Dabrafenib 50 and 75 mg capsules Trametinib 0.5 and 2 mg tablets
Dosing Regimen	Dabrafenib 150 mg twice daily and trametinib 2 mg once daily
Applicant Proposed Indication(s)/Population(s)	The treatment of adult and pediatric patients 6 years of age and older with (b) (4) with BRAF V600E mutation who have progressed following prior treatment or have no satisfactory alternative treatment options. The proposed Limitations of Use (LOU): is not indicated for treatment of patients with colorectal cancer or wild-type BRAF solid tumors.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	The treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.

	Limitations of Use: Dabrafenib and trametinib are not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition. Dabrafenib and trametinib are not indicated for treatment of patients with wild-type BRAF solid tumors.

Table of Contents

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Table of Tables

Table of Figures

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

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Glossary

AE	adverse event
ASI	adenocarcinoma of small intestine
ATC	anaplastic thyroid cancer
ATS	all-treated subjects
BLA	biologics license application
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BOR	best overall response
BRF	benefit Risk Framework
BTC	biliary tract cancer
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DCR	disease control rate
DOR	duration of response
DLT	dose limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GIST	gastrointestinal stromal cancer
HGG	high-grade gliomas
HCL	hairy cell leukemia
ICH	International Conference on Harmonization
ITT	intent to treat
LCH	Langerhans cell histocytosis
LGG	low-grade gliomas
LVEF	left ventricular ejection fraction
MAP	managed access program
MedDRA	medical Dictionary for Regulatory Activities
MM	multiple myeloma
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSCLC	non-small cell lung cancer

NSGCT	non-seminomatous germ cell tumors
OCS	office of Computational Science
OPQ	office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	office of Surveillance and Epidemiology
OSI	office of Scientific Investigation
PBRER	periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFS	progression free survival
PI	prescribing information
PK	pharmacokinetics
PRO	patient reported outcome
RANO	response assessment in neuro oncology
REMS	risk evaluation and mitigation strategy
RSD	rolling 6 design
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Dabrafenib (TAFINLAR ®) is a BRAF inhibitor. It is FDA-approved as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutations. In combination with trametinib, it is FDA-approved for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations, metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation, and locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment option.

Trametinib (MEKINIST®) is a MEK inhibitor that inhibits MEK1 and MEK2. It is FDA-approved as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. In combination with dabrafenib, it is FDA-approved for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations, metastatic NSCLC with BRAF V600E mutation, and locally advanced or metastatic ATC with BRAF V600E mutation and with no satisfactory locoregional treatment option.

The Applicant's proposed indication is for the treatment of adult and pediatric patients 6 years of age and older with (b) (4) with BRAF V600E mutation who have progressed following prior treatment or have no satisfactory alternative treatment options. The proposed Limitations of Use (LOU) is that it is not indicated for treatment of patients with colorectal cancer or wild-type BRAF solid tumor.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The data submitted by the Applicant has provided substantial evidence for the effectiveness of dabrafenib 150 mg orally twice daily (BID) in combination with trametinib 2 mg once daily (qd) and based on body weight for pediatric patients (ages 6-17 years) for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options and supports Accelerated approval in this indication. As part of the Limitations of Use, dabrafenib in combination with trametinib are not indicated for the treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition and for the treatment of patients with wild-type BRAF solid tumors.

This conclusion is based on the results of three clinical trials, Trials CDRB436X2201 (X2201) and CTMT212XUS35T (NCI-MATCH/XUS35T) in adult patients, and trial CTMT212X2101 (X2101) in

pediatric patients. The conclusion is also supported by the results of clinical trials in patients with melanoma, lung cancer, and anaplastic thyroid cancer (i.e., COMBI-d, COMBI-v, and BRF113928).

Trial X2201 is a multi-cohort, multi-center, non-randomized, open-label trial in adult patients with selected tumors with a BRAF V600E mutation. A total of 105 patients with high grade glioma (HGG), biliary tract cancer (BTC), low grade glioma (LGG), adenocarcinoma of small intestine (ASI), gastrointestinal stromal tumor (GIST), and anaplastic thyroid cancer (ATC) were enrolled. The primary endpoint was overall response rate (ORR). The ORR was 41% (95% confidence interval [CI]: 31, 51) with 6 (6%) patient having a complete response (CR). The duration of response was at least ≥6 months for 58% of patients, ≥12 months for 40% of patients, and ≥24 months for 16% of patients. Trial XUS35T is a single-arm, open-label study that enrolled patients with a BRAF V600E mutation that included multiple tumor types. Efficacy data from Arm H was used to support the proposed indication. A total of 26 patients with solid tumors were enrolled across a variety of tumor types. The primary endpoint was ORR. The ORR was 42% (95% CI: 23, 63) with 1 (3.8%) patient having a CR. DOR was ≥6 months for 82% of patients, ≥12 months for 64% of patients, and ≥24 months for 36% of patients. Patients enrolled in trials X2201 and XUS35T with tumor types for which dabrafenib in combination with trametinib are approved for patients having a BRAF V600 mutation (i.e., melanoma, non-small cell lung cancer, and ATC) were either excluded from the efficacy analyses or not allowed to enroll. Trial X2101 was a multi-center, open-label, multiple cohort study in pediatric patients with BRAF V600 refractory or recurrent solid tumors. Patients enrolled in Part C (dose escalation of dabrafenib in combination with trametinib in patients with a BRAF V600E mutation) and Part D (patients with LGG with a BRAF V600E mutation) were included. The only solid tumor types evaluated for this application were LGG and HGG. The ORR for the 34 pediatric patients with LGG was 25% (95% CI: 12, 42). DOR was ≥6 months for 78% of patients, ≥12 months for 56% of patients, and ≥24 months for 44% of patients. Refer to Section 8.1.4 for a more granular discussion of the rationale for approval including consideration of data outside of these trials and brief discussion of BRAF inhibition in CRC.

The safety of dabrafenib in combination with trametinib has been adequately characterized by data submitted from studies X2201, XUS35T, and X2101. The safety data from adult patients is consistent with the known safety profile of this combination. The safety data from pediatric patients did not identify any new safety signals and was consistent with the known safety profile of the combination. The review team believes that the response rate and durability of response provides a benefit that outweighs the risks associated with systemic treatment with dabrafenib in combination with trametinib for this patient population with no FDA approved therapies.

Therefore the review team recommends granting Accelerated Approval to dabrafenib in combination with trametinib for the treatment of adult and pediatric patients 6 years of age

and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options with the Limitations of Use that dabrafenib and trametinib are not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition or patients with wild-type BRAF solid tumors.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

A favorable benefit-risk assessment has been established for dabrafenib in combination with trametinib for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options based on the results of two clinical studies in adults (CDRB436X2201X2201 [X2201]and CTMT212XUS35T [XUS35T]) and one study (CTMT212X2101 [X2101]) in pediatric patients. The conclusion is also supported by the results of clinical trials in patients with melanoma, lung cancer, and anaplastic thyroid cancer (i.e., COMBI-d, COMBI-v, and BRF113928). In melanoma, improvements in clinical outcomes (i.e., PFS and OS) in randomized trial shave been demonstrated with similarly high response rates.

Accelerated Approval is recommended based on a demonstrated effect on an intermediate endpoint. Clinical benefit will be established for this indication via additional data in at least 80 additional patients with BRAF-positive tumors. The additional data will provide increased precision of treatment effect on the intermediate endpoint (and more data in different tumor types) as well as information on the durability of the treatment effect (supported by randomized trials in one tumor type). Pediatric data from an ongoing study will be submitted for the pediatric formulation for patients < 6 years with LGG and HGG as part of the initial Pediatric Study Plan (iPSP) submitted by the Applicant and agreed to by FDA. Safety and efficacy data from this study in patients 1 year of age to 17 years will also be submitted.

Depending on the tumor type, standard of care treatments exist which may vary. For patients that do not respond to treatment, progress while on treatment, or relapse, treatment options are often limited and overall survival is negatively impacted.

Patients with BRAF V600E mutation positive solid tumors are relatively rare and have a heterogenous group of tumor types with varying prevalence. The most common types of cancer harboring the BRAF V600E mutation are colorectal cancer (CRC), melanoma, non-small cell lung cancer (NSCLC), and thyroid cancer (Owsley et al 2021). Currently, dabrafenib in combination with trametinib are approved for patients with melanoma, NSCLC, and anaplastic thyroid cancer (ATC). For patients with BRAF V600E mutation positive CRC, there is intrinsic resistance to BRAF V600 because of feedback activation of EGFR (ErbB1) in response to BRAF inhibitors (Prahallad, et al 2015) leading to adverse outcomes compared to CRC with BRAF wild-type disease (Samowitz, et al 2005). There are no drugs approved specifically for the treatment of patients with the rarer solid tumors harboring a BRAF V600E mutation outside of melanoma, NSCLC, and ATC (including glioma and biliary tract cancers).

The efficacy of dabrafenib in combination with trametinib in adult patients with BRAF V600E mutation positive solid tumors was demonstrated based on results from two adult studies that enrolled patients with BRAF V600E mutation positive solid tumors enrolled in 1 of 2 multi-cohort, multi-center, single-arm studies (X2201 [n=105] and XUS35T [n=26]). Study X2201 enrolled only select solid tumors with BRAF V600E mutation, including high grade glioma (HGG), biliary tract cancer (BTC), low grade glioma (LGG), adenocarcinoma of small intestine (ASI), gastrointestinal stromal tumor (GIST), and ATC. Patients with ATC enrolled were excluded from the efficacy analysis. The overall response rate (ORR) was 41% (95% confidence interval [CI]: 31, 51). Six (6%) patients had a complete response (CR). DOR was ≥6 months for 58% of patients, ≥12 months for 40% of patients, and ≥24 months for 16% of patients. Study XUS35T enrolled 26 patients. The ORR was 42% (95% CI: 23, 63) with 1 (3.8%) having a CR and DOR was ≥6 months for 82% of patients, ≥12 months for 64% of patients, and ≥24 months for 36% of patients.

The efficacy of dabrafenib in combination with trametinib in pediatric patients 6 years of age and older was established based on Parts C and D of study X2101, a multi-center, open-label, multiple cohort study in pediatric patients with BRAF V600 refractory or recurrent solid tumors. The only solid tumor types evaluated were low grade glioma (n=34) and high-grade glioma (n=2). The ORR for the 34 pediatric patients with LGG was 25% (95% CI: 12, 42). DOR was ≥6 months for 78% of patients, ≥12 months for 56% of patients, and ≥24 months for 44% of patients. The effectiveness of dabrafenib in combination with trametinib in pediatric patients younger than 6 years has not been established an appropriate dose using the current formulation was not identified.

Safety data supporting the proposed indication reflected exposure to dabrafenib and trametinib in 206 adult patients enrolled on trial X2201. The safety in adults of dabrafenib in combination with trametinib has been well-characterized in the treatment of metastatic melanoma, NSCLC and ATC. The safety profile of the combination in BRAF V600E positive solid tumors was consistent with the known safety profile in the other approved indications in adults. No new safety signals were identified in Studies X2201 or XUS34T.

The safety of dabrafenib in combination with trametinib in pediatric patients 6 years of age and older that weigh at least 26 kg was established based on data in adults and data from pediatric study X2101. In study X2101, Parts C and D enrolled a total of 48 patients (ages 1 to 17) with the following tumor types: LGG (n = 34), HGG (n = 2), LCH (n = 11), and juvenile xanthogranulomatosis. Overall the toxicity profile was consistent with that seen in the adult population. Although dabrafenib in combination with trametinib poses a risk of toxicity, these risks are considered acceptable in the context of the observed clinical efficacy. Risk minimization via the product label includes the current management guidelines for adverse events (AEs) and a Medication Guide.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Solid tumors with BRAF V600E mutations are a group of heterogenous tumors. • The incidence of BRAF V600E mutations in solid tumors vary depending on the specific tumor type and are most commonly found in colorectal cancer, melanoma, and non-small cell lung cancer. • When metastatic or unresectable, solid tumors are rarely curable.	BRAF V600E mutation positive solid tumors that have progressed following treatment or have no satisfactory alternative treatment options are life-threatening. Patients have a poor outcomes.
Current Treatment Options	• Patients with BRAF V600E solid tumors are treated with standard of care therapy for their specific tumor type. • There are no treatments approved specifically for patients with BRAF V600E mutation except for patients with melanoma, non-small cell lung cancer, and anaplastic thyroid cancer (encorafenib in combination with cetuximab is approved for patients with BRAF-positive CRC; this regimen relies upon also inhibiting the EGFR axis – see review below).	There are no approved therapies for the proposed indication. Given the poor prognosis there remains a need for treatment options for this patient population.
Benefit	• Efficacy analyses from adult studies X2201 and XUS35T, and pediatric study X2101, demonstrated a clinically significant ORR with durability of response. • ORR was 41% (95% CI: 31, 51) for adult study X2201. DOR was ≥6 months for 58% of patients, ≥12 months for 40% of patients, and ≥24 months for 16% of patients • ORR was 42% (95% CI: 23, 63) for adult study XUS35T. Durability was ≥6 months for 82% of patients, ≥12 months for 64% of patients, and ≥24 months for 36% of patients. • ORR was 25% (95% CI: 12, 42) in pediatric study X2101. DOR was ≥6 months for 78% of patients, ≥12 months for 56% of patients, and ≥24 months for 44% of patients.	The magnitude and duration of responses observed in patients with BRAF V600E-positive solid tumors who have progressed following prior treatment or who had no available treatment options was clinically meaningful. For unresectable or metastatic solid tumors that are refractory to available therapy or for which there is no satisfactory therapy, ORR may be considered an intermediate endpoint reasonably likely to predict clinical benefit when the treatment effect is large and the responses are durable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		The submitted evidence meets the statutory evidentiary standard for accelerated approval. As a condition of approval, the Applicant is required to submit additional evidence to verify and confirm the clinical benefit of dabrafenib in combination with trametinib in patients with BRAF V600E solid tumors. As part of the pediatric development program, the Applicant is required to submit data for the pediatric formulation from an ongoing study in patients with LGG and HGG to support the formulation in patients 1 years of age to <6 years.
Risk and Risk Management	• The safety profile of dabrafenib in combination with trametinib appears acceptable for a therapy used to treat a serious and life-threatening condition. • The combination of dabrafenib in combination with trametinib in adult patients has a well-characterized safety profile based on the approvals in melanoma, NSCLC, and ATC. • There is no safety data for the pediatric patient population.	The safety data submitted was sufficient to characterize the toxicity profile of dabrafenib in combination with trametinib for both adults and pediatric patients and the risks are considered acceptable in the context of the clinical efficacy in the advanced or metastatic disease setting. As part of the pediatric development program, the Applicant is required to submit safety data from an ongoing study in patients with LGG

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		and HGG.

1.4. 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: See text below			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Section 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[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)		See text below

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x	Patient experience data that was not submitted in the application, but was considered in this review.

Changes from baseline in HRQOL using EORTC-QLC-C30 was an exploratory endpoint in study X2201. Quality of life questionnaires were to be completed by the patient before any other study procedures were performed. Completed questionnaires were immediately checked for completeness at the site and full completion was encouraged. No source data verification was performed. This data from this single-arm experience was not submitted as part of the application. Studies XUS35T and X2101 did not collect PRO data.

X

Leslie Doros, MD
Cross-Disciplinary Team Leader
see electronic signature page at the end of the document

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

The RAS/RAF/MEK/ERK pathway, also known as the mitogen-activated protein kinase (MAPK) pathway, is a critical signal transduction cascade implicated in normal growth and the uncontrolled proliferation of many human cancers. Under normal physiological conditions, signal transduction through the MAPK pathway is tightly regulated through multiple negative feedback mechanisms. Activating mutations can frequently occur within the MAPK pathway, with RAF mutations being predominant. Class I BRAF mutations, which affect amino acid V600 and signal as RAS-independent active monomers, are by far the most commonly identified mutations of the MAPK pathway in human tumors. Among the Class I mutations, approximately 90% of all identified mutations that occur in human cancers are an activating missense mutation resulting in an amino acid substitution at position 600 in BRAF from a valine to a glutamic acid (BRAF V600E). BRAF V600E mutations have been identified at a varying prevalence across a wide range of rare tumor types, with tumor-specific rates ranging from 3% in WHO grade 3 and 4 glioma to 90% in HCL. Owsley et al (2021) have estimated an average BRAF mutation prevalence of 3.9% across tumor types in a large (114,662 cancer patients) genomic database. Out of 3,633 pediatric (median 10.5 years, (range < 1–21 years) cancer samples, a BRAF alteration was seen in 6.1% (Rankin et al 2021). Out of those, BRAF V600E accounted for 50% of all identified activating variants encompassing 6 primary histological categories: brain tumors (74.4%; 18 subtypes), other solid tumors (10.8%; 6 subtypes), hematological malignancies (9.1%; 5 subtypes), sarcomas (3.4%; 3 subtypes), and extracranial embryonal tumors (2.3%; 2 subtypes). BRAF V600E is recognized as an actionable mutation for targeted therapy with BRAF/MEK inhibitor combination therapy across a range of advanced solid tumors including melanoma, NSCLC and anaplastic thyroid cancer. However, many additional rare BRAF V600 mutated cancers have no effective treatment options available either in the first-line setting or relapsed / refractory setting.

The FDA's Assessment:

The tables below represent Novartis's estimates of the prevalence of BRAF-positive tumors across different malignancies. The estimates were compiled from a number of sources including SEER, CancerMPact by Kantar Health, National Organization for Rare Disorders (NORD) disease reports, Institute for Health Metrics and Evaluation (IHME), and Global Burden of Disease (GBD).

Table 1 below copied from the sNDA submission is from a study by Owsley et al., 2021, where 114,662 tumors were retrospectively assessed for BRAF aberrations after being tested using the Caris Life Sciences NGS platform (Owsley et al, 2021). The results show that after considering already approved indications (e.g., BRAF-positive melanoma and NSCLC), BRAF mutations were uncommon events across most tumor types.

Table 1 FDA - BRAF V600 Mutations in 114,662 Sequenced Tumors

Tumor types	N of tumors sequenced	BRAF V600 mutations	BRAF V600 mutation rate (%)
Thyroid carcinoma	496	161	32.46%
Melanoma	3203	985	30.75%
Multiple myeloma	39	3	7.69%
Colorectal adenocarcinoma	14680	1012	6.89%
Low grade glioma	478	12	2.51%
All cancer types	114662	2841	2.48%
Cancer of unknown primary	2894	68	2.35%
Cholangiocarcinoma	2068	38	1.84%
High grade glioma	3186	55	1.73%
Others	1551	23	1.48%
Small intestinal malignancies	742	11	1.48%
Non-small cell lung cancer	18944	237	1.25%
Neuroendocrine tumors	1956	22	1.12%
Uveal melanoma	268	2	0.75%
Ovarian surface epithelial carcinomas	16583	122	0.74%
Lymphoma	295	2	0.68%
Pancreatic adenocarcinoma	4565	27	0.59%
Gastric adenocarcinoma	1791	10	0.56%
Soft tissue tumors	2439	10	0.41%
Non-melanoma non-Merkel skin cancers	460	1	0.22%
Small cell lung cancer	1015	2	0.20%
Breast carcinoma	10478	18	0.17%
Esophageal and esophagogastric junction	2399	3	0.13%
Kidney cancer	1312	1	0.08%
Head and neck cancers	1487	1	0.07%
Uterine cancers	10889	7	0.06%
Cervical cancer	1862	1	0.05%
Bladder cancer	1959	1	0.05%
Prostatic adenocarcinoma	2009	0	0.00%

Source: Submitted as SCE Appendix 3 – US Prevalence

The table below (Table 2), also copied from the sNDA submission, shows rates for BRAF mutations in 45,678 patient samples performed by the cBioPortal for Cancer Genomics across 184 clinical studies. (Cerami 2012, Gao 2013). The results are largely consistent with the study above. Although it cannot be confirmed whether the above studies are representative of the totality of patients with cancer in the US, it is expected based on these and on other data (in the submission) that most tumors (other than thyroid cancer and melanoma) have low incidence rates of BRAF-mutations.

Table 2 FDA - BRAF Mutations in Tumor Types Reported from cBIOPortal Data

Tumor types	N of samples	BRAF mutations	BRAF mutation rate (%)
Well-Differentiated Thyroid Cancer	490	287	58.57%
Melanoma	1824	819	44.90%
Thyroid Cancer	235	91	38.72%
Histiocytosis	68	14	20.59%
Small Bowel Cancer	36	6	16.67%
Colorectal Adenocarcinoma	1153	189	16.39%
Colorectal Cancer	1380	151	10.94%
Penile Cancer	11	1	9.09%
Gastrointestinal Neuroendocrine Tumor	46	4	8.70%
Skin Cancer, Non-Melanoma	519	45	8.67%
Undifferentiated Stomach Adenocarcinoma	13	1	7.69%
Cancer of Unknown Primary	211	12	5.69%
Non-Small Cell Lung Cancer	4048	200	4.94%
Endometrial Carcinoma	574	26	4.53%
Glioma	1002	39	3.89%
Endometrial Cancer	262	10	3.82%
Bladder Cancer	1107	42	3.79%
Bladder Urothelial Carcinoma	410	13	3.17%
Anal Cancer	34	1	2.94%
Ampullary Cancer	178	5	2.81%
Cholangiocarcinoma	36	1	2.78%
Mature T and NK Neoplasms	73	2	2.74%

Source: submitted as SCE Appendix 3 - US Prevalence

2.2. Analysis of Current Treatment Options

The Applicant's Position:

In addition to melanoma, NSCLC and ATC, targeted BRAF-inhibitor based therapies have been recently approved for two V600-mutation-positive solid tumors (vemurafenib as monotherapy for ECD, and encorafenib + cetuximab for metastatic colorectal cancer). Other BRAF V600E-mutated advanced solid tumors have no mutation specific FDA-approved treatments and have typically been treated with standard-of-care regimens for these cancers without the benefit of molecularly targeted therapies. Given BRAF V600-mutations are driver mutations in many cancers, only representative examples are described in Table 3.

Table 3 Applicant - Disease Type and Respective Available Treatments

Disease type	Adult subjects
BTC	For unresectable or metastatic BTC patients who progressed after gemcitabine based chemotherapy, there are no established second line treatments (Lamarca 2014, Valle 2016). Active symptom control (ASC) addressing the development of biliary obstruction and its complications along with oxaliplatin/5-FU chemotherapy can be considered as the standard of care in this population (Lamarca 2019). The overall median survival of BTC patients receiving second line chemotherapy was only 9.9 months (Schweitzer 2019). ORR with pembrolizumab (approved for patients with MSI-H/dMMR) was also reported to be low at 27% (Lemery 2017). In addition, MSI-H/dMMR occurs in only up to 3% of BTC (Zhao 2019).
LGG	Surgery remains a mainstay of therapy (NCCN 2021, Bush 2016), however, most patients with incompletely resected tumors will require additional treatment. Chemotherapy and radiotherapy are options for patients with unresectable tumors or in whom recurrence was observed after surgery. Systemic therapies are limited for patients with grade I glioma, grade II gangliogliomas and pleomorphic xanthroastrocytomas who progress after surgery/radiotherapy, or grade II astrocytomas and oligodendrogliomas progressing after chemotherapy (NCCN 2021). No standard of care exists for this population and further chemotherapy and radiation have been suggested by NCCN for astrocytomas and oligodendrogliomas. The ORR with chemotherapy for subjects who are progressing after prior chemotherapy is 10-25% (Van den Bent 2003, Soffietti 2003, Kaloshi 2010).
HGG	Surgery is commonly the initial therapeutic approach for tumor debulking and obtaining tissue for diagnosis (Stupp et al 2014). Adjuvant treatment with fractionated external beam radiotherapy + temozolomide in adjuvant, neoadjuvant and/or concurrent setting or radiotherapy + neoadjuvant or adjuvant PCV is the standard of care for grade 3 gliomas. Standard brain radiotherapy with concomitant and adjuvant temozolomide chemotherapy is the current standard of care for subjects with glioblastoma up to 70 years of age and good performance (NCCN 2021, Stupp et al 2014). For subjects with poor performance score , hypofractionated radiotherapy or temozolomide or best palliative/supportive care are the only recommended options available. For adult HGG subjects at recurrence, Bevacizumab monotherapy for recurrent glioblastoma in subjects who had undergone prior chemoradiotherapy has been approved by the FDA based on non-comparative study and a single arm study (Avastin USPI 2021), but improvement in overall survival appears to be limited (Birk 2017, Verhoeff 2009, Wick 2010). Other approved treatments such as carmustine wafers (Gliadel® wafers) showed no OS benefit (Chowdhary 2015) and treatment with tumor-treating fields had an objective response rate of 14% (Mun 2017). Clinical trials are the preferred option for eligible patients (NCCN 2021). Finding new treatments that can show clinical benefit is highly desired in these patients.

GIST	Although imatinib is an effective first-line treatment, most patients inevitably relapse or progress. Sunitinib and regorafenib are approved agents for second and third-line treatment, but they have shown limited activity and/or tolerability, defining an unmet need for patients with imatinib-resistant GIST (Mei 2018).
ASI	Curative surgical resection is the treatment of choice for ASI. However, no standard protocol has been defined for use when the disease is unresectable or relapsed. There are no approved treatments for advanced ASI. Recent NCCN guidelines suggest Folfox regimen, Capox or Folfoxiri ± bevacizumab as frontline therapy and nivolumab ± ipilimumab for MSI-H tumors for advanced or metastatic disease (NCCN 2021). Given the rarity of the disease, no large-scale prospective studies have been conducted to compare efficacy of various chemotherapeutic agents. Retrospective studies have demonstrated that chemotherapy, including Folfox and Capox provide clinical benefit with longer survival time (de Bree 2018). In general, response rates with chemotherapy agents have ranged from 6% and 41% and the median overall survival was between 9 to 18.6 months (Speranza et al 2010).
Pediatric subjects	
LGG	For unselected pediatric subjects with LGG requiring first systemic therapy, the anticipated ORR is about 40-50% with chemotherapy (Ater et al 2012). However, for the population selected for BRAFV600-mutation, the ORR is approximately 20% (Lassaletta et al 2017). There are no published data on the ORR for second systemic therapy for subjects with BRAFV600 mutation-positive LGG, as studied in this trial but expected to be lower given the adverse prognostic significance of BRAF V600-mutations.
LCH	The BRAFV600-mutation is associated with a worse prognosis in pediatric subjects with LCH (Heritier et al 2016), including more severe disease at diagnosis, reduced response rate to first line chemotherapy (78% ORR vs 97% ORR with wild type BRAF), and greater rate of reactivation of disease. Although salvage therapy with cladribine and cytarabine may be effective initially, responses are not durable in R/R MS RO+ high risk LCH patients. In addition, WHO grade 4 hematologic toxicities and severe infections are common with this therapy (Donedieu 2015).

The FDA's Assessment:

As indicated by the applicant above, treatment options may vary for patients with BRAF-mutation positive tumors.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Tafinlar (dabrafenib; 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).

The FDA's Assessment:
Dabrafenib and trametinib have been approved for patients with BRAF V600E (or K for melanoma) metastatic melanoma, NSCLC, and ATC. Trials in metastatic melanoma have demonstrated improvements in PFS, OS, and/or ORR. The approvals in NSCLC and ATC were based on clinically meaningful effects on ORR and response duration.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

The key FDA interactions related to this sNDA (discussion of the design of the pivotal ROAR study CDRB436X2201, and agreement on the sNDA format and content) are summarized in Table 4.

Table 4 Applicant - Key FDA interactions

Meeting Type	Date	Meeting Purpose
Type C	02-Nov-2012	Discuss the design of Study X2201 to obtain a mutually agreed upon design for one study in multiple rare cancers.
Type C	27-Mar-2013	Obtain agreement on the design and Bayesian statistical analysis plan of Study X2201 as a possible registration study supporting effectiveness claims in rare cancers.
Type C	16-Dec-2019	Discuss the updated results of Study X2201 along with supportive data from Study XUS35T (NCI-MATCH) Subprotocol H, and seek feedback on the acceptability of the data to support the use of dabrafenib in combination with trametinib for the treatment of patients with BRAF V600 mutation-positive tumors.
Type C	22-Oct-2020	Discuss adequacy of the content and format of the proposed sNDA submission package and overall regulatory submission strategy.
Type B	11-May-2021	Share updated results from Study X2201, Interim Analysis 16; results from the pediatric studies A2102 and X2101; and discuss the proposed filing strategy, content, and format of the planned efficacy supplement for the tumor agnostic indication.

The FDA's Assessment:
During the Dec 16, 2019, meeting, FDA acknowledged the potential merits of developing dabrafenib and trametinib for uncommon cancers with a V600E mutation; however, FDA stated

the data (March 2019 data cutoff) were not yet sufficient to assess that the effect is expected to occur across tumor types (also acknowledging the lack of effect in patients with mCRC). Novartis indicated during the meeting that in the NCI MATCH trial, only 0.4% of systemically screened patients with cancers other than NSCLC, CRC, ATC, or melanoma had an identified BRAF mutation; as such, studying the effect of dabrafenib and trametinib was difficult. It was Novartis's position that the consequence of not approving dabrafenib and trametinib for patients with known rare tumor types where the combination has high activity was greater than the drugs not being effective for extremely rare individual patients with, for example, a specific BRAF-positive rare tumor type. During the meeting, FDA also provided advice regarding the response classification for patients with low grade gliomas.

The October 2020 meeting did not provide updated data but discussed Novartis's proposed approach to future sNDA submissions for dabrafenib and trametinib. The information provided by Novartis regarding the May 11, 2021, Type B meeting are accurate.

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

4.1. Office of Scientific Investigations (OSI)

Although bias in the assessment of this application is reduced via blinded independent central review of imaging, one high enrolling site was selected for an on-site inspection. The site enrolled 30 patients with BRAF V600E mutated rare cancers. The inspection of the clinical site (NIH) was classified as NAI as no objectional conductions or practices were identified by the FDA inspector.

4.2. Product Quality

The indication to be approved under these supplements is served by formulations described in approved product labeling. (b) (4)

4.3. Devices and Companion Diagnostic Issues

Across protocols for Studies X2201, X2101, A2102, and XUS35T (NCI-MATCH), central confirmation of BRAF mutation status was not required for enrollment. In Studies X2201, X2101, and A2102, patients with a BRAF V600 mutation-positive result per local test in a

certified laboratory or equivalent were eligible for enrollment per the inclusion criteria. Archival or fresh tumor tissue at screening for retrospective central confirmation was also required. In Studies X2101 and A2102, retrospective central confirmation was for determination of BRAF V600 mutation status where in Study X2201, central confirmation determination was for BRAF V600E mutation status. The NCI-MATCH study required patients who had their BRAF mutation status assessed by designated external laboratory assays to be subsequently confirmed by the MATCH assay.

For Study X2201, 89% of patients with solid tumors enrolled by local tests had confirmation of V600E centrally (see Table 5); the 90% result in the Table below includes patients with hematological malignancies.

Table 5: BRAF V600E Central Confirmation Status - Study X2201

n (%)	ATC N=36	BTC N=43	GIST N=1	LGG N=13	HGG N=45	ASI N=3	HCL N=55	MM N=10	Total N=206
BRAF V600E mutation confirmed	33 (92)	39 (91)	1 (100)	8 (62)	42 (93)	3 (100)	50 (91)	10 (100)	186 (90)
No BRAF V600E or V600K mutation detected	2 (6)	0	0	2 (15)	1 (2)	0	4 (7)	0	9 (4)
Quantity not sufficient to test	1 (3)	2 (5)	0	1 (8)	0	0	0	0	4 (2)
Invalid	0	1 (2)	0	2 (15)	2 (4)	0	0	0	5 (2)
No tumor Indicated	0	1 (2)	0	0	0	0	0	0	1 (<1)

Source: copied from submission, Table 10-11, CSR Study X2201

The majority of patients without central confirmation were patients without identifiable tumor in the sample sent for central assessment (defined as no tumor indicated) or had missing samples (e.g., due to withdrawal of consent or site inability to obtain sample).

Other reasons for inability to centrally confirm the BRAF result were due to the test (invalid test that did not yield positive or negative results), quantity of biopsy not sufficient, or that the specimen was received but not tested (SNRT, e.g., sample did not meet assay requirements).

In supportive study XUS35T (NCI-MATCH), 3 patients (out of a total of 33 patients) did not have their external (non-MATCH) laboratory test result for BRAF mutation status confirmed by the MATCH assay, see Table 6. If these patients are excluded, the ORR by investigator assessment would increase slightly from 13/33 (39%) to 13/30 (43%), whilst ORR by independent reviewer assessment would decrease slightly from 14/33 (42%) to 12/30 (40%).

Table 6: Response in Patients without Central BRAF V600E Confirmation- Study XUS35T

Patient ID (b) (6)	Investigator assessed response	Independent reviewer assessed response
	SD	PR
	PD	PD
	SD	PR

Source: modified from IR response from Novartis received on Feb 4, 2022

In Study Pediatric X2101, central BRAF V600 mutant status for patients with BRAF V600 mutant low grade glioma treated with combination therapy in Part C and Part D showed that 13 patients (36.1%) had samples with positive results, 15 patients (41.7%) had samples with no tumor indicated, 4 patients had samples missing, and 4 patients had samples with results that were not evaluable.

FDA asked Novartis to perform a sensitivity analysis for response in Study X2101 for BRAF V600E tumors that were centrally validated vs not validated (i.e. local only).

Table 7: INV-Response in Patient with Glioma without Central BRAF V600E Confirmation- Study X2101

	Centrally confirmed N=13 n(%)	Not centrally confirmed N=23 n(%)	All subjects N=36 n(%)
Best overall response			
Complete response (CR)	1 (7.7)	2 (8.7)	3 (8.3)
Partial response (PR)	7 (53.8)	9 (39.1)	16 (44.4)
Stable disease (SD)	4 (30.8)	11 (47.8)	15 (41.7)
Progressive disease (PD)	1 (7.7)	0	1 (2.8)
Unknown	0	1 (4.3)	1 (2.8)
Objective response rate (ORR: CR+PR)	8 (61.5)	11 (47.8)	19 (52.8)
ORR 95% CI	(63.1, 100)	(71.5, 100)	(82.4, 100)
Clinical benefit rate (CBR: CR+PR+SD)	12 (92.3)	22 (95.7)	34 (94.4)
CBR 95% CI	(64.0, 99.8)	(78.1, 99.9)	(81.3, 99.3)

Source: copied from IR response from Novartis received on Feb 4, 2022

Table 8: Independent Response in Patients with Glioma without Central BRAF V600E Confirmation- Study X2101

RANO Criteria: Old RANO (2010)

	Centrally confirmed N=13 n (%)	Not centrally confirmed N=23 n (%)	All subjects N=36 n (%)
Best overall response			
Complete response (CR)		1 (4.3)	1 (2.8)
Partial response (PR)	3 (23.1)	3 (13.0)	6 (16.7)
Stable disease (SD)	9 (69.2)	16 (69.6)	25 (69.4)
Progressive disease (PD)	1 (7.7)	2 (8.7)	3 (8.3)
Non-CR/Non-PD (NN)			
Unknown		1 (4.3)	1 (2.8)
Objective response rate (ORR: CR+PR)	3 (23.1)	4 (17.4)	7 (19.4)
ORR 95% CI	(5.0, 53.8)	(5.0, 38.8)	(8.2, 36.0)
Clinical benefit rate (CBR: CR+PR+SD)	12 (92.3)	20 (87.0)	32 (88.9)
CBR 95% CI	(64.0, 99.8)	(66.4, 97.2)	(73.9, 96.9)

Source: copied from IR response from Novartis received on Feb 4, 2022

The post-hoc sensitivity analyses of response rates in centrally confirmed BRAF V600E LGG compared to local review only was higher overall, in both investigator (62%; 95% CI: 63.1, 100 vs 47.8%; CI 71.5,100, respectively) and independent review (23.1%; 95% CI: 5, 53.8 vs 17.4; CI: 5, 38.8). This could potentially be due to the central confirmation that the tumor specimen was truly BRAF V600E; however, this cannot be verified.

CDRH was consulted in regard to the development of a companion diagnostic (CDx). In summary, at the time of this review, CDRH stated:

a. Since there is no contemporaneous submission submitted to CDRH for a CDx for the indication sought, there should be a PMC for a companion diagnostic to identify BRAF V600E positive patients for treatment with Tafinlar and Mekinist.

b. (b) (4)

c. (b) (4)

(b) (4)

For post-marketing commitments (PMC), see Section 13.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This section is not applicable.

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Dabrafenib is an inhibitor of certain mutated forms of BRAF kinases. Trametinib is a reversible inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2. The current supplemental NDA submissions are for the use dabrafenib in combination with trametinib for the treatment of patients (b) (4) with BRAF V600E mutation who have progressed following prior treatment or have no alternative treatment options.

The proposed dosage in adult patients is the same as the recommended dosage for melanoma and NSCLC indications, i.e., 150 mg of dabrafenib orally twice a day (BID) in combination with trametinib 2 mg orally once daily (QD) administered at least one hour before or at least two hours after a meal. The safety and efficacy of dabrafenib in combination with trametinib were demonstrated in Study X2201 for adult patients with BRAF V600E mutated cancers with several histologies and in Study X2101 for pediatric patients with BRAF V600E mutated cancers.

The Applicant proposed the body weight (BW)-based tiered dosing shown below for pediatric patients ≥6 years old using the currently available strengths for dabrafenib (50 and 75 mg capsules) and trametinib (0.5 and 2 mg tablets) supported by data from two pediatric dosing finding studies and a population pharmacokinetics (popPK) analysis.

Table 9 - FDA Dosing by Body Weight

Body Weight	Recommended dabrafenib dose	Recommended trametinib dose
(b) (4)		
26 to 37 kg	75 mg twice daily	1 mg once daily
(b) (4)		

Body Weight	Recommended dabrafenib dose	Recommended trametinib dose
[redacted] (b) (4)		
≥ 51 kg	150 mg twice daily	2 mg once daily

Source: USPI trametinib and dabrafenib

The FDA recommends removing [redacted] (b) (4)

(b) (4)

The FDA also recommends changing [redacted] (b) (4)

(b) (4)

FDA observed that the simulated Cavg for trametinib for pediatric patients weighing 26 – 37 kg is below the target Cavg. This concern was resolved with additional data from ongoing study G2201 showing that 11 out of these 12 patients achieved a Cavg at or above the target Cavg.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in these supplemental NDAs and recommends approval from a clinical pharmacology perspective. The key review issues with the specific recommendations/comments are summarized below:

Review Issue	Recommendation and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness come from two studies: • Phase 2 Study X2201 in adult patients with cancers with a BRAF V600E mutation. Study X2201 demonstrated clinically meaningful improvements in the overall response rate (ORR) for a wide range of tumors including anaplastic thyroid cancer (ATC), biliary tract cancer (BTC), low grade glioma (LGG), high grade glioma (HGG), hairy cell leukemia (HCL), and multiple myeloma (MM). • Phase 1/2a Study X2101 in pediatric patients with BRAF V600-positive solid tumors. Patients with glioma or Langerhans cell histiocytosis (LCH) treated with dabrafenib plus trametinib demonstrated clinically meaningful improvements in the ORR.

<table>
<tr><th>Review Issue</th><th>Recommendation and Comments</th></tr>
<tr><td>General dosing instructions</td><td>The proposed adult dosage regimen of dabrafenib 150 mg BID in combination with trametinib 2 mg orally QD is acceptable based on efficacy and safety results from Study X2201 that demonstrated clinical benefit for patients with BRAF V600E-positive tumors.</td></tr>
<tr><td>Dosing in pediatric patients</td><td>The Applicant proposed the following BW-based tiered dosing for pediatric patients ≥6 years old for dabrafenib and trametinib supported by data from two pediatric dosing finding studies and a popPK analysis.
<table>
<tr><th>Body Weight</th><th>Recommended dabrafenib dose</th><th>Recommended trametinib dose</th></tr>
<tr><td>(b) (4)</td><td></td><td></td></tr>
<tr><td>26 to 37 kg</td><td>75 mg twice daily</td><td>1 mg once daily</td></tr>
<tr><td>(b) (4)</td><td></td><td></td></tr>
<tr><td>≥ 51 kg</td><td>150 mg twice daily</td><td>2 mg once daily</td></tr>
</table>

The FDA recommends removing (b) (4) (b) (4)
The FDA also recommends changing (b) (4) (b) (4)
FDA observed that the simulated Cavg of 9 ng/mL for trametinib for this weight group is below the target Cavg of 10 ng/mL. However, this concern has been resolved with additional data from ongoing Phase 2 pediatric study G2201, which shows that the mean Cavg in the 12 patients in this weight group was 15 ng/mL, above the target Cavg.
</td></tr>
</table>

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

A comprehensive overview of the ADME properties, clinical pharmacokinetics (PK), and drug-drug interaction (DDI) potential of dabrafenib and trametinib in the adult population is available in prior submissions. The clinical pharmacology assessment in this application focused on clinical PK data and analyses to support the additional use in patients with rare BRAF-positive tumors and pediatric dosing in subjects aged 6 to 17 years, based on:

- The dabrafenib and trametinib concentrations observed in Study X2201 for supporting the adult dose used in subjects with BRAF V600 mutation-positive solid tumors;
- The dabrafenib and trametinib PK observed in Studies A2102 and X2101 for supporting the weight adjusted dose used for 6 to 17 year old pediatric subjects;
- Pediatric population PK analyses, which were used to determine the recommended doses of dabrafenib and trametinib in rare BRAF V600E mutation-positive advanced solid tumors in pediatric 6 to 17 year old subjects receiving currently marketed solid oral formulations (dabrafenib capsules and trametinib tablets).

Steady state dabrafenib and trametinib pre-dose concentrations in the pivotal adult study X2201 were comparable with those observed in previous phase 3 studies in the adult population. The pre-dose median concentrations at week 8 were 66.9 ng/mL for dabrafenib (n=39) and 11.1 ng/mL for trametinib (n=40)), and were comparable to previously determined pre-dose concentrations for dabrafenib (33.8 ng/mL and 60.2 ng/mL in metastatic melanoma, studies MEK115306 and BRF113220; 76.3 ng/mL in adjuvant treatment of melanoma in study BRF115532 and 70.2 ng/mL in NSCLC in study BRF113928) and trametinib (9.5 ng/mL and 10.8 ng/mL in metastatic melanoma in studies MEK115306 and BRF113220; 8.77 ng/mL in adjuvant treatment of melanoma in study BRF115532 and 12.9 ng/mL in NSCLC in study BRF113928).

Studies A2102 and X2101 in pediatric subjects investigated weight-based dosing of both dabrafenib and trametinib. The dose escalation parts of each study were used to identify recommended doses for the expansion phases. For both compounds, PK data were collected in both the dose finding and expansion parts of the studies. The combination of dabrafenib with trametinib in the pediatric population was studied in Study X2101.

A PopPK analysis using the pediatric PK data collected with both solid and liquid dosage forms in studies A2102 and X2101 (and limited additional data from the ongoing pediatric study G2201) was performed to support a pediatric dosing posology that aimed to match previously established exposures in adult patients. The PopPK analysis determined apparent clearance rates in pediatric patients aged 6 to 17 years old (14.77 L/h for dabrafenib and 5.02 L/h for trametinib) that were comparable to the previously established rates in adult patients (16.7 L/h

for dabrafenib and 5.07 L/h for trametinib). For both compounds, body weight was a significant PopPK covariate and was the main patient-related factor affecting exposure in pediatric patients. While an additional age-based distinction was used for dosing in the pediatric clinical trials (studies A2102 and Study X2101), weight was identified as the most appropriate determinant to guide pediatric dosing in clinical practice (both because of large variability in weight for a given age and to avoid the requirement for a dose change when reaching an age threshold).

For dabrafenib, a target dose of 4.5 ± 1.4 mg/kg/d (to be given in two equally divided doses BID, and capped at the adult dose of 150 mg BID) was determined for pediatric patients. The ±30% range (3.1 to 5.9 mg/kg/d) was based on the interpatient PK variability of 37-38 % previously determined in adult patients.

For trametinib, a target dose of 0.03 ± 0.009 mg/kg/d (capped at the adult dose of 2 mg/d) was determined for pediatric patients. The ±30% range (0.021 to 0.039 mg/kg/d) was based on the interpatient PK variability of 32-58% previously determined in adult patients and was also selected to remain below the dose level at which Dose Limiting Toxicities (DLTs) were observed in study X2101 (0.04 mg/kg/d).

In conjunction with the currently available strengths for dabrafenib (50 and 75 mg capsules) and trametinib (0.5 and 2 mg tablets) and with a view to align the dosing guidance for both products to the extent possible, the posology weight ranges shown in Table 10 were identified.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's summary of the pharmacokinetics of dabrafenib and trametinib in adult patients and the approach for using a PopPK analysis to bridge pediatric exposure for dabrafenib and trametinib in support of the proposed pediatric dosages. Refer to Section 6.2.2.1 for the FDA assessment on the proposed dosages for pediatric patients, specifically the inadequate dosages for pediatric patients with BW of (b) (4)

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

Adult population: The recommended posology of dabrafenib + trametinib combination therapy for the treatment of adult patients with rare BRAF V600E mutation-positive advanced solid tumors is proposed to be the same as for the currently approved indications (melanoma, ATC, NSCLC): A flat (non-weight-adjusted) dose of dabrafenib 150 mg BID + trametinib 2 mg QD, with treatment to be continued until disease progression or unacceptable toxicity. This is supported by pharmacokinetic data from Study X2201, which do not indicate any substantial differences in exposure between adult patients with rare BRAF-positive tumors and the (adult) subjects in any of the currently approved indications.

Pediatric population: The proposed posology in pediatric patients is based on PK data from pediatric studies A2102 and X2101 (which used weight-adjusted dosing) and a PopPK analysis which indicated a similar drug clearance in adult and pediatric (6 to 17 year old) subjects for dabrafenib and trametinib, with geo-mean average plasma concentrations that were close to the target effective exposures previously established in adults (average concentrations (Cavg) of approximately 300 ng/mL for dabrafenib and of ≥ 10 ng/mL for trametinib).

Table 10 Applicant – Proposed dabrafenib and trametinib posology in pediatric patients

Body Weight	Recommended dabrafenib dose	Recommended trametinib dose
(b) (4)		
26 to 37 kg	75 mg twice daily	1 mg once daily
(b) (4)		
≥ 51 kg	150 mg twice daily	2 mg once daily

The FDA's Assessment:

The FDA agrees with the Applicant's recommended dosages of dabrafenib 150 mg BID + trametinib 2 mg QD in adult patients.

For pediatric patients, the FDA does not agree with the proposed dosages for pediatric patients (b) (4)

The FDA was also concerned that the predicted exposures for the trametinib dose of 1 mg/day in pediatric patients weighing 26 to 37 kg indicate that only 36% of pediatric patients in this weight group would achieve the target Cavg of ≥10 ng/mL; however, during the review of the current sNDA, the Applicant submitted additional PK data in their ongoing pediatric study G2201 showing that the Cavg for patients in this weight tier was 15 ng/mL, above the target Cavg. The FDA therefore finds the trametinib dosage for this weight tier to be acceptable.

(b) (4)

(b) (4)

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

No therapeutic individualization of dabrafenib and trametinib is proposed for adult patients based on demographic factors or specific populations, consistent with the posology in the currently approved indications. Weight-based dosing in pediatric patients weighing 50kg or less is discussed in Section 6.2.2.1. 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:

The FDA generally agrees with the Applicant that no additional therapeutic individualization of dabrafenib and trametinib is needed in the adult population. No new data for therapeutic individualization has been submitted for this submission.

See Section 6.2.2.1 for FDA's assessment for weight-based pediatric dosing.

BRAF inhibition and tumor-specific resistance:

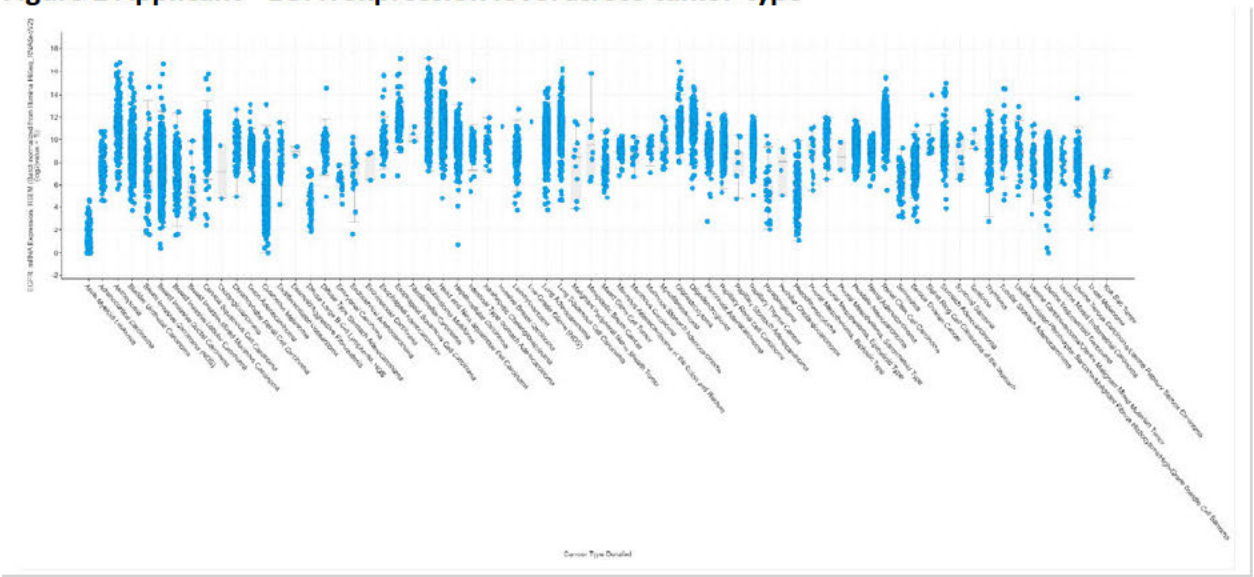
The proposed labeling includes a limitation of use for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition and for patients with wild-type BRAF solid tumors.

Differences in the magnitude of response to BRAF inhibitors (BRAFi) between BRAF V600E melanoma (50-60%) and BRAF V600E colorectal cancer (>5%) support that some tumor types present significant levels of intrinsic/adaptive resistance to BRAFi. Resistance mechanisms are diverse and not systematically characterized, especially for rare BRAF V600E tumors. Intrinsic resistance has generally been attributed to pre-existing genetic alterations in the tumor or surrounding stromal cells leading to activation of oncogenic pathways such as PI3K/AKT and MAPK pathways (Hanrahan 2022, McKenna 2021). Adaptive resistance mechanisms arise to compensate for the loss of BRAF signaling in response to BRAFi and are developed early in response to therapy. A well-documented example is the reactivation of MAPK pathway through the relief of ERK-generated negative feedback inhibition of EGFR in colorectal cancer. In contrast to colorectal cancer cells, melanoma cells are reported to express lower levels of EGFR, and as such may not be as susceptible to BRAFi-induced MAPK pathway activation (Turski 2016). In response to an FDA information request (February 25, 2022), the Applicant argued that papillary thyroid carcinoma (Shah 2017), NSCLC (Planchard 2017, Subbiah 2019) and

glioma (Wen 2018a, Wen 2018b, Kaley 2018) were reported to respond to BRAFi despite having EGFR expression levels similar to those observed in colorectal cancer (Figure 1 Applicant - EGFR expression level across tumor type (Figure 1). The reviewer acknowledges that EGFR expression levels are heterogeneous and vary within and across tumor types. While high EGFR expression levels may represent a mechanism driving resistance to BRAFi in colorectal cancer, it may not explain resistance in other tumor types. Therefore, even though some of the driver resistance mechanisms may share a common theme (e.g., MAPK (re)activation), potential variations of these mechanisms within and across tumor types may hinder the proper identification of BRAF V600E tumors less likely to respond to BRAFi and present a challenge to a tumor agnostic indication.

The current evidence supports a limitation of use in colorectal cancer as proposed in labeling. Data are not sufficient to extend the limitation of use to other tumors based on intrinsic/adaptive resistance. For a discussion of paradoxical activation of MAPK, and limitation of use in the context of BRAF wild-type, please refer to Section 8 and original dabrafenib NDA review.

Figure 1 Applicant - EGFR expression level across tumor type



Source: Applicant's Figure 4.1 Appendix (cBioPortal, Response to FDA information request received February 25, 2022)

OOD DD Comment: Although EGFR-mediated resistance has been overcome to some extent through EGFR blockade with a competing BRAF-inhibitor (in combination with cetuximab), data are not available from randomized trials to establish a treatment regimen for dabrafenib in CRC. Therefore, I agree with the proposed limitation of use. Furthermore, although one cannot exclude the possibility that another BRAF-positive tumor type would not share a similar

resistance mechanism, data appear to show that the more common (relative) BRAF-positive tumor types are sensitive to treatment (e.g., BTC, glioma [activity was also observed in hematological malignancies for which Novartis did not seek approval]). Given the data in the application, if a resistant tumor type existed, patients with the BRAF-tumor combination would be exceedingly rare such that even in this setting the overall risk-benefit of the tumor agnostic approach would be favorable given that individual studies in many tumor types would be highly difficult to conduct (e.g., ameloblastoma). In the post-market setting, Novartis will obtain additional data with respect to treatment effect in different tumor types.

6.2.2.3. Outstanding Issues

The Applicant's Position:

None.

The FDA's Assessment:
There is no dose available in pediatric patients with body weight <26 kg. This issue is to be addressed in a future submission with results from the ongoing pediatric study G2201.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

A comprehensive overview of the ADME properties, clinical pharmacokinetics, and DDI potential of dabrafenib and trametinib in the adult population is available in previous submissions. The PopPK analysis determined apparent clearance rates in pediatric patients (14.77 L/h for dabrafenib and 5.02 L/h for trametinib) that were comparable to the previously established rates in adult patients (16.7 L/h for dabrafenib and 5.07 L/h for trametinib). For both compounds, body weight was a significant PopPK covariate and was the main patient-related factor affecting exposure in pediatric patients.

The FDA's Assessment:
Clinical PK data were collected in Trials X2201, X2101, and A2101 in addition to clinical pharmacology and PK characteristics of dabrafenib and trametinib from the adult population provided in previous submissions. Topline PK data from each trial are summarized below.

Study X2201
The clinical pharmacology data in adults is derived from pivotal trial X2201 (N= 206), which was a Phase 2, open-label, basket study in adult patients with rare cancers (ATC, BTC, GIST, glioma, ASI, GST, HCL or MM) with a BRAF V600E mutation. Patients were dosed with dabrafenib 150

mg BID in combination with trametinib 2 mg QD, PK samples were collected at Week 4, Week 8, and Week 12. The exposure parameter values of dabrafenib and trametinib are in the same range of those observed in the BRAF V600-positive unresectable or metastatic melanoma population from the previous original NDA submission. (See Table 11 and Table 12)

Table 11 FDA – Summary of dabrafenib and its metabolites PK concentration-time data for all cohorts – Primary and expansion Cohorts Combined (Study X2201)

Visit	Collection time	Dabrafenib (ng/mL)	Hydroxy-dabrafenib (GSK2285403) (ng/mL)	Desmethyl-dabrafenib (GSK2167542) (ng/mL)
Week 4	Pre-dose	74.0 (65) (11-1950)	73.9 (65) (12-740)	333.0 (65) (48-1190)
Week 4	1 to 3 hours post-dose	1330.0 (145) (9-6080)	642.0 (145) (7-2400)	352.0 (145) (0-2250)
Week 8	Pre-dose	66.9 (39) (10-1710)	66.8 (39) (10-1360)	319.0 (39) (57-1320)
Week 12	Pre-dose	62.2 (29) 12-2580	73.5 (29) (16-1540)	319.0 (29) (127-687)

Data are expressed as median (n) (minimum-maximum).
Note: Hydroxy-dabrafenib and desmethyl-dabrafenib are dabrafenib metabolites that are likely to contribute to the clinical activity of dabrafenib. Their pharmacokinetics and clinical pharmacology have been reviewed in previous submissions.
Source: X2201 CSR, pg 215.

Table 12 FDA – Summary of trametinib PK concentration-time data for all cohorts combined—Primary and expansion cohorts combined (Study X2201)

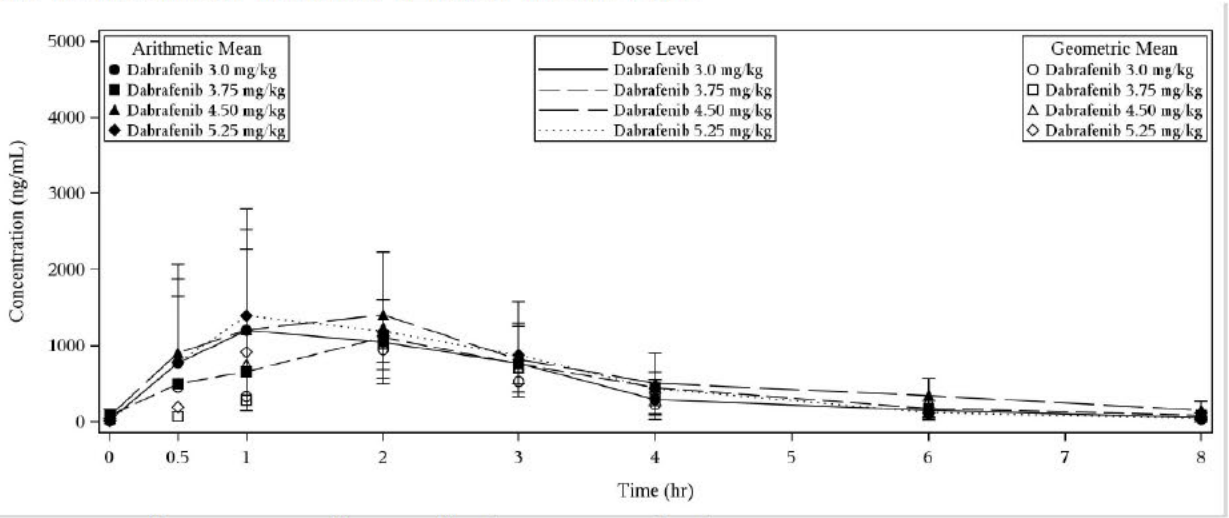
Visit	Collection time	n	Trametinib (ng/mL) median (min-max)
Week 4	Pre-dose	65	10.2 (5-20)
Week 4	1 to 3 hours post-dose	135	19.6 (5-48)
Week 8	Pre-dose	40	11.1 (7-31)
Week 12	Pre-dose	22	9.8 (4-20)

Source: X2201 CSR, pg 215.

Study A2102

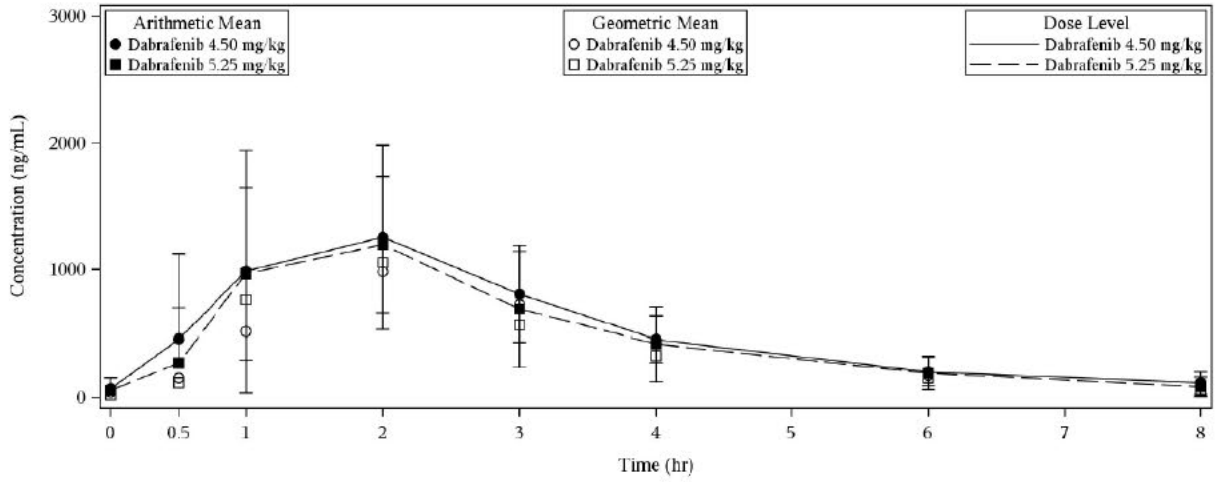
Study A2102 was a two-part, Phase 1/2a, open-label, dabrafenib monotherapy dose escalation and dose expansion study in pediatric patients with BRAF V600-positive cancers. Limited PK data were collected for Day 1 in Study A2102; therefore AUC0-12 and AUC0-inf could not be calculated for single dose PK profile. Plasma concentration-time profiles after repeat doses for dabrafenib are presented in Figure 2 (Part 1) and Figure 3 (Part 2). Tmax at the RP2D in Part 2 is 2 hours, similar to the Tmax in adults. The dabrafenib clearance (CL/F) was estimated to be 16.7 L/h, and the apparent central volume (Vc/F) was estimated to be 58.5 L based on PopPK modeling. Table 13 shows pre-dose median dabrafenib plasma concentrations at Day 15 of Week 3 (steady state) for Parts 1 and 2.

Figure 2 FDA - Geometric Mean and Arithmetic Mean for Plasma Dabrafenib Concentration-Time Profiles in Part 1 of Study A2102 at Week 3 Day 5



Source: Appendix 16.2.5—Compliance and/or drug concentration data, pg. 27.

Figure 3 FDA - Geometric Mean and Arithmetic Mean for Plasma Dabrafenib Concentration-Time in Part 2 of Study A2101 at Week 3 Day 15



Source: Appendix 16.2.5—Compliance and/or drug concentration data, pg. 29.

Table 13 FDA – Day 15 of Week 3 pre-dose median concentrations of dabrafenib in Study A2101.

Dose (mg/kg)	Number of Patients	Dabrafenib Concentration (ng/mL)	Hydroxy-dabrafenib Concentration (ng/mL)	Desmethyl-dabrafenib Concentration (ng/mL)
Part 1				

3	3	11.8	19.3	111
3.75	10	23.6	37.4	268
4.5	8	58.4	47.4	288
5.25	6	13.1	12.3	193
Part 2				
4.5	27	40	56.6	266
5.25	37	20.0	24.0	218

Source: Adapted from data in Study A2102 CSR.

Study X2101

Study X2101 was a four-part, Phase 1/2a, open-label study in pediatric patients with BRAF V600-positive cancers to study both trametinib monotherapy and dabrafenib/trametinib combination therapy. Steady state PK parameters for dabrafenib and trametinib were calculated and reported for Day 15 of Cycle 1 only, as there is limited PK data for Day 1 and Day 22. Further PK analyses were not performed by disease type due to small sample sizes within each disease type. See Table 14 and Table 15 below for summary of trametinib average steady state plasma concentrations for each part of the trial. See Table 17 and Table 18 for summary of dabrafenib average steady state plasma concentrations for Parts C and D.

Table 14 FDA – Summary of trametinib average steady state plasma concentration, Cycle 1 Day 15 – Part A (PK population).

Age group	Statistics of Cavg (ng/mL)	TMT 0.0125 mg/kg/day	TMT 0.025 mg/kg/day	TMT 0.032 mg/kg/day	TMT 0.04 mg/kg/day
< 2 years	n	0	4	1	2
	Geo mean		10.9	13.4	20.5
	CV% geo mean		18.0	NE	36.5
2 - < 6 years	n	1	5	8	0
	Geo mean	5.63	13.5	15.4	
	CV% geo mean	NE	13.9	17.4	
6 - < 12 years	n	1	3	0	8
	Geo mean	4.56	17.3		22.5
	CV% geo mean	NE	33.9		18.6
≥ 12 years	n	1	6	0	5
	Geo mean	7.44	15.0		19.7
	CV% geo mean	NE	28.3		20.7

N/A: not applicable, NE: not estimable

Source: X2101 CSR, pg. 157.

Table 15 FDA – Summary of trametinib average steady state plasma concentration, Cycle 1 Day 15 - Part B (PK population).

Age group	Statisitcs of Cavg (ng/mL)	Neuro-blastoma	LGG fusion	NF-1 with PN	BRAF V600 mutant solid tumor^	All subjects 0.025 mg/kg/day
< 2 years	n	1	0	1	0	2
	Geo mean	15.9		16.9		16.4
	CV% geo mean	NE		NE		4.3
2 - < 6 years	n	1	4	4	5	14
	Geo mean	14.0	9.86	12.9	14.3	12.5
	CV% geo mean	NE	16.1	35.3	16.0	26.2
6 - < 12 years	n	5	5	3	1	14
	Geo mean	13.2	14.9	14.3	36.0	15.1
	CV% geo mean	31.5	40.2	22.6	NE	40.0
≥ 12 years	n	2	1	2	3	8
	Geo mean	21.2	22.2	12.0	14.2	15.9
	CV% geo mean	55.8	NE	3.7	52.1	43.7

N/A: not applicable, NE: not estimable

Source: X2101 CSR, pg. 157.

Table 16 FDA – Summary of trametinib average steady state plasma concentration, Cycle 1 Day 15 - Part C (PK population).

Age group	Statistics of Cavg (ng/mL)	TMT 0.025 mg/kg/day + 50% DRB RP2D	TMT 0.025 mg/kg/day + 100% DRB RP2D	TMT 0.032 mg/kg/day + 100% DRB RP2D
< 2 years	n	0	0	1
	Geo mean			11.5
	CV% geo mean			NE
2 - < 6 years	n	0	0	5
	Geo mean			9.54
	CV% geo mean			30.7
6 - < 12 years	n	1	1	0
	Geo mean	12.1	13.8	
	CV% geo mean	NE	NE	
≥ 12 years	n	0	0	0
	Geo mean			
	CV% geo mean			

N/A: not applicable, NE: not estimable

Source: X2101 CSR, pg. 165.

Table 17 FDA – Summary of dabrafenib average steady state plasma concentration, Cycle 1 Day 15 - Part C (PK population).

Age group	Statistics of Cavg (ng/mL)	TMT 0.025 mg/kg/day + 50% DRB RP2D	TMT 0.025 mg/kg/day + 100% DRB RP2D	TMT 0.032 mg/kg/day + 100% DRB RP2D
< 2 years	n	0	0	1
	Geo mean			360
	CV% geo mean			NE
2 - < 6 years	n	0	2	5
	Geo mean		324	332
	CV% geo mean		15.4	54.1
6 - < 12 years	n	1	1	0
	Geo mean	294	449	
	CV% geo mean	NE	NE	
≥ 12 years	n	2	4	0
	Geo mean	215	336	
	CV% geo mean	205.4	301	

N/A: not applicable, NE: not estimable

Source: X2101 CSR, pg. 166.

Table 18 FDA – Summary of trametinib average steady state plasma concentration, Cycle 1 Day 15 - Part D (PK population).

Age group	Statistics of Cavg (ng/mL)	LGG	LCH	All subjects TMT 0.032 mg/kg/day + 100% DRB RP2D	All subjects TMT 0.025 mg/kg/day + 100% DRB RP2D
2 - < 6 years	n	2	3	5	0
	Geo mean	13.3	7.59	9.50	
	CV% geo mean	2.0	13.5	33.1	
6 - < 12 years	n	9	2	0	11
	Geo mean	13.4	9.12		12.5
	CV% geo mean	16.6	35.3		24.3
≥ 12 years	n	9	1	0	10
	Geo mean	12.2	6.00		11.4
	CV% geo mean	25.0	NE		33.2

N/A: not applicable, NE: not estimable

Source: X2101 CSR, pg. 173.

Table 19 FDA –Summary of dabrafenib average steady state plasma concentration, Cycle 1 Day 15 - Part D (PK population).

Age group	Statistics of Cavg (ng/mL)	LGG	LCH	All subjects TMT 0.032 mg/kg/day + 100% DRB RP2D	All subjects TMT 0.025 mg/kg/day + 100% DRB RP2D
2 - < 6 years	n	1	5	6	0
	Geo mean	278	362	346	
	CV% geo mean	NE	31.5	30.2	
6 - < 12 years	n	9	2	0	11
	Geo mean	387	354		381
	CV% geo mean	44.2	6.7		39.4
≥ 12 years	n	9	1	0	10
	Geo mean	304	165		286
	CV% geo mean	50.6	NE		52.1

N/A: not applicable, NE: not estimable
Source: X2101 CSR, pg. 173.

Population PK analyses for pediatric patients
The Applicant conducted PopPK analyses with the PK data from pediatric patients ages 6 to 17 years old from three clinical studies (A2101, X2101 and G2201). The analyses described PK of dabrafenib and trametinib in pediatric patients ages 6 to 17 years old and projected PK exposures for dabrafenib and trametinib to navigate the pediatric dosing regimen. No significant discrepant PK characteristics were reported other than body weight effect on PK, compared to those previously reported in adult patients. The PopPK analyses support weight-based dosing regimen in pediatric patients. It should be noted that current PopPK analyses for both dabrafenib and trametinib have limitations in characterizing covariate effects (i.e., formulation). See Section 19.4 OCP Appendices for detailed assessment.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data and the Applicant's Position:

Pediatric geo-mean average plasma concentrations were close to the target effective exposures previously established in adults (average concentrations (Cavg) of approximately 300 ng/mL for dabrafenib and of ≥ 10 ng/mL for trametinib). The exposure observed in adult and pediatric patients with rare BRAF V600E mutation-positive solid tumors was comparable to the clinically effective exposure reported in previous adult Phase 3 studies in the approved indications (BRAF mutation-positive melanoma, NSCLC and ATC).

The FDA's Assessment:

The FDA generally agrees with the Applicant that the clinical pharmacology program provides supportive evidence of effectiveness of dabrafenib in combination with trametinib for treatment of patients with tumors with BRAF V600E mutations for adults and pediatric patients with the exception of pediatric patients weighing <26 kg, who should be removed from the indication due to insufficient exposure at the proposed dosage. See Section 6.3.2.2.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data and the Applicant's Position:

The proposed dosing schedule (BID for dabrafenib and QD for trametinib) and exposure range in this sNDA matches the currently approved dosing schedule.

The FDA's Assessment:

The FDA agrees with the Applicant's position on the proposed dosing regimen for adult patients and pediatric patients with the exception of pediatric patients weighing < 26 kg. (b) (4)

Dabrafenib Pediatric Dosing

The pediatric dosing for dabrafenib was determined based on safety and tolerability data from Study A2101 and the popPK analysis. In Study A2101, dabrafenib monotherapy doses ranging from 3 to 6 mg/kg/day were studied in Phase 1 to determine the recommended Phase 2 dose (RP2D). Notably, patients in the study could potentially take a liquid or capsule formulation. A maximum tolerated dose (MTD) was not established during Phase 1, as dose escalation was concluded when the observed exposure met or exceeded the target exposure derived from adults (Cavg of 300 ng/mL). The RP2D of 5.25 mg/kg/day for patients < 12 years old and 4.5 mg/kg/day for patients ≥ 12 years old were therefore determined based on exposure comparisons between pediatric and adult patients. However, the Applicant's proposed dose is based on weight tiers and the capsule formulation (See Section 6.1), and therefore does not strictly follow the RP2D determined in Study A2101.

PopPK analysis predicted that although patients in the lowest weight tier (b) (4) . See Table 20 for predicted dabrafenib steady state exposures based on the PopPK model. (b) (4) .

Table 20 FDA – Predicted dabrafenib steady-state exposures following Applicant's proposed dosage.

Geometric mean (5th-95th percentiles)					
	Dose, BID	Cavg, ng/mL	Cmax, ng/mL	AUC, ng*h/mL	Ctrough, ng/mL
Adults	150 mg BID	**Target: 300 ng/mL**	1819 (747, 4444)	5362 (2797, 9077)	86.5 (24.1, 286)
(b) (4)					
26-37 kg	75 mg BID	378.7 (188, 691)	1816 (758, 4362)	4545 (2252, 8291)	42.5 (8.6, 191)
(b) (4)					
>=51 kg	150 mg BID	458.9 (247, 737)	2095.4 (875, 4991)	5507 (2960, 8844)	74.8 (18.4, 253)

Source: Adapted from Applicant's Population PK analysis report, Table 6-3 (pg. 21) and Table 11-1 (pg. 100).

In addition, the FDA recommends changing the dosing for pediatric patients in the (b) (4) This recommendation is based on analyses showing that patients (b) (4)

Table 21 FDA – Predicted dabrafenib steady-state exposures for FDA recommended dose for (b) (4) kg.

Geometric mean (5th-95th percentiles)					
	Dose, BID	Cavg, ng/mL	Cmax, ng/mL	AUC, ng*h/mL	Ctrough, ng/mL
Adults	150 mg BID	**Target: 300 ng/mL**	1819 (747, 4444)	5362 (2797, 9077)	86.5 (24.1, 286)
(b) (4)					

Source: Adapted from Applicant's response (received on 1/14/2022) to Clinical Pharmacology IR (dated 1/7/2022).

Trametinib Pediatric Dosing

The pediatric dosing for trametinib was determined based on safety and tolerability data from Study X2101 and a popPK analysis. In Study X2101 part A, trametinib monotherapy was studied at doses ranging from 0.0125 mg/kg/day to 0.04 mg/kg/day to determine RP2D. Three out of 19 patients experienced a DLT in the 0.025 mg/kg/day cohort, and 5 out of 15 patients experienced a DLT in the 0.04 mg/kg/day cohort. PK results from the 0.025 mg/kg/day cohort also showed that patients in this cohort achieve target exposures of 10 ng/mL based on the adult populations. The RP2D for trametinib was therefore determined to be 0.025 mg/kg/day based on safety and PK data obtained from Part A for patients ≥6 years old. However, similar to dabrafenib, the Applicant's proposed dose is based on weight cohorts and the tablet

formulation, and therefore does not strictly follow the RP2D determined in Part A. PopPK analysis showed that patients in the lowest weight cohort (b) (4) See Table 22 for predicted trametinib steady-state exposures. Therefore, the Applicant's proposed trametinib dosing regimen is not appropriate for patients weighing (b) (4) and should be removed from the proposed indication.

Table 22 FDA – Predicted trametinib steady-state exposures following Applicant's proposed dosage.

Geometric mean (5th-95th percentiles)					
	Dose	Cavg, ng/mL	Cmax, ng/mL	AUC, ng*h/mL	Ctrough, ng/mL
Adults	2 mg QD	**Target: 10 ng/mL**	23.8 (14.6, 40.9)	312.5 (204, 476)	11 (6.8, 17.4)
(b) (4)					
26-37 kg	1 mg QD	9 (6, 13.7)	18.4 (11.7, 30.4)	217 (144, 328)	6.8 (4.2, 11)
38-50 kg	1.5 mg QD	11.9 (8, 17.9)	23.2 (14.7, 37.8)	287 (192, 430)	9.5 (5.9, 15.1)
>=51 kg	2 mg QD	13 (8.4, 20.2)	24.2 (15, 40.5)	311 (201, 485)	10.9 (6.8, 17.5)

Source: Adapted from Applicant's Population PK analysis report, Table 6-4 (pg. 21) and Table 11-2 (pg. 101).

Although the simulated Cavg for trametinib in the second lowest weight tier of 26-37 kg is also lower than the target Cavg, additional data from the ongoing Study G2201, a phase 2 trial evaluating dabrafenib in combination with trametinib in pediatric patients with BRAF V600-positive LGG or HGG, showed that mean trametinib exposure levels in this weight tier were higher than the target exposure level. For 12 pediatric patients weighing 26 – 37 kg who were given trametinib 0.75 to 1 mg QD as either the solid or liquid formulation, the mean Cavg was 15 ng/mL, with a range of 9.8 to 23.5 ng/mL (Table 23). The dosage of trametinib for pediatric patients in this weight tier is therefore acceptable.

Table 23 FDA – Trametinib Cavg data for patients in the 26 to 37 kg BW group in pediatric Study G2201.

Patient ID	Body Weight (kg)	Trametinib Dose (mg)	Cavg (ng/mL)	Trametinib Formulation	corr-Cavg (ng/mL) equivalent to 1 mg tablet*
(b) (6)	37	1	12.6	solution	11.2
	36	1	9.8	tablet	9.8
	33	1	16.1	tablet	16.1
	33	1	14.1	tablet	14.1
	32	0.75	10.9	solution	12.9
	30	0.75	13.9	solution	16.5
	29	0.75	10.3	solution	12.3
	29	0.75	19.7	solution	23.5
	28	0.75	10.2	solution	12.2
	28	0.75	19.8	solution	23.5
	28	0.88	16.3	solution	16.6
	27	0.75	16.7	solution	19.9
				Geo-mean =	**15**
				CV =	**29%**

Note: AUC_{inf} for the oral solution formulation was observed to be 12% higher than AUC_{inf} for the tablet formulation. The Cavg is shown as both the observed Cavg as well as the corrected Cavg normalized to 1 mg and corrected for the difference in bioavailability.
Source: Applicant Response to Information Request, received Feb 18, 2022.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data and the Applicant's Position:

Weight-based dosing in pediatric patients weighing 50kg or less is discussed in Section 6.2.2.1.

The FDA's Assessment:

There is no additional data pertinent to dosing for subpopulations based on intrinsic factors. Weight-based dosing in pediatric patients weighing 50 kg or less is reviewed in Section 6.2.2.1 and Section 6.3.2.2.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data and the Applicant's Position:

No new food-drug or drug-drug interaction data were generated for this sNDA. The interaction profile determined in previous applications continues to apply.

The FDA's Assessment:

FDA agrees with the Applicant that there is no new data for food-drug or drug-drug interactions, and that the interaction profile determined in previous submissions applies here.

X X

Lingshan Wang, PhD
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Primary Reviewer

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Description

Table 24 Listing of Clinical Trials in adults 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
CDRB436X2201 (ROAR) NCT02034110	Phase II, open-label	dabrafenib 150 mg BID plus trametinib 2 mg QD, oral	ORR by investigator assessment DoR, PFS, OS	Until unacceptable toxicity, disease progression, or death **Follow-up**: post treatment every 4 weeks for 6 months, then every 3 months	206	Adult subjects (≥18 years of age) with rare cancers (ATC, BTC, GIST, glioma, ASI, GST, HCL or MM) with a BRAF V600E mutation	41 centers in 14 countries
CTMT212XUS35T (NCI-MATCH-H) NCT04439292	Phase II, open-label	dabrafenib 150 mg BID plus trametinib 2 mg QD, oral	ORR by investigator assessment, PFS, DoR, OS	Until unacceptable toxicity, disease progression, death, study withdrawal or extraordinary medical circumstances **Follow-up**: for response until progression and for survival for 3 years from date of registration	35	Adult subjects with solid tumors with BRAF V600E, V600K, V600R or V600D mutations	30 centers in the US
ORR: Overall response rate, PFS: Progression free survival, DoR: Duration of response, OS: Overall survival							

Supportive studies in Pediatric population

Table 25 Listing of Clinical Trials in pediatric population 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

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
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

Other sources of supportive evidence

Source	N (subjects enrolled)	Target subpopulation (BRAF V600+ solid tumors)	Age (n)	Treatment and tumor types / histology details (n)
Managed Access Program (MAP)	263	255	Adult (n=131); Pediatric (<6y: n=38; 6-17y: n=41); age not reported (n=53)	Dabrafenib + trametinib combination therapy: CNS; Thyroid; Histiocytic disorders; BTC; GI tumors (9); Gynecological cancers (4); Other (ameloblastoma 2, neuroblastoma 1, glomus tumor 1, breast cancer 1, hepatic cancer 2, squamous cell carcinoma 2, non-small cell lung cancer 1, salivary gland cancer 2, sarcoma 1, colorectal cancer 1, NoS 7)
Literature case reports		126	Adult (n=87) Pediatric (n=39)	Dabrafenib + trametinib (n=76); dabrafenib monotherapy (n=50): CNS cancers (56), histiocytic disorders (38), BTC (9), ameloblastoma (4), pancreatic cancer (4), gynecologic cancers (3), PTC (3), renal tumors (3), sarcomas (2), GIST (1), pituitary cancer (1), breast cancer (1), salivary duct cancer (1)
Investigator-initiated trials		74	Adult (n=74)	PTC (53), differentiated thyroid cancer (21)

Source: Summary of Clinical Efficacy-Table 1-11

The FDA's Assessment:

FDA agrees with the Applicant's summary of clinical trials relevant to the application. For this sNDA application, the clinical data for FDA analysis of efficacy were based on data from 105 adult patients from study X2201, 26 adult patients from study XUS35T, and 36 pediatric patients from study X2101 with solid tumor and excluded patients enrolled in these studies with non-solid tumors, ATC, and NSCLC. Novartis also provided supportive information from the literature and their managed access program. Because these did not include a denominator or could be subject to publication bias (case reports in literature) or did not specifically assess tumor size (managed access program), these data were not relied upon to assess the treatment effects for the intended population (rather they were exploratory or supportive information). Safety analysis was based on 206 adult patients enrolled in study X2201 and 48 pediatric patients enrolled in study X2101.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant's Description:

This submission is based mainly on the results from 4 clinical studies: study CDRB436X2201 (GSK code: BRF117019; the ROAR study), study CTMT212XUS35T (NCI code: EAY131-H; the NCI-MATCH subprotocol H study), study CTMT212X2101 (GSK code: MEK116540) and study CDRB436A2102 (GSK code: BRF116013). In the following text, these studies are referred to by their abbreviated Novartis study codes X2201, XUS35T, X2101 and A2102 respectively. Studies X2201 and XUS35T are ongoing, and studies X2101 and A2102 are completed.

8.1.1. Study X2201

Study Design

This is an ongoing (data cut-off 14-Sep-2020 for interim analysis #16) Phase II, open-label, non-randomized, multi-center "basket" study of oral dabrafenib in combination with oral trametinib in adult subjects with rare cancers harboring the BRAF V600E mutation. Subjects could be included in one of 9 tumor cohorts: anaplastic thyroid cancer (ATC), biliary tract cancer (BTC), gastrointestinal stromal cancer (GIST), adenocarcinoma of small intestine (ASI), low-grade gliomas (LGG), high-grade gliomas (HGG), Non-seminomatous germ cell tumors (NSGCT/NGGCT), multiple myeloma (MM) and hairy cell leukemia (HCL). Enrolment was based on local determination of BRAF V600E mutation status.

Subjects received dabrafenib 150 mg twice daily orally plus trametinib 2 mg once daily orally on a continuous dosing schedule, with dose reductions allowed for toxicity. Disease assessments for solid tumors (CT or MRI scans) were conducted at baseline, then every 8 weeks during the first 48weeks, then every 12 weeks thereafter. Response assessment criteria were based on the specific histology (RECIST version 1.1 for ATC, BTC, GIST, ASI and NSGCT/NGGCT and RANO for glioma). Treatment continued until unacceptable toxicity, disease progression, or death. Post-treatment follow-up visits were conducted monthly for 6 months, then every 3 months.

Discussion of the study design

A basket trial design with multiple cohorts or "baskets" such as the one employed in this study allows for the simultaneous evaluation of clinical activity and early signals of efficacy in multiple tumor types in a short period and with fewer subjects (Subbiah et al 2018).

To investigate clinical activity, an adaptive design utilizing a Bayesian hierarchical model was employed. Due to the common pathway activation with the BRAF V600E mutation, multiple

histologies may demonstrate substantial response to BRAF plus MEK inhibition. However, pathways of resistance may vary between histologies resulting in different responses to the targeted combination therapy. There may be 'clusters', or subsets of histologies, some in which the combination therapy is effective, and others not. The design based on a hierarchical Bayesian model borrows information from histologies that demonstrate similar response rates based on the accumulated study data allowing for the possibility that the response rate for each histology may differ. If response rates are sufficiently different across particular histologies, the design recognizes this difference and borrowing is minimal. This design allows for multiple interim evaluations of the accumulating data to determine if at least one histologic cohort should discontinue enrollment early due to either success or futility. The number of clusters used to characterize the distribution of histologies is solely based on the observed responses. At each interim analysis as well as the final analysis, the entire model including clustering specification is fit based on the available data. If a given cohort was stopped early for efficacy, an uncapped histology specific expansion cohort was opened to allow for additional subject enrollment. Subjects in the expansion cohort provided supportive efficacy and safety data and did not contribute to the Bayesian modelling of ORR.

Selection of dose: The dosing regimen in this study was dabrafenib 150 mg twice daily with trametinib 2 mg once daily (the currently approved posology in adult melanoma, NSCLC and ATC patients)**.**

The FDA's Assessment:

FDA agrees with the Applicant's summary of the study design for Study X2201, the pivotal trial. The basket trial design was considered appropriate for evaluation of treatment of unresectable or metastatic rare BRAF-positive tumors. The doses were based on the US package inserts for each drug (U.S. package insert, Tafinlar, and Mekinist, accessed on 22 Feb 2022). The primary objective was ORR based on the investigator assessed tumor response as defined by RECIST v1.1 for solid tumor types, modified RANO (HGG), and RANO (LGG) for gliomas or established response criteria for specific hematologic malignancies. The study allowed for an assessment of response rate in various tumor types. Because the study over or under-represented tumors compared to a general population of patients tested for BRAF mutations, the study better captured treatment effects among the various tumor types (rather than all patients with BRAF-positive tumors).

Study population:

Key inclusion criteria

- Male or female, ≥ 18 years old
- Eastern Cooperative Oncology Group (ECOG) performance status: 0, 1 or 2
- Advanced disease and no standard treatment options as determined by locally/regionally available standards of care and treating physician's discretion.

- BRAF V600E mutation-positive tumor confirmed by an approved local laboratory or a Sponsor designated central reference laboratory.
- ATC, BTC, GIST, NSGCT/NGGCT, and ASI: at least one measurable lesion per RECIST 1.1 outside of a prior radiation field or within the field with evidence of progression.
- Able to swallow and retain orally administered medication.

Cohort specific eligibility criteria for the solid tumor cohorts were:

- **ATC cohort**: histologically or cytologically confirmed, unresectable, metastatic ATC, including ATC originating from within well-differentiated thyroid cancers or an ATC as part of a thyroid carcinoma of another histologic type. Must have undergone prior external beam radiotherapy and/or surgery to the primary tumor unless primary tumor that has been totally removed by surgical excision whereby no radiotherapy was indicated or has only metastatic disease that does not require radiation or surgery
- **BTC cohort**: histologically or cytologically confirmed, unresectable, metastatic or locally advanced or recurrent adenocarcinoma of the biliary tract or gallbladder; and had progressed on or demonstrated intolerance (despite standard measures of supportive care and dose reduction) to treatment with a gemcitabine-based chemotherapy regimen.
- **GIST cohort**: histologically confirmed diagnosis of c-Kit and platelet-derived growth factor receptor A (PDGFRA) wild-type GIST, metastatic or locally advanced, unresectable, or recurrent post-surgical disease, and progressed on or demonstrated intolerance (despite standard measures of supportive care and dose reduction) to treatment with a TKI.
- **ASI cohort**: histologically confirmed, metastatic or locally advanced ASI, adenocarcinoma of the ampulla, or adenocarcinoma of the peri-ampulla, progressed on or demonstrated intolerance (despite standard measures of supportive care and dose reduction) to one line of chemotherapy.
- **LGG cohort**: histologically confirmed recurrent or progressive WHO Grade 1 or 2 glioma; measurable non-enhancing disease based on RANO criteria. Enhancing disease was acceptable for pilocytic astrocytomas. For WHO Grade 2 glioma, subject must not have been eligible for treatment with chemotherapy.
- **HGG cohort**: histologically confirmed recurrent or progressive WHO Grade 3 or 4 glioma, prior treatment with radiotherapy and first-line chemotherapy or concurrent chemoradiation therapy, measurable disease as per RANO.

Key exclusion criteria:

- Prior treatment with BRAF and/or MEK inhibitor(s); Chemotherapy, immunotherapy, biologic therapy or chemoradiation with delayed toxicity within 21 days (or within 42 days if prior therapy contained nitrosourea or mitomycin C) prior to enrollment Chemotherapy or biologic therapy without evidence of delayed toxicity within 14 days prior to enrollment; Investigational product(s) within 30 days or 5 half-lives, whichever was longer, prior to enrollment; In France, subject had participated in any study using investigational products

within 30 days prior to enrollment in this study.

- History of malignancy with confirmed activating RAS mutation at any time.
- Prior radiotherapy less than 14 days prior to enrollment, except for glioma and ATC. Treatment-related AEs had to be resolved prior to enrollment.
- Prior major surgery less than 14 days prior to enrollment. Any surgery-related AE had to be resolved prior to enrollment.
- Prior solid organ transplantation or allogenic stem cell transplantation.
- History of another malignancy.
- Presence of active brain metastases (except for glioma cohorts), symptomatic or untreated leptomeningeal or spinal cord compression, interstitial lung disease or pneumonitis, history or evidence of cardiovascular risk including left ventricular ejection fraction below the institutional lower limit of normal or history of retinal vein occlusion.

The FDA's Assessment:

FDA agrees with the Applicant's description of the study population. Patients with NSCLC and melanoma were not allowed to enroll on this study. The term "low grade glioma" encompasses a heterogeneous group of tumors with variable biology, clinical features, standards of care and natural histories. For example, diffuse astrocytomas (WHO grade II) are highly infiltrative gliomas, occurring primarily in adults, that typically progress to high grade glioma (HGG) despite treatment with radiation therapy (RT) and chemotherapy while pilocytic astrocytomas (WHO grade I) are generally well-circumscribed pediatric tumors with low potential for malignant transformation that may be considered cured after complete surgical resection. Therefore, as described in the updated WHO classification of tumors of the central nervous system (CNS) (Louis, 2016) gliomas with a more circumscribed growth pattern that lack IDH mutations (e.g., pilocytic astrocytoma, pleomorphic xanthoastrocytoma [PXA]) were categorized as a distinct group of tumors from diffuse astrocytoma or oligodendroglioma. Similarly, anaplastic ganglioglioma is a glioneuronal tumor with distinct features from glioblastoma multiforme (GBM) and were not included in the category of HGG. Additional molecular features were captured (e.g., IDH mutation, RELA fusion) to assist in characterizing these tumors.

Study Endpoints

The Applicant's description:

All the study objectives and their respective endpoints are presented in Table 26.

Table 26 Applicant – Study X2201 objectives and their respective endpoints

Objectives	Endpoints
Primary	

Objectives	Endpoints
To determine the ORR of dabrafenib and trametinib combination therapy in subjects with selected rare BRAF V600E mutated solid tumors or hematologic malignancies	Investigator assessed tumor response as defined by: RECIST, v1.1 for solid tumor histologies (ATC, BTC, GIST, ASI, and NSGCT/NGGCT), RANO (LGG) and modified RANO (HGG), for gliomas or established response criteria for specific hematologic malignancies
Secondary	
To determine the duration of response (DoR) of dabrafenib in combination with trametinib in subjects with selected rare BRAF-mutated cancers	Investigator assessed duration of response
To determine PFS of dabrafenib in combination with trametinib in subjects with selected rare BRAF-mutated cancers	Investigator-assessed PFS
To determine OS of dabrafenib in combination with trametinib in subjects with selected rare BRAF-mutated cancers	Overall survival
To determine the safety of dabrafenib in combination with trametinib in subjects with selected rare BRAF-mutated tumors	Change from baseline in physical examination findings, vital signs, AEs, laboratory values and cardiac assessments
Exploratory	
To identify candidate predictive and prognostic molecular features for each histology; to characterize treatment-emergent malignancies and to characterize the mechanisms of underlying AEs of special interest	Comprehensive characterization of molecular background (DNA, RNA, protein) in tumor tissue at baseline and disease progression
To investigate the relationship between plasma trametinib, dabrafenib, and dabrafenib metabolite concentrations, changes from baseline in tumor DNA, RNA or proteins and evaluate progressive disease (PD) response.	Plasma concentrations at the end of the dosing interval (Ctau) for dabrafenib metabolites hydroxy-dabrafenib and desmethyl dabrafenib. Predicted average plasma dabrafenib and trametinib concentrations (Cavg). Parameters describing the relationship between Ctau or Cavg and changes from baseline in tumor DNA, RNA or proteins. Assessments of progressive disease (PD) markers of the MAPK pathway.
To evaluate changes from baseline in HRQOL	Changes from baseline in HRQOL using the EORTC-QLQ-C30

The FDA's Assessment:

FDA agrees with the Applicant's summary of endpoints for Study X2201. FDA notes that PFS and OS are considered exploratory endpoints in this single-arm study.

For HGG, modified RANO (Wen et al 2010) criteria was used and required to have contrast enhancing lesions with clearly defined margins by MRI scan as target lesions. In addition, assessments of T2/fluid attenuated inversion recovery (FLAIR) abnormalities, neurological and steroid status were required for assessment. RANO for LGG criteria (Van den Bent et al 2011) were developed with the intent to assess diffuse gliomas with limited enhancement (e.g., diffuse astrocytoma) and are not appropriate to evaluate pilocytic astrocytoma or pleomorphic xanthoastrocytoma. Therefore, evaluation of both gadolinium enhancing disease and non-enhancing disease was required. Hence, a modified RANO criteria by Van den Bent et al (2011) was used and both contrast non-enhancing or enhancing lesions with clearly defined margins by MRI scan could be selected as measurable lesions. In addition, assessments of T2/FLAIR abnormalities, neurological and steroid status were required for assessment.

Even with appropriate characterization, assessing radiographic response is challenging as many of these tumors will have variable MRI enhancement depending on multiple factors (e.g., prior RT, histology). Additionally, RANO for LGG includes a category for "minor response" that was excluded in the definition of ORR, as agreed upon in the Type C meeting on Dec 16, 2019.

For independent review of ATC, BTC, GIST, and ASI, RECIST 1.1 was used and for patients with glioma, RANO with similar requirements described above for investigator assessment were followed.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The interim statistical reporting and analysis plan for Study X2201 was finalized on 26-Oct-2020.

Data from all participating centers were pooled prior to analysis. There were no formal plans for any stratification or for investigating any covariates. Data was reported by histologic cohort. Bayesian hierarchical model-based interim decision rules were used to identify whether one or more histologic cohorts halt enrolment early for futility/harm or benefit based on efficacy data.

The following analysis populations were defined:

- Intent-to-Treat (ITT): all enrolled subjects regardless of whether or not treatment was administered.
- BRAF V600E Population: all ITT subjects with BRAF V600E mutation verified by a certified central reference laboratory.
- ITT/Evaluable: all enrolled subjects who had either progressive disease, withdrawn consent or died, or had sufficient data to determine the best overall response at the interim analysis.
- BRAF V600E/Evaluable: all subjects with BRAF V600E mutation verified by a certified central laboratory, who had either progressive disease, withdrawn consent or died, or had sufficient data to determine the best overall response at the interim analysis.
- All-Treated Subjects (ATS): all subjects who received at least one dose of dabrafenib or trametinib.

The analysis populations used for assessment of efficacy and safety endpoints are summarized in Table 27.

Table 27 Applicant – Study X2201 Analysis populations used for efficacy and safety endpoint assessments

Analysis Intent	Analysis Populations
Bayesian modelling of ORR	ITT/Evaluable (primary analysis cohort). BRAF V600E/Evaluable (primary analysis cohort)

Analysis Intent		Analysis Populations
Futility/expansion	Other analyses of ORR, DoR, PFS and OS	ITT/Evaluable (primary analysis cohort). ITT/Evaluable (primary analysis + expansion cohorts)
Efficacy		BRAF V600E/Evaluable (primary analysis cohort). BRAF V600E/Evaluable (primary analysis + expansion cohorts)
Safety	All	ATS (primary analysis + expansion cohorts)

Analysis of ORR: The primary efficacy endpoint is the overall response rate (ORR), based on Investigator assessment of response and calculated as the proportion of subjects who had a confirmed response relative to the total number of subjects in the corresponding analysis population. The best confirmed overall response was the best confirmed response recorded based on Investigator assessment from the start of treatment until disease progression or start of new anti-cancer therapy, whichever was earlier, and was determined programmatically based on Investigator response assessment at each time point.

Confirmed ORR was analyzed using an integrated analysis across the histologic cohorts with a Bayesian hierarchical model. Model-based interim decision rules were used to identify whether one or more histologic cohorts halt enrolment early for futility/harm or benefit based on efficacy data. A summary of the Bayesian hierarchical model-based analysis was provided.

Descriptive summaries of best confirmed response and standard frequentist estimates of ORR along with the corresponding 95% exact confidence interval was provided for each histologic cohort in order to characterize the observed response data and support the model-based analyses for ORR.

Supportive analysis of primary efficacy assessment included independent radiology review of solid tumor cohorts as was performed for the previously approved ATC indication (NDA 202806/S-010). These data were provided separately for each histological cohort.

Other efficacy endpoints: All secondary efficacy endpoints (DOR, PFS, and OS) were analyzed for cohorts with n>1. Investigator-assessment and IRC-assessment (solid tumor cohorts) of DoR and PFS were provided.

- For responders, DoR is defined as the time from first documented evidence of CR or PR (the first response prior to confirmation) until time of documented disease progression or death from any cause.
- PFS is defined as the interval between the first dose and the date of disease progression or death from any cause.
- OS is defined as the time from first dose until death from any cause.

SAP Amendments

The SAP was amended 5 times and the key features of each amendment are presented below.

Table 28 Applicant – Study X2201 SAP amendments

Version and date	Summary of key changes
Amendment 01 24-Feb-2016	The original RAP was updated to reflect changes adopted in Protocol Amendment 06 and to refine various details of the plan.
Amendment 02 26-Mar-2018	Changes are made to align with the analysis plan for the ATC regulatory submission and to add new analyses for publication of results (from IA#13).
Amendment 03 14-May-2019	Updates for IA#15: Clarified criteria for confirmed response in section 11.1. Addition of clinical review of anti-cancer therapies (section 9.3.5). Addition of subgroup analyses for WHO Grade 3/4 Glioma cohort. Addition of 24-month Kaplan-Meier estimates of duration of response, progression-free survival and overall survival in place of 18-month estimates. Removal of analyses which include only the expansion cohort.
Amendment 04 20-Oct-2020	Later timing of final analysis and change to primary analysis population (from BRAF V600E to ITT) as included in protocol amendment 11. Change to on-therapy period to include 30 days after last dose. Modification of protocol deviation displays to present t COVID-19 deviations separately. Addition of tables displaying censoring reasons for DoR and PFS with additional information about censoring due to COVID-19 related protocol deviations. Addition of tables and listings to display MGMT methylation and IDH1/2 mutation status for glioma cohorts. Update to hepatic lab displays based on updated Novartis guidance. Addition of best response and duration of response summaries for WHO Grade 1 or 2 Glioma excluding Minor Response from overall response categories, per FDA feedback. Change to derivation of extended time without adequate assessment in HCL following the change to disease assessment schedule in protocol amendment 11.
Amendment 05 26-Oct-2020	Amended to include PK tables and listings for IA#16.

The FDA's Assessment:

FDA agrees with the Applicant's description of the SAP and Amendments.

Protocol Amendments

The Applicant's description

The study protocol was amended 11 times (Table 29).

Table 29 Applicant – Study X2201 Protocol amendments

Version and date	Summary of key changes
Amendment 1 25-Jul-2013	Removed cardiac enzyme (troponin) from clinical laboratory assessments to be completed. Clarified inclusion criteria. Mandatory tumor sample and BM aspirate sample required at Screening. Added confirmation that no histology-specific exclusion criteria were included. Corrected reference to CT scan (i.e., changed to MRI scan) as CT is not permitted in these cohorts. Removed statement that progressive disease sample collection was mandatory for ATC, HCL and MM cohorts as it was inconsistent with the time and events tables.
Amendment 2 18-Dec-2013	Revised primary endpoint table to reflect use of Modified RANO and RANO is assessing tumor response in gliomas. Added new general inclusion criterion #5 to clarify inclusion of subjects with specified histology and no available treatment options per local or regional standard of care.

Version and date	Summary of key changes
	Inserted new text (safety) to provide estimation of blood volume collected during the study. Removed reference to QTcF as stopping criteria are based on QTcB.
	Removed the use of MUGA scan to assess cardiac ejection fraction; request procedure to be performed by same operator throughout the study; removed requirement of reporting symptomatic events as SAE, and to provide that in case of asymptomatic absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institutional LLN, study treatment (dabrafenib and trametinib) must be temporary or definitely discontinued.
	Added a new section "Monitoring of Non-Cutaneous Secondary/Recurrent Malignancy" to reflect required monitoring for use of dabrafenib as per the special warnings and precautions. Added new inclusion criterion #4 applicable to GIST subjects requiring progression with imatinib and sunitinib treatment.
	Added new criterion applicable to WHO Grade 2 glioma subjects: only subjects for whom chemotherapy are not an option may be eligible for study participation.
	Revised inclusion criterion #2 to clarify prior treatment received by subjects with MM. Revised cardiovascular events to indicate that cardiovascular events may occur with not only trametinib but also dabrafenib or both in combination.
	Revised QTc prolongation in line with special warnings and precautions for dabrafenib.
	Clarified the management of hypertension referring to subjects with persistent increase in systolic and/or diastolic BP that may be treatment-related and thus to be managed by recommendations. It also guides on actions to be taken with the study treatment in the event of justified asymptomatic or symptomatic hypertension.
	Added new section/text to address management of asymptomatic (Grade 2) and symptomatic (Grade 3 or 4) valvular toxicity. Revised cutaneous SCC to remove reference to keratoacanthomas; added requirement of dermatological examinations monthly for 6 months after treatment discontinuation. Revised "Medications to be Used with Caution" to update reference for drugs known to induce QTc prolongation.
	Revised to include guidelines for management and dose reduction for renal insufficiency when considered treatment related. Added Table 26 deleted the reference to a CLIA approved laboratory under Tumor Tissue for BRAF V600E mutation pre-screening as this certification is not applicable to countries other than the US.
	Added new section to announce the formation of a data monitoring committee to review safety and efficacy data during the interim analyses and to indicate that an independent hematologist and oncologist will serve on this committee.
Amendment 3 21-Jul-2014	Revised the "Concomitant medication and non-drug therapies section" to clarify the use of anticoagulants, palliative radiation and use of dabrafenib during radiotherapy.
	Added language pertaining to retrospective confirmation of histology type for ATC cohort.
	Revised the vision changes and ophthalmic exam language with standard asset language.
	Revised disease assessment sections to clarify type of assessment, timing and evaluation criteria.
	Revised the stopping criteria, management, and dose modification for special events to reflect changes in standard asset language. Added Ex Vivo sub study for HCL cohort.
Amendment 4 24-Oct-2014	Revised the protocol in response to the recent decision for the substantial amendment of a Voluntary Harmonization Procedure (VHP-SA) submission of Amendment 3 of the protocol. Revised to update regulatory approval status of trametinib monotherapy and trametinib in combination with dabrafenib. Revised Inclusion criteria #5 and #4, respectively, to clarify that the criterion applies to subjects who are already receiving corticosteroid therapy. Revised criterion #1 to clarify that the status of delayed toxicity applies to all types of therapy and not solely chemotherapy. Revised text to align with the Summary of Product Characteristics language (VHP request).

Version and date	Summary of key changes
Amendment 5 28-apr-2015	Revised LVEF stopping criteria to indicate when to report as SAE. Removed BRAT diet from diarrhea management guidelines. Removed oral contraceptives from the prohibited medications list and provided supporting information regarding interaction with dabrafenib. Specified oral formulation for selected prohibited medications and medications to be used with caution. Clarified which samples to be submitted for confirmation of BRAF mutation status; definition of SAEs revised for protocol specific SAEs based on updated list of AE of special interest. Removed ATC sample collection for possible independent histology confirmation. Added new section for malignancies to include section on cutaneous squamous cell carcinoma, new primary melanoma and non-cutaneous malignancies based on updated asset language for dabrafenib and trametinib. Clarified use of NSAIDs in subjects with MM for pyrexia and action to be taken with dabrafenib with pneumonitis. Revised disease assessments for solid tumors to clarify imaging modality to be used for specific cohorts. Revised statistical section to reflect change in study sample size and trial simulation output.
Amendment 6 05-Jan 2016	Updated the risk assessment for dabrafenib and trametinib combination therapy. Clarified the dose modification wording for dabrafenib and trametinib with respect to drug reductions and re-escalation. Re-implemented ATC pathology sample collection for a potential independent histology confirmation. It also implemented samples collection for a potential independent histology confirmation for WHO Grade 1-4 Glioma cohorts. Clarified the disease assessment method for WHO Grade 1-4 Glioma cohort. Updated the baseline and on-treatment assessments for the HCL cohort. Added additional analysis populations that are planned for the interim analyses. Added expansion cohorts for all cohorts that meet the criteria for early stopping for efficacy at an interim analysis. Clarified the definition for DOR for all response categories.
Amendment 7 19-Jul-2016	Changes to reflect change of sponsorship (from GlaxoSmithKline to Novartis); administrative changes to align with Novartis processes and procedures.
Amendment 8 14-Dec-2017	Updated Time and Event table for pregnancy, blood sample for CBC, peripheral blood sample staining for hairy cell count, flow cytometry for peripheral blood sample, and extended follow-ups to align with the footnotes. Added TSH, free T4 for ATC cohort only. Reduced the frequency of response assessment evaluation for HCL subjects who were tolerating study drug treatment beyond week 48: from every 4 weeks (+/-3 days) to every 8 weeks (+/-3 days) if appropriate in the judgement of the treating investigator. Evaluations at extended follow up were updated. Updated post-baseline Laboratory and Disease Assessments for HCL subjects. Clarified HbA1c testing is included in "Clinical Chemistry". Updated the contraception requirements for male subjects. Removed statement regarding Dabrafenib solubility at higher pH. Removed proton pump inhibitors from Medications to be used with Caution. Reinstated a sentence outlining the time period for detecting adverse events and serious adverse events inadvertently removed at amendment 7. Corrected the number of samples and amount of peripheral blood to be collected. Updated RANO Criteria under 'Disease progression (PD) for WHO Gr 1 or 2 Glioma.
Amendment 9 12-Feb-2019	Updated change to contraception requirements for female subjects. Updated definition for study completion and updated language clarifying the possible options for alternative supply of study treatment for those subjects who continue to derive clinical benefit at study completion. Clarified the analysis population for supportive final efficacy analysis. Updated date of final analyses to a minimum follow up of approx. 2 years for all subjects Removed reference to pooled ORR calculations across histologies.

Version and date	Summary of key changes
Amendment 10 09-Jan-2020	Aligned the dose modification section related to severe cutaneous adverse reactions, as updated in the dabrafenib and trametinib investigator's brochures edition 11. Baseline results of IDH mutation status and MGMT methylation status were to be collected as part of disease characteristics (LGG or HGG cohorts only). Data collected only where available as part of medical records; retrospective testing is not requested or required. References to the use of oral (hormonal) contraceptives being "permitted" or "used with caution" were removed from the relevant sections in alignment with protocol amendment #9.
Amendment 11 04-Jun-2020	Study extended by one additional year for more mature estimates of DoR, PFS and OS; primary analysis population of final efficacy analysis changed from BRAF V600E to ITT. To reduce burden on subjects, collections for blood and tissue samples for predictive and pharmacodynamic biomarker research as well as PK sampling at follow up were discontinued. Disease assessment intervals after the first 48 weeks of study treatment for subjects in the HCL cohort was extended from "at least every 8 weeks" to "at least every 12 weeks".

The FDA's Assessment:

FDA notes Amendment 2, in which a revision to the primary endpoint table reflected use of modified RANO and RANO tumor response in gliomas, and Amendment 6, which clarified the disease assessment method for the WHO Grade 1-4 glioma cohort. See discussion above in "Study Endpoints". Amendment 10 was implemented to collect baseline results of IDH mutation status and MGMT methylation status as part of disease characteristics (LGG or HGG cohorts only). See discussion above in "Study Population."

FDA notes Amendment 9 and the removal of reference to pooled ORR calculations across histologies. See discussion of pooling across histologies in 8.1.2 below.

8.1.2. Study CDRB436X2201-Results

Compliance with Good Clinical Practices

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 with the Applicant's position and there is no evidence that compliance with good clinical practices was violated during conduct of Study X2201.

Financial disclosure

The Applicant's Position:

The details of financial disclosure for Study X2201 are presented in Appendix 16.2.

The FDA's Assessment:

The Applicant's financial disclosure information was reviewed by FDA. Additional information is

provided in 16.2.

Patient Disposition

The Applicant's Description:

The study enrolled 206 subjects. Enrollment was completed in Jul-2018. At the time of data cut-off date (IA#16, 14-Sep-2020), 47 subjects (23%) continued to receive treatment, 22 subjects (11%) were in post-treatment follow-up, 105 subjects (51%) had died, and 32 subjects (16%) had withdrawn from the study. The most common reason for study withdrawal was subject's decision to withdraw consent (25 subjects, 12%) (Table 30). The median time since first dose to last contact (follow-up) was 104.5 weeks (range: 0.6 – 332.9).

Table 30 Applicant – Study X2201 Subject disposition (ITT population)

	ATC N=36	BTC N=43	GIST N=1	LGG N=13	HGG N=45	ASI N=3	HCL N=55	MM N=10	Total N=206
Subject status, n (%)									
Died	24 (67)	32 (74)	1 (100)	4 (31)	26 (58)	3 (100)	7 (13)	8 (80)	105 (51)
Ongoing	6 (17)	4 (9)	0	6 (46)	10 (22)	0	42 (76)	1 (10)	69 (33)
- On study treatment	2 (6)	1 (2)	0	5 (38)	6 (13)	0	33 (60)	0	47 (23)
- In follow-up	4 (11)	3 (7)	0	1 (8)	4 (9)	0	9 (16)	1 (10)	22 (11)
- Withdrawn from study	6 (17)	7 (16)	0	3 (23)	9 (20)	0	6 (11)	1 (10)	32 (16)
Primary reason for study withdrawal, n (%)									
Investigator discretion	0	0	0	0	2 (4)	0	1 (2)	0	3 (1)
Lost to follow-up	1 (3)	0	0	0	1 (2)	0	2 (4)	0	4 (2)
Withdrew consent	5 (14)	7 (16)	0	3 (23)	6 (13)	0	3 (5)	1 (10)	25 (12)

Source: Study X2201-Table 141.1013.

The FDA's Assessment:

Overall, FDA agrees with the Applicant's description of patient disposition. All data for patients with ATC, HCL and MM were not independently verified by FDA as these tumor types were not part of the efficacy analyses to support the proposed indication (ATC was assessed in a prior efficacy supplement).

Protocol Violations/Deviations

The Applicant's Description:

Important protocol deviations (PD) that were not related to the COVID-19 pandemic were reported in 56 subjects (27%). The most frequently reported important PD were related to "missed assessments or procedures" (15 subjects, 7%), "informed consent process" and "subjects received wrong treatment or incorrect dose" (10 subjects, 5% each) and "eligibility criteria not met" (8 subjects, 4%). None of the PD resulted in subject exclusion from any

analysis or discontinuation of therapy except one subject who discontinued treatment due to non-compliance (Study X2201-Table 141.1043).

In addition, 42 subjects (20%) had PD related to COVID-19 pandemic. The most frequent PD across all cohorts were related to "missed assessments or procedures" (mostly due to subject concern, 30 subjects, 15%), "other protocol deviation category" (i.e. drug supply issue, 28 subjects, 14% primarily due to drug supply method changed) and "window for safety assessment" (mostly due to lockdown/quarantine for 25 subjects, 12%).

The FDA's Assessment:

FDA agrees with the Applicant's summary of protocol deviations; however, the Applicant refers to Table 141.1043 but did not present the data. Table 31 below depicts data from Table 141.1043, including the important protocol deviations not related to the COVID pandemic.

Table 31: Important protocol deviations not related to COVID pandemic

Category/Subcategory	ATC (N=36)	BTC (N=43)	GIST (N=1)	LGG (N=13)	HGG (N=45)	ASI (N=3)	HCL (N=55)	MM (N=10)	Total (N=206)
Any protocol deviations not related to COVID-19	6 (17%)	8 (19%)	1 (100%)	2 (15%)	12 (27%)	1 (33%)	19 (35%)	7 (70%)	56 (27%)
Assessments and/or procedures									
Biological specimen sample procedures	1 (3%)	0	0	0	0	0	1 (2%)	2 (20%)	4 (2%)
Failure to report SAE, pregnancy, or liver function abnormalities per-protocol	0	0	0	0	1 (2%)	0	1 (2%)	0	2 (<1%)
Informed consent process	1 (3%)	4 (9%)	0	1 (8%)	1 (2%)	0	2 (4%)	1 (10%)	10 (5%)
Missed assessment or procedure	2 (6%)	0	0	1 (8%)	2 (4%)	0	6 (11%)	4 (40%)	15 (7%)
Other	0	0	0	0	0	1 (33%)	1 (2%)	1 (10%)	3 (1%)
Eligibility criteria not met	1 (3%)	2 (5%)	0	0	2 (4%)	0	2 (4%)	1 (10%)	8 (4%)
Other protocol deviation category	2 (6%)	1 (2%)	0	0	1 (2%)	0	2 (4%)	0	6 (3%)
Prohibited medication or device	1 (3%)	0	0	0	1 (2%)	0	2 (4%)	0	4 (2%)
Received wrong treatment or incorrect dose	0	0	1 (100%)	0	5 (11%)	0	4 (7%)	0	10 (5%)
Visit, assessment or time point window									
Window for dose administration	0	0	0	0	1 (2%)	0	1 (2%)	0	2 (<1%)
Window for safety assessments	0	2 (5%)	0	0	0	0	0	0	2 (<1%)
Other	0	0	0	0	1 (2%)	0	1 (2%)	0	2 (<1%)

Important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. Table 31 depicts deviations that can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. It is difficult to determine if protocol deviations had an influence on results across the solid tumor cohorts as there are few patients in each cohort to compare. However, in general, deviations in "Failure to report SAE, pregnancy, or liver function abnormalities per-protocol" have potential for safety issues, and there were <1% in this category across all cohorts.

Analysis sets:

The Applicant's Description:

All enrolled subjects met the evaluability criteria as defined in the analysis plan. The ITT, ATS population and the ITT/evaluable population were identical; 20 subjects were excluded from the BRAF V600E/Evaluable population. The only reason for exclusion of these subjects was that even though BRAF V600E mutation was confirmed by the local laboratory, it was not confirmed by the certified central reference laboratory. PK samples were not available for 11 subjects who therefore were excluded from the PK population (Table 32).

Table 32 Applicant – Study X2201 analysis populations

Population	ATC	BTC	GIST	LGG	HGG	ASI	HCL	MM	Total
Intent-to-treat (ITT)									
Primary analysis cohort	15	18	1	13	24	3	24	10	108
Expansion cohort	21	25	0	0	21	0	31	0	98
All-treated subjects (ATS)									
Primary	15	18	1	13	24	3	24	10	108
Expansion	21	25	0	0	21	0	31	0	98
ITT/Evaluable population									
Primary analysis cohort	15	18	1	13	24	3	24	10	108
Expansion cohort	21	25	0	0	21	0	31	0	98
BRAF V600E/Evaluable									
Primary analysis cohort	14	17	1	8	22	3	22	10	97
Expansion cohort	19	22	0	0	20	0	28	0	89
Pharmacokinetics (PK) population									
Primary analysis Cohort	15	17	1	12	23	2	23	9	102
Expansion Cohort	19	24	0	0	20	0	30	0	93

Source: Study X2201-Table 141.2010.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the analysis sets.

Demographic Characteristics

The Applicant's Description:

Demographic characteristics are summarized in Table 33.

Table 33 Applicant – Study X2201 Demographics and baseline characteristics (ITT)

	ATC N=36	BTC N=43	GIST N=1	ASI N=3	LGG N=13	HGG N=45	HCL N=55	MM N=10	Total N=206
Age (years)									
Mean (SD)	69.6 (9.53)	57.0 (11.88)	77.0	58.3 (3.21)	33.1 (11.51)	41.9 (14.70)	64.8 (10.77)	66.9 (6.89)	57.1 (16.40)

	ATC N=36	BTC N=43	GIST N=1	ASI N=3	LGG N=13	HGG N=45	HCL N=55	MM N=10	Total N=206
Median	71.0	57.0	77.0	57.0	33.0	42.0	66.0	68.0	60.5
Min, Max	47, 85	26, 77	77, 77	56, 62	18, 58	18, 72	40, 89	56, 79	18, 89
Age group, n (%)									
18 – 64	9 (25)	29 (67)	0	3 (100)	13 (100)	43 (96)	21 (38)	4 (40)	122 (59)
65 – 74	13 (36)	13 (30)	0	0	0	2 (4)	24 (44)	5 (50)	57 (28)
75 – 84	12(33)	1 (2)	1(100)	0	0	0	9 (16)	1 (10)	24 (12)
≥85	2 (6)	0	0	0	0	0	1 (2)	0	3 (1)
Sex, n (%)									
Male	16 (44)	19 (44)	0	2 (67)	4 (31)	23 (51)	47 (85)	5 (50)	116 (56)
Female	20 (56)	24 (56)	1 (100)	1 (33)	9 (69)	22 (49)	8 (15)	5 (50)	90 (44)
Race, n (%)									
African American/ African Heritage	0	0	0	1 (33)	0	2 (4)	0	1 (10)	4 (2)
American Indian or Alaska Native	0	0	0	0	0	1 (2)	0	0	1 (<1)
Asian - Central/South Asian Heritage	1 (3)	0	0	0	0	0	0	0	1 (<1)
Asian - East Asian Heritage	11 (31)	1 (2)	0	0	0	4 (9)	0	1 (10)	17 (8)
Asian - Japanese Heritage	2 (6)	2 (5)	0	0	2 (15)	1 (2)	0	0	7 (3)
Asian - South East Asian Heritage	2 (6)	0	0	0	1 (8)	1 (2)	0	0	4 (2)
White - Arabic/North African Heritage	1 (3)	1 (2)	0	0	0	2 (4)	1 (2)	0	5 (2)
White - White/Caucasian/ Europ. heritage	17 (47)	39 (91)	1 (100)	2 (67)	10 (77)	32 (71)	48 (87)	8 (80)	157 (76)
Missing	2 (6)	0	0	0	0	2 (4)	6 (11)	0	10 (5)
Baseline ECOG, n (%)									
0	3 (8)	16 (37)	1 (100)	3 (100)	5 (38)	13 (29)	28 (51)	2 (20)	71 (34)
1	31 (86)	26 (60)	0	0	7 (54)	26 (58)	26 (47)	7 (70)	123 (60)
2	2 (6)	1 (2)	0	0	1 (8)	6 (13)	1 (2)	1 (10)	12 (6)

Source: Study X2201-Table 141.3013, Table 141.3023.

The FDA's Assessment:

FDA agrees with Applicant's description of demographic and baseline characteristics described above. Additionally, the FDA reviewed the demographic and disease baseline characteristics of patients with solid tumors excluding ATC, and hematologic malignancies HCL and MM (see Table 33). FDA's analyses are primarily conducted in patients with solid tumors; however, patients with ATC were not included in the final efficacy analysis because this indication is already approved for the dabrafenib in combiantion with trametinib. FDA did not conduct

independent analyses to verify the results that are not relevant for inclusion in product labeling.

Table 34: FDA – Study X2201 Demographics and baseline characteristics (solid tumors)

	BTC N=43	GIST N=1	ASI N=3	LGG N=13	HGG N=45	Total N=105
Age (years)						
Mean (SD)	57.0 (11.88)	77.0	58.3 (3.21)	33.1 (11.51)	41.9 (14.70)	47.8 (15.9)
Median	57.0	77.0	57.0	33.0	42.0	50
Min, Max	26, 77	77, 77	56, 62	18, 58	18, 72	18, 77
Age group, n (%)						
18 – 64	29 (67)	0	3 (100)	13 (100)	43 (96)	88 (84)
65 – 74	13 (30)	0	0	0	2 (4.4)	15 (14)
75 – 84	1 (2)	1(100)	0	0	0	2 (1.9)
≥85						
Sex, n (%)						
Male	19 (44)	0	2 (67)	4 (31)	23 (51)	48 (46)
Female	24 (56)	1 (100)	1 (33)	9 (69)	22 (49)	57 (54)
Race, n (%)						
White	40 (93)	1 (100)	2 (67)	10 (77)	34 (79)	87 (84)
Asian	3 (7)	0	0	3 (23)	6 (14)	12 (12)
Black or African American	0	0	1 (33)	0	2 (4.4)	3 (2.9)
American Indian Or Alaska Native	0	0	0	0	1 (2.2)	1 (097)
Baseline ECOG, n (%)						
0	16 (37)	1 (100)	3 (100)	5 (38)	13 (29)	36 (38)
1	26 (60)	0	0	7 (54)	26 (58)	59 (56)
2	1 (2.3)	0	0	1 (8)	6 (13)	8 (8)

Source: FDA reviewer's analysis.

Other Baseline Characteristics

The Applicant's Description:

Disease characteristics

At screening, all subjects had measurable disease except for 1 HGG subject (Table 36).

• **In the ATC cohort**, the median time since diagnosis was 125 days (range: 14 to 4606 days). The tumor histology at initial diagnosis was undifferentiated/poorly differentiated/anaplastic in 94% of subjects. All except 1 subject (97%) had Stage IVC with an M stage (distal metastasis) of M1 at screening per AJCC 7.

• **In the BTC cohort**, the median time since diagnosis was 347 days (range: 26 to 3224 days). The predominant tumor histology was adenocarcinoma reported in 74% of subjects. The anatomical location of primary tumor type was intrahepatic bile duct in 91% of subjects and perihilar bile duct in 2% of subjects. All except 3 subjects (93%) had Stage IVB with an M stage (distal metastasis) of M1 at screening per AJCC 7.

• **In the GIST cohort**, the time since diagnosis in 1 subject enrolled in this cohort was 325 days. The tumor histology was poorly differentiated spindle cell at stage IV with an M stage (distal metastasis) of M1 per AJCC 7.

• **In the ASI cohort**, the median time since diagnosis was 595 days (range: 147-1014 days). The tumor histology in all 3 subjects were adenocarcinoma and the histological grade was moderately differentiated in 2 subjects (67%) and well differentiated in 1 subject (33%). Two subjects (67%) had stage IV disease and 1 subject (33%) had stage IVA disease per AJCC.

• **In the LGG cohort**, the median time since diagnosis was 2536 days (range: 45 days - 9367 days). Predominant tumor histology was ganglioglioma in 4 subjects (31%), followed by diffuse astrocytoma and pleomorphic xanthoastrocytoma (2 subjects, 15% each). Seven subjects (54%) had grade 2 and 6 subjects (46%) had grade 1 glioma.

• **In the HGG cohort**, the median time since diagnosis was 525 days (range: 59-9549 days). The predominant tumor histology was glioblastoma in 31 subjects (69%), followed by anaplastic astrocytoma and anaplastic pleomorphic xanthoastrocytoma (5 subjects, 11% each). Thirteen (29%) subjects had grade 3 and 31 (69%) subjects had grade 4 glioma (Table 36).

Table 35 Applicant – Study X2201 Disease characteristics of ATC, BTC, GIST and ASI cohorts (ITT/Evaluable)

		ATC N = 36 n (%)	BTC N = 43 n (%)	GIST N=1 n (%)	ASI N=3 n (%)
Measurable disease at Screening	Yes	36 (100)	43 (100)	1 (100)	3 (100%)
Non-Target lesions at Screening	No	7 (19)	12 (28)	1 (100)	2 (67%)
	Yes	29 (81)	31 (72)	0	1 (33%)
Stage	II	0	1 (2)	0	0
	IV	1 (3)	1 (2)	1 (100)	2 (67%)
	IVA	0	0	0	1 (33%)
	IVB	0	40 (93)	0	0
	IVC	35 (97)	0	0	0
	Missing	0	1 (2)	0	0
TNM Staging: primary tumor	T1	0	1 (2)	0	0
	T2	1 (3)	3 (7)	0	0
	T2B	0	4 (9)	0	0
	T3	3 (8)	2 (5)	1 (100)	0
	T4	0	8 (19)	0	1 (33%)

		ATC N = 36 n (%)	BTC N = 43 n (%)	GIST N=1 n (%)	ASI N=3 n (%)
	T4A	5 (14)	0	0	0
	T4B	10 (28)	0	0	0
	TX	17 (47)	24 (56)	0	2 (67%)
	Missing	0	1 (2)	0	0
TNM staging: primary lymph nodes	N0	2 (6)	6 (14)	1 (100)	1 (33%)
	N1	0	12 (28)	0	0
	N1A	9 (25)	0	0	0
	N1B	9 (25)	0	0	0
	NX	16 (44)	24 (56)	0	2 (67%)
	Missing	0	1 (2)	0	0
TNM staging: distant metastasis	M0	0	1 (2)	0	0
	MX	1 (3)	0	0	0
	M1	35 (97)	41 (95)	1 (100)	3 (100%)
	Missing	0	1 (2)	0	0
Prior radiotherapy regimens	0	7 (19)	38 (88)	1 (100)	3 (100%)
	1	18 (50)	4 (9)	0	0
	2	11 (31)	1 (2)	0	0

Source: Study X2201-Table 141.3043, Table 141.3063, Table 141.3081, and Table 141.3161.

Table 36 Applicant – Study X2201 Disease characteristics of LGG and HGG cohorts (ITT/Evaluable)

		LGG N = 13 n (%)	HGG N = 45 n (%)
Measurable disease at Screening	No	0	1 (2%)
	Yes	13 (100)	44 (98%)
Non-target lesions at Screening	No	10 (77)	35 (78%)
	Yes	3 (23)	10 (22%)
Grade	I	6 (46)	0
	II	7 (54)	0
	III	0	13 (29%)
	IV	0	31 (69%)
	Missing	0	1 (2%)
Prior radiotherapy regimens	0	5 (38)	1 (2%)
	1	7 (54)	36 (80%)
	2	1 (8)	7 (16%)
	3	0	1 (2%)

Source: Study X2201-Table 141.3101 and Table 141.3123.

Central BRAF V600E confirmation status

Across all cohorts (N=206), 186 subjects (90%) had BRAF V600E mutation confirmed by the central reference laboratory. Nine subjects (4%) (2 each from ATC and LGG, 1 from HGG and 4 from HCL cohort) had a negative test result for the BRAF V600E or V600K mutation by the central reference laboratory. For 5 subjects central confirmation testing was not performed: for 4 subjects (2%) the samples submitted was not sufficient to test (1 subject each from ATC and LGG, and 2 subjects from BTC cohort), and for 1 subject no tumor was indicated (from the BTC cohort). Five subjects (2%) had an invalid result. Additionally, 1 subject had missing central confirmation status in the HCL cohort because a sample was not submitted (Table 37).

For all cases where the BRAF V600E status was not confirmed, the local assessment was positive for BRAF V600E status and there was extensive follow-up with sites to obtain another, evaluable tissue sample.

Table 37 Applicant – Study X2201 BRAF V600E central confirmation status (ITT)

n (%)	ATC N=36	BTC N=43	GIST N=1	LGG N=13	HGG N=45	ASI N=3	HCL N=55	MM N=10	Total N=206
BRAF V600E mutation confirmed	33 (92)	39 (91)	1 (100)	8 (62)	42 (93)	3 (100)	50 (91)	10 (100)	186 (90)
No BRAF V600E or V600K mutation detected	2 (6)	0	0	2 (15)	1 (2)	0	4 (7)	0	9 (4)
Quantity not sufficient to test	1 (3)	2 (5)	0	1 (8)	0	0	0	0	4 (2)
Invalid	0	1 (2)	0	2 (15)	2 (4)	0	0	0	5 (2)
No tumor Indicated	0	1 (2)	0	0	0	0	0	0	1 (<1)

Note: One subject had missing central confirmation status in the HCL cohort because a sample was not submitted.
Source: Study X2201-Table 141.3293.

Prior anti-cancer therapy

All subjects, except 1 (>99%), had received at least one form of prior anti-cancer therapy. Chemotherapy was the most commonly used prior anti-cancer therapy (83%), followed by surgery (59%) and radiotherapy (46%) (Table 38).

Table 38 Applicant – Study X2201 Summary of prior anti-cancer therapy (ITT)

	ATC N = 36 n (%)	BTC N = 43 n (%)	GIST N = 1 n (%)	ASI N = 3 n (%)	LGG N = 13 n (%)	HGG N = 45 n (%)	HCL N = 55 n (%)	MM N = 10 n (%)	Total N = 206 n (%)
Any therapy	36 (100)	43 (100)	1(100)	3 (100)	12 (92)	45 (100)	55 (100)	10 (100)	205 (>99)
Biologic therapy	0	5 (12)	0	2 (67)	2 (15)	7 (16)	45 (82)	4 (40)	65 (32)
Chemotherapy	15 (42)	42 (98)	0	3 (100)	5 (38)	42 (93)	55 (100)	10 (100)	172 (83)

	ATC N = 36 n (%)	BTC N = 43 n (%)	GIST N = 1 n (%)	ASI N = 3 n (%)	LGG N = 13 n (%)	HGG N = 45 n (%)	HCL N = 55 n (%)	MM N = 10 n (%)	Total N = 206 n (%)
Hormonal therapy	0	0	0	0	0	0	0	0	0
Immunotherapy	4 (11)	2 (5)	0	0	0	1 (2)	15 (27)	10 (100)	32 (16)
Radioactive therapy	11 (31)	0	0	0	0	0	0	0	11 (5)
Small molecule targeted therapy	7 (19)	3 (7)	1 (100)	0	0	3 (7)	5 (9)	10 (100)	29 (14)
Radiotherapy	30 (83)	5 (12)	0	0	8 (62)	44 (98)	1 (2)	7 (70)	95 (46)
Surgery	30 (83)	24 (56)	1(100)	3 (100)	12 (92)	42 (93)	6 (11)	3 (30)	121 (59)

Source: Study X2201-Table 141.3233.

The FDA's Assessment:

FDA performed analyses for BRAF V600E mutation status and prior anti-cancer therapy based on the 105 patients in the efficacy population and these are described in Table 39 and Table 40. For the majority of patients (89%), the BRAF V600E mutation was confirmed. Almost all patients (99%) received prior therapy with the most common being chemotherapy.

Table 39 FDA - Study X2201 BRAF V600E central confirmation status (ITT)

	BTC N=43 n (%)	GIST N=1 n (%)	LGG N=13 n (%)	HGG N=45 n (%)	ASI N=3 n (%)	Total N=105 n (%)
BRAF V600E mutation confirmed	39 (91)	1 (100)	8 (62)	42 (93)	3 (100)	93 (89)
No BRAF V600E or V600K mutation detected	0	0	2 (15)	1 (2.2)	0	3 (2.9)
Quantity not sufficient to test	2 (4.7)	0	1 (8)	0	0	3 (2.9)
Invalid	1 (2.3)	0	2 (15)	2 (4.4)	0	5 (4.8)
No tumor Indicated	1 (2.3)	0	0	0	0	1 (<1)

Source: FDA reviewer's analysis

Table 40 FDA - Study X2201 Summary of prior anti-cancer therapy (ITT)

	BTC N = 43 n (%)	GIST N = 1 n (%)	ASI N = 3 n (%)	LGG N = 13 n (%)	HGG N = 45 n (%)	Total N = 105 n (%)
Any therapy	43 (100)	1(100)	3 (100)	12 (92)	45 (100)	104 (99)
Biologic therapy	5 (12)	0	2 (67)	2 (15)	7 (16)	16 (15)
Chemotherapy	42 (98)	0	3 (100)	5 (38)	42 (93)	92 (88)
Hormonal therapy	0	0	0	0	0	0
Immunotherapy	2 (4.7)	0	0	0	1 (2.2)	3 (2.9)

	BTC N = 43 n (%)	GIST N = 1 n (%)	ASI N = 3 n (%)	LGG N = 13 n (%)	HGG N = 45 n (%)	Total N = 105 n (%)
Radioactive therapy	0	0	0	0	0	0
Small molecule targeted therapy	3 (7)	1 (100)	0	0	3 (7)	7 (7)
Radiotherapy	5 (12)	0	0	8 (62)	44 (98)	57 (54)
Surgery	24 (56)	1(100)	3 (100)	12 (92)	42 (93)	82 (78)

Source: FDA reviewer's analysis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Description

Treatment compliance: Median overall treatment compliance (assessed using subject dosing diaries) with dabrafenib and trametinib was 95.1% and 97.2%, respectively (Study X2201-Section 10.6.3).

Concomitant medications: Almost all subjects (199 subjects, 97%) received at least one concomitant medication during the study. The most commonly used concomitant medications included paracetamol (53%), amoxicillin (27%), dexamethasone and ibuprofen (24% each) (Study X2201-Table 141.5013).

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

The FDA's Assessment:

There were no clinically significant issues relating to treatment compliance or need for concomitant or rescue medication that could impact the results of the trial or warrant further discussion.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Note: As the primary focus of this submission is on solid tumors, the efficacy results for hairy cell leukemia (HCL) and multiple myeloma (MM) cohorts are not shown.

The Applicant's Description:

The interim analysis (IA#16) showed clinically meaningful activity of dabrafenib + trametinib combination therapy across BRAF V600E mutation-positive solid tumor cohorts.

Anaplastic thyroid cancer cohort

A high ORR of over 50% was consistently observed across assessment types (Investigator/ independent) and analysis populations (Table 41). Evidence of efficacy was also seen from reduction of baseline sum of lesion diameters (SLD) of target lesions in the corresponding

waterfall plots: 75% of subjects (27/36) experienced at least a 30% decrease in SLD (

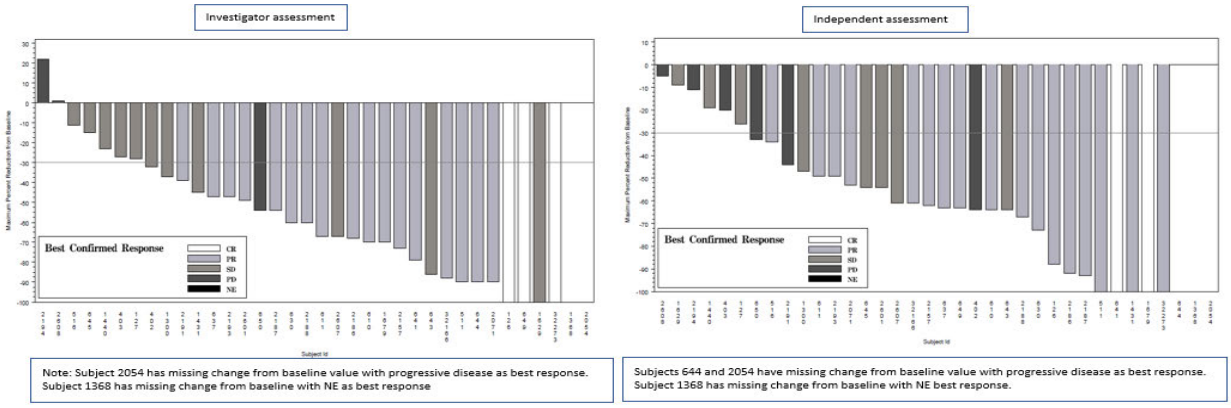
.

Table 41 Applicant – Study X2201 Response rates in ATC (ITT/Evaluable and BRAF V600E/Evaluable)

	ATC cohort			
	ITT/Evaluable population		BRAF V600E/Evaluable population	
	Investigator	Independent	Investigator	Independent
Response category	**N=36**	**N=36**	**N=33**	**N=33**
Best response - n (%)				
Complete response (CR)	3 (8)	2 (6)	3 (9)	2 (6)
Partial response (PR)	17 (47)	17 (47)	17 (52)	17 (52)
Stable disease (SD)	11 (31)	8 (22)	8 (24)	6 (18)
Progressive disease (PD)	4 (11)	8 (22)	4 (12)	7 (21)
Not evaluable (NE)	1 (3)*	1 (3)*	1 (3)*	1 (3)*
Response rate – n (%)				
CR + PR	20 (56)	19 (53)	20 (61)	19 (58)
95% Confidence Interval[1]	(38.1, 72.1)	(35.5, 69.6)	(42.1, 77.1)	(39.2, 74.5)

[1] Exact two-sided 95% confidence interval based on Clopper-Pearson method
*No post-baseline assessments.
Source: Study X2201-Table 142.1050, Table 142.1410, Table 142.1080, Table 142.1440.

Figure 4 Applicant - Study X2201 ATC Cohort - Maximum percent reduction from baseline in the sum of target lesion diameters (ITT/Evaluable population)



Source: Study X2201-Figure 142.5010 and Figure 142.5020

Biliary tract cancer cohort

A high ORR of over 40% was consistently observed across assessment types (Investigator/ independent) and analysis populations (Table 42)Table 42 Applicant – Study X2201 BTC cohort - Overall response rate (ITT/Evaluable population and BRAF V600E/Evaluable). Evidence of tumor

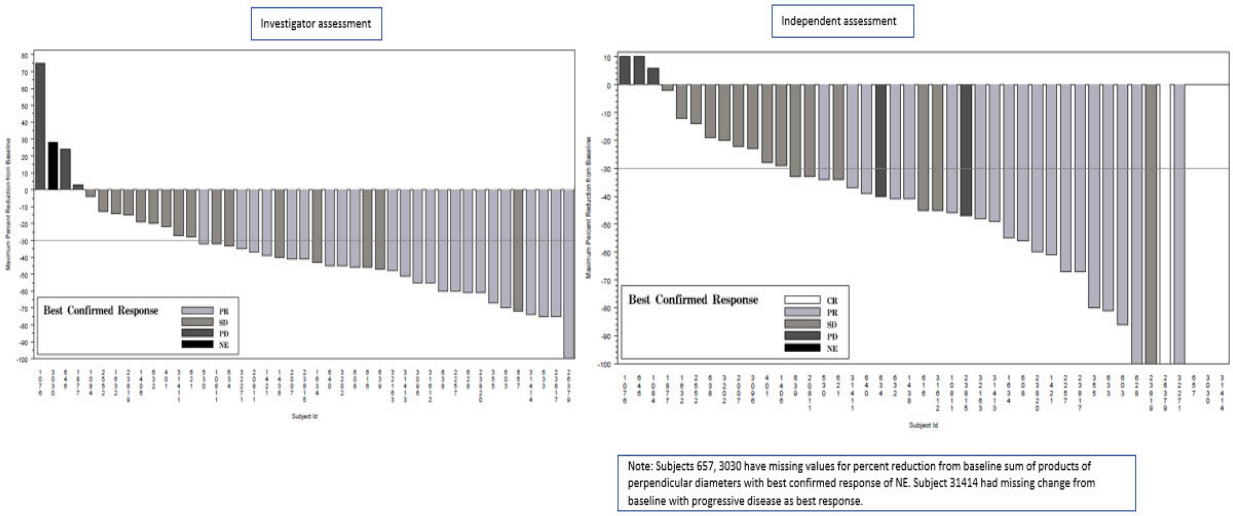
reduction was also evident from the corresponding waterfall plots, with >65% of subjects Table 42experiencing at least a 30% decrease in the sum of longest diameters of target lesion (Figure 5).

Table 42 Applicant – Study X2201 BTC cohort - Overall response rate (ITT/Evaluable population and BRAF V600E/Evaluable)

	BTC cohort			
	ITT/Evaluable population		BRAF V600E/Evaluable population	
	Investigator	Independent	Investigator	Independent
Response category	**N=43**	**N=43**	**N=39**	**N=39**
Best response - n (%)				
Complete response (CR)	0	1 (2)	0	0
Partial response (PR)	23 (53)	19 (44)	21 (54)	17 (44)
Stable disease (SD)	16 (37)	15 (35)	15 (38)	15 (38)
Progressive disease (PD)	3 (7)	6 (14)	2 (5)	5 (13)
Not evaluable (NE)	1 (2)*	2 (5)**	1 (3)*	2 (5)**
Response rate – n (%)				
CR + PR	23 (53)	20 (47)	21 (54)	17 (44)
95% Confidence Interval[1]	(37.7, 68.8)	(31.2, 62.3)	(37.2, 69.9)	(27.8, 60.4)

[1]Exact two-sided 95% confidence interval based on Clopper-Pearson method.
* Received anti-cancer therapy before disease progression observed (at first post-baseline assessment)
** No measurable disease at baseline.
Source: Study X2201-Table 142.1050, Table 142.1490.Table 142.1080, Table 142.1500.

Figure 5 Applicant - Study X2201 BTC cohort - Maximum percent reduction from baseline sum of diameters by Investigator and Independent-assessed best response with confirmation (ITT/evaluable)



Source: Study X2201-Figure 142.5030 and Figure 142.5070

Gastrointestinal stromal tumor cohort (n=1)

The GIST cohort only enrolled 1 subject. The subject was included in both the ITT/Evaluable population and the BRAFV600E/Evaluable population and had stable disease as per the Investigator assessment (Study X2201-Section 11.1.1.3).

Adenocarcinoma of small intestine cohort (n=3)

Of the 3 subjects enrolled in the ASI cohort, a partial response was observed in 2 subjects (67%) and progressive disease was observed in 1 subject (33%). The ORR as determined by Investigator assessment and by independent radiologist review was 67% (95% CI: 9.4%, 99.2%) (Study X2201-Section 11.1.1.4).

Low grade (WHO G1/G2) glioma cohort

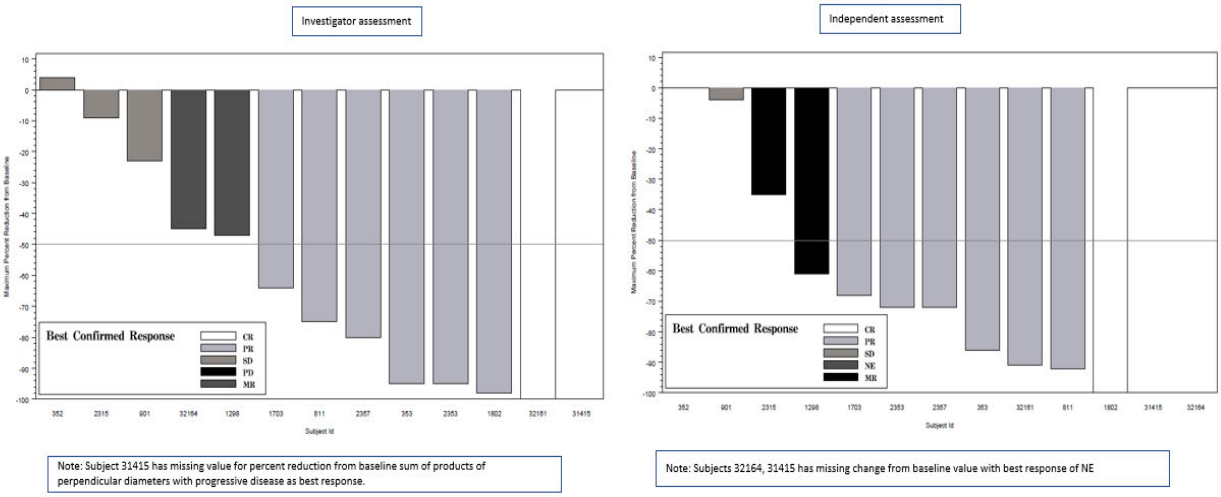
The ORR based on both investigator and independent assessment in primary analysis cohort was 69% (95% CI: 38.6%, 90.9%) in the ITT/Evaluable population (n=13; **Error! Reference source not found.**). Evidence of efficacy was also seen from the reduction of baseline sum of product of perpendicular diameters of target lesions in corresponding waterfall plots, with 53.8% of subjects experiencing a decrease of at least 50% based on investigator assessment (61.5% of subjects based on independent radiology review; Figure 6).

Figure 6 Applicant - Study X2201 LGG cohort ORR (ITT/Evaluable and BRAFV600E/Evaluable - Primary analysis cohort)

LGG cohort	ITT/Evaluable population		BRAF V600E/Evaluable population	
	Investigator	Independent	Investigator	Independent
Response category	N=13	N=13	N=8	N=8
Best response - n (%)				
Complete response (CR)	1 (8)	1 (8)	0	0
Partial response (PR)	6 (46)	6 (46)	3 (38)	3 (38)
Minor response (MR)	2 (15)	2 (15)	2 (25)	1 (13)
Stable disease (SD)	3 (23)	2 (15)	2 (25)	2 (25)
Progressive disease (PD)	1 (8)	0	1 (13)	0
Not evaluable (NE)	0	2 (15)*	0	2 (25)*
Response rate including MR – n (%)				
CR + PR + MR	9 (69)	9 (69)	5 (63)	4 (50)
95% Confidence Interval[1]	(38.6, 90.9)	(38.6, 90.9)	(24.5, 91.5)	(15.7, 84.3)
Response rate excluding MR - n (%)[2]				
CR+PR	7 (54)	7 (54)	-	-
95% Confidence Interval[1]	(25.1, 80.8)	(25.1, 80.8)	-	-

[1]Exact two-sided 95% confidence interval based on Clopper-Pearson method.
[2]Minor response (MR) was excluded from ORR.
*Subject (b) (6) had no measurable disease at baseline; and subject (b) (6) had no post-baseline assessments
Source: Study X2201-Table 142.1150, Table 142.1530, Table 142.1151, Table 142.1531, Table 142.1180, Table 142.1540.

Figure 7 Applicant - Study X2201 LGG cohort - Maximum percent reduction from baseline sum of products of perpendicular diameters by Investigator and Independent-assessed best response with confirmation (ITT/Evaluable - Primary analysis cohort



Source: Study X2201-Figure 142.5050 and Figure 142.5090.

High grade (WHO G3/G4) glioma cohort

A high ORR of over 30% was consistently observed across assessment types (Investigator/ independent) and analysis populations (Table 43). Evidence of efficacy was also seen from the reduction of baseline sum of product of perpendicular diameters of target lesions in corresponding waterfall plots, with 48.9% of subjects experiencing at least a 50% decrease tumor size based on investigator assessment (42.2% of subjects based on independent radiology review; Figure 8).

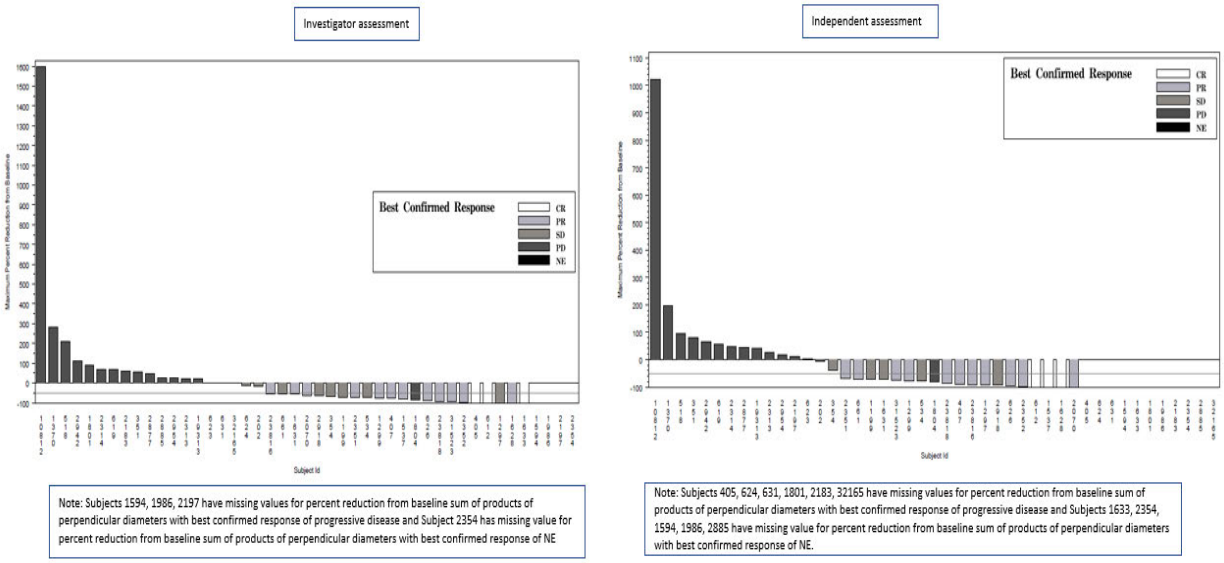
Table 43 Applicant – Study X2201 HGG cohort – ORR (ITT/Evaluable and BRAFV600E/ Evaluable)

HGG cohort	ITT/Evaluable population		BRAF V600E/Evaluable population	
	Investigator	Independent	Investigator	Independent
Response category	N=45	N=45	N=8	N=8
Best response - n (%)				
Complete response (CR)	3 (7)	3 (7)	3 (7)	3 (7)
Partial response (PR)	12 (27)	11 (24)	12 (29)	11 (26)
Stable disease (SD)	10 (22)	5 (11)	10 (24)	5 (12)
Progressive disease (PD)	19 (42)	20 (44)	16 (38)	18 (43)
Not evaluable (NE)	1 (2)*	6 (13)**	1 (2)*	5 (12)**
Response rate – n (%)				
CR + PR + MR	15 (33)	14 (31)	15 (36)	14 (33)
95% Confidence Interval [1]	(20.0, 49.0)	(18.2, 46.6)	(21.6, 52.0)	(19.6, 49.5)

HGG cohort	ITT/Evaluable population		BRAF V600E/Evaluable population	
	Investigator	Independent	Investigator	Independent
Response category	N=45	N=45	N=8	N=8

[1]Exact two-sided 95% confidence interval based on Clopper-Pearson method
*No measurable disease at baseline;
**Subject (b) (6) had no measurable disease at baseline; subjects (b) (6) had no post-baseline assessments. All progressed by investigator assessment before first radiological assessment; and subject (b) (6) had an SD assessment which was before the minimum 6 weeks after first dose of study treatment
Source: Study X2201-Table 142.1230, Table 142.1550, Table 142.1260, Table 142.1560

Figure 8 Applicant - Study X2201 HGG cohort - Maximum percent reduction from baseline sum of products of perpendicular diameters by Investigator and Independent-assessed best response with confirmation (ITT/evaluable)



Source: Study X2201-Figure 142.5060 and Study X2201-Figure 142.5100

Bayesian hierarchical model-based analysis of Investigator-assessed ORR

Confirmed overall response rates using the Bayesian hierarchical model

Confirmed ORR was analyzed using an integrated analysis across the histologic cohorts with a Bayesian hierarchical model. Model-based interim decision rules was used to identify whether one or more histologic cohorts halt enrolment early for futility/harm or benefit based on efficacy data. The model-based ORR results along with the observed ORR per investigator review are summarized in (ITT/Evaluable population; Table 44) and (BRAF V600E/Evaluable population; Table 45). The differences between the observed response rates and the model-based estimates are attributable to the shrinkage estimation and dynamic borrowing across

cohorts. The posterior probability of the ORR exceeding the historical control was high in all cohorts with a caveat that the GIST cohort enrolled only 1 subject.

Table 44 Applicant – Study X2201 Summary of Bayesian hierarchical model-based analysis for Investigator-assessed best response with confirmation (ITT/Evaluable - Primary analysis cohort)

Cohort	Historical control response rate	Number of ITT/Evaluable subjects	Number of confirmed responses [1]	Observed overall response rate	Estimated response rate and 95% credible interval[2]	Probability that the ORR exceeds historical control rate [2]
ATC	15%	15	11	73%	70% (46.8, 89.3)	1.00
BTC	10%	18	7	39%	41% (21.3, 62.2)	1.00
GIST	10%	1	0	0%	34% (0.1, 81.7)	0.78
LGG	10%	13	9	69%	64% (38.8, 87.1)	1.00
HGG	10%	24	6	25%	30% (13.0, 47.9)	0.99
ASI	10%	3	2	67%	57% (21.2, 91.2)	1.00

[1] Response = Complete Response (CR) + Partial Response (PR) for ATC, BTC, GIST, HGG and ASI; Response = CR + PR + Minor Response (MR) for LGG; Response= CR+PR for HGG; Response = Stringent complete response + CR + Very Good Partial Response + PR for MM; Response = Complete Response with/without minimal residual disease
[2] Based on Bayesian Hierarchical model-based analysis
Source: Study X2201-Table 142.1010

Table 45 Applicant – Study X2201 Summary of Bayesian hierarchical model-based analysis for Investigator-assessed best response with confirmation (BRAF V600E/Evaluable - Primary analysis cohort)

Cohort	Historical control response rate	Number of BRAF V600E/ evaluable subjects	Number of confirmed responses [1]	Observed overall response rate	Estimated response rate and 95% credible interval [2]	Probability that the ORR exceeds historical control rate [2]
ATC	15%	14	11	79%	74% (50.0, 92.4)	1.00
BTC	10%	17	7	41%	43% (22.8, 64.4)	1.00
GIST	10%	1	0	0%	34% (0.1, 81.9)	0.78
LGG	10%	8	5	63%	57% (29.3, 85.5)	1.00
HGG	10%	22	6	27%	32% (14.7, 51.1)	1.00
ASI	10%	3	2	67%	57% (21.6, 91.1)	1.00
HCL	10%	22	20	91%	85% (66.7, 96.9)	1.00
MM	15%	10	5	50%	53% (27.6, 78.1)	1.00

[1] Response = Complete Response (CR) + Partial Response (PR) for ATC, BTC, GIST, HGG and ASI; Response = CR + PR + Minor Response (MR) for LGG; Response= CR+PR for HGG; Response = Stringent complete response + CR + Very Good Partial Response + PR for MM; Response = Complete Response with/without minimal residual disease + PR for HCL
[2] Based on Bayesian Hierarchical model-based analysis
Source: Study X2201-Table 142.1020

Secondary efficacy results

The Applicant's Description:

The results of the secondary efficacy endpoints for each cohort are presented in Table 46.

Table 46 Applicant – Study X2201 DoR, PFS and OS

Histology	DoR (95% CI)		PFS (95% CI)		OS (95% CI)
	by Investigator	by Independent review	by Investigator	by Independent review	
BTC (N=43)	Median: 38.9 weeks (24.3, 59.4) 6 months: 68.8% (45.5%, 83.8%) 12 months: 32.1% (14.4%, 51.5%) 24 months: 13.8% (3.4%, 31.1%)	Median: 40.7 weeks (20.1, 64.9) 6 months: 53.3% (28.0%, 73.3%) 12 months: 33.3% (12.6%, 55.8%) 24 months: 20.0% (5.0%, 42.1%)	Median: 39.0 weeks (24.1, 41.0) 6 months: 63.3% (46.5%, 76.0%) 12 months: 29.3% (16.0%, 43.9%) 24 months: 10.7% (3.4%, 22.7%)	Median: 32.6 weeks (23.6, 56.0)	Median: 58.9 weeks (45.4, 76.6) 6 months: 83.5% (68.5%, 91.8%) 12 months: 53.9% (37.0%, 68.1%) 24 months: 28.4% (14.9%, 43.4%)
ATC (N=36)	Median: 62.4 weeks (32.1,189.6) 6 months: 80.0% (55.1%, 92.0%) 12 months: 50.0% (27.1%, 69.2%) 24 months: 43.7% (21.6%, 64.0%)	Median: 59.1 weeks (16.6, not reached) 6 months: 72.2% (45.6%, 87.4%) 12 months: 55.6% (30.5%, 74.8%) 24 months: 38.1% (16.6%, 59.5%)	Median: 29.1 weeks (20.3, 59.9) 6 months: 52.5% (35.1%, 67.2%) 12 months: 43.2% (26.6%, 58.8%) 24 months: 27.0% (13.2%, 42.9%)	Median: 24.1 weeks (16.1, 56.0)	Median: 62.9 weeks (29.6, 100.9) 6 months: 73.5% (55.2%, 85.2%) 12 months: 51.7% (33.6%, 67.1%) 24 months: 31.5% (16.3%, 47.9%)
ASI (N=3)	Median: 33.4 weeks (not evaluable, not evaluable) Of the 2 responding subjects, 1 subject had disease progression and 1 subject was censored due to end of follow-up.	Median: 32.8 weeks (32.1, 33.4) Of the 2 responding subjects, both subjects had disease progression.	Median: 41.3 weeks (not evaluable, not evaluable) One disease progression and 2 censored at time of data cut-off.	Median: 40.1 weeks (4.1, 41.3) All 3 subjects had disease progression.	Median: 94.6 weeks (14.9, 154.7) 6 months: 66.7% (5.4%, 94.5%) 12 months: 66.7% (5.4%, 94.5%) 24 months: 33.3% (0.9%, 77.4%)
GIST (N=1)	The single subject in this cohort experienced stable disease per investigator assessment.				
HGG (N=45)	Median: 160.4 weeks (32.0,192.0) 6 months: 85.1% (52.3%, 96.1%) 12 months: 77.4% (44.9%, 92.1%) 24 months: 68.8% (36.4%, 87.1%)	Median: 59.3 weeks (20.1,188.6) 6 months: 66.7% (19.5%, 90.4%) 12 months: 66.7% (19.5%, 90.4%) 24 months: 35.7% (13.0%, 59.4%)	Median: 16.4 weeks (7.9, 39.9) 6 months: 42.2% (27.3%, 56.3%) 12 months: 34.7% (20.9%, 49.0%) 24 months: 24.8% (13.0%, 38.6%)	Median: 19.7 weeks (8.0, 32.1)	Median: 76.4 weeks (41.1, 196.6) 6 months: 78.2% (62.3%, 88.0%) 12 months: 60.1% (43.3%, 73.4%) 24 months: 41.8% (26.3%, 56.5%)
LGG[1] (N=13)	Median: Not reached (24.1, Not reached) 6 months: 85.7% (33.4%, 97.9%)	Median: 119.4 weeks (24.1, 171.9) 6 months: 85.7% (33.4%, 97.9%)	Median: Not reached (32.1, Not reached) 6 months: 84.6% (51.2%, 95.9%)	Median: 60.7 weeks (20.3, 204.0)	Median: Not reached (50.4, Not reached) 6 months: 92.3% (56.6%, 98.9%)

Histology	DoR (95% CI)		PFS (95% CI)		OS (95% CI)
	by Investigator	by Independent review	by Investigator	by Independent review	
	12 months: 85.7% (33.4%, 97.9%) 24 months: 71.4% (25.8%, 92.0%)	12 months: 71.4% (25.8%, 92.0%) 24 months: 57.1% (17.2%, 83.7%)	12 months: 69.2% (37.3%, 87.2%) 24 months: 52.7% (23.4%, 75.5%)		12 months: 83.9% (49.4%, 95.7%) 24 months: 83.9% (49.4%, 95.7%)

[1] Minor response (MR) was excluded from ORR.
Source: Study X2201 IA#16-Section 11.2, Study X2201-Table 142.2251, Table 142.2351, 142 3060, Table 142.3310, Table 142.3330, Table 142.3350, Table 142.3370

The FDA's Assessment:

During the review cycle, a major error of the DOR data for the LGG cohort was found. See FDA's Assessment in the Data quality section for details. FDA's assessment was conducted based on the corrected datasets submitted on March 8, 2022.

The ITT, ATS, and ITT/Evaluable population were identical in Study X2201. In FDA's analyses, the ATS population is used as the primary efficacy analysis population. The data cut-off was September 14, 2020, for interim analysis #16 which was the analysis used for the efficacy evaluation. The ORR and DoR results by histology as assessed by the investigator and by the independent review are summarized in Table 47. The ORR estimate was 45% as assessed by the investigators and 41% by the independent review.

Treatment benefit in terms of tumor response was observed for each histology except GIST. While patients with HGG had a slightly lower point estimate of ORR compared to the pooled ORR, its 95% CI still covered the point estimate of the pooled ORR. There was not sufficient data to evaluate the treatment benefit for patients with GIST since there was only one patient with GIST and a response was not observed for that patient. We observed slightly shorter duration of response for BTC patients and ASI patients. Note that the data for each cohort may be limited to provide accurate estimates for ORR and DoR when the sample size is relatively small.

Table 47 FDA – Study X2201 ORR and DoR by Histology (Solid Tumors, ATS)

		Investigator N=105				Independent Review N=105			
Histology	N	ORR	DOR in responder, months			ORR	DOR, months		
		n(%) 95% CI[1]	Median[2]	DOR ≥6[3]	DOR ≥12[3]	n(%) 95% CI	Median[2]	DOR ≥6[3]	DOR ≥12[3]
BTC	43	23 (53) (38, 69)	8.9	65%	30%	20 (47) (31, 62%)	9.4	45%	25%
GIST	1	0 (0)	NE	NE	NE	0 (0)	NE	NE	NE
ASI	3	2 (67) (9, 99)	7.7	100%	0%	2 (67) (9, 99)	7.5	100%	0%
LGG	13	7 (54) (25, 81)	NR	86%	86%	7 (54) (25, 81)	13.2	71%	57%
HGG	45	15 (33) (20, 49)	36.9	73%	60%	14 (31) (18, 47)	13.6	64%	57%

NE = Not Estimable.
[1] Exact two-sided 95% confidence interval based on Clopper-Pearson method.
[2] Based on Kaplan-Meier method.
[3] Based on raw data.
Source: FDA reviewer's analyses.

To further evaluate if prior radiation therapy had an impact on the lower observed ORR in HGG, FDA performed a sensitivity analysis of ORR in patients with HGG excluding those who received radiotherapy within 12 weeks prior to enrollment. These results are summarized in Table 48. The estimated ORR was 33% by the investigator and 31% by the independent review. These ORR point estimates were the same as those observed for all HGG patients. Therefore, we did not observe an apparent impact of receiving radiotherapy within 12 weeks prior to enrollment on the treatment efficacy for patients with HGG.

Table 48 FDA – Study X2201 ORR and DoR (HGG, excluding patients who received radiotherapy within 12 weeks prior to enrollment)

	Investigator (N=42)	Independent Review (N=42)
ORR (CR+PR)		
n (%) 95% CI[1]	**14 (33)** (20, 50)	**13 (31)** (18, 47)
CR (n, %) PR (n, %)	3 (7) 11 (26)	2 (5) 11 (26)
DOR in responder, months		
Median[2], 95% CI	31.2 (5.5, NE)	12.7 (4.6, 26.7)

NE = Not Estimable.
[1] Exact two-sided 95% confidence interval based on Clopper-Pearson method.
[2] Based on Kaplan-Meier method.
Source: FDA reviewer's analyses.

The overall ORR for the pooled analysis for all tumor types by independent review was 41% (95% CI: 31, 51). The duration of response was durable up to 24 months.

Table 49 FDA – Study X2201 ORR and DoR (Pooled Solid Tumors excluding ATC, ATS)

	Independent Review (N=105)
ORR (CR+PR)	
n (%) 95% CI[1]	**43 (41)** (31, 51)
CR (n, %) PR (n, %)	6 (6) 37 (35)
DOR in responder, months	N=43
Median[2], 95% CI	10.1 (5.8, 14.9)
Median follow-up[2]	28.5
Number of patients with DOR ≥ 6[3]	25 (58%)
Number of patients with DOR ≥ 12[3]	17 (40%)
Number of patients with DOR ≥ 24[3]	7 (16%)

[1] Exact two-sided 95% confidence interval based on Clopper-Pearson method.
[2] Based on Kaplan-Meier method.
[3] Based on raw data.
Source: FDA reviewer's analyses.

Per the SAP, if any cohort stopped early for efficacy based on the pre-specified Bayesian

analysis, an expansion cohort would be opened for additional enrollment for that particular histology. Table 50 shows the disposition of patients in the primary and expansion cohorts by histology. Note that the adaptation of sample size based on efficacy results to allow additional enrollment may potentially result in a biased estimate for the ORR when conducting analysis in all patients (i.e., primary and expansion combined). Table 51 compares the ORR estimates by the investigator in patients from the primary cohort only and in patients from the primary and expansion combined cohort. It appears that the treatment benefit was consistently observed in the primary cohort as well as in the primary and expansion combined cohort for each histology (except for GIST). The potential bias of the ORR estimate may not change our conclusion on the efficacy of the treatment, albeit that numerical differences were observed in the two populations.

Table 50 FDA – Patient Disposition for Primary and Expansion Cohorts (ITT)

Histology	Primary Cohort	Expansion Cohort	Total
BTC	18	25	43
GIST	1	0	1
ASI	3	0	3
LGG	13	0	13
HGG	24	21	45

Source: FDA reviewer's analyses.

Table 51 FDA – ORR by Investigator for Primary vs. Primary and Expansion Combined Cohorts

Histology	Primary Cohort		Primary + Expansion Cohort	
	#Responders /Total	ORR (95% CI)	#Responders /Total	ORR
BTC	7/18	39 (17, 64)	23/43	53 (38, 69)
GIST	0/1	0	0/1	0
ASI	2/3	67 (9, 99)	2/3	67 (9, 99)
LGG	7/13	54 (25, 81)	7/13	54 (25, 81)
HGG	6/24	33 (20, 49)	15/45	33 (20, 49)
Pooled	33/74	45 (33, 56)	67/141	48 (39, 56)

Source: FDA reviewer's analyses.

The Bayesian estimates and the 95% credible intervals presented by the applicant are considered exploratory. It may not be appropriate to borrow information from other histologies using a Bayesian hierarchical model in the tumor agnostic setting because we cannot confirm the assumed consistent treatment benefit across tumor types. The performance of the Bayesian hierarchical model to evaluate the tumor response data in the tumor agnostic setting is not clear and the results may be potentially biased.

Data Quality and Integrity

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets. The details of audit and HA inspections are presented in Study X2201-Appendix 16.1.8. The COVID-19 pandemic had minimal impact on this study.

The FDA's Assessment:
A major error of the DOR data was found during the review cycle. In the Applicant's Response to FDA Information Request dated February 10, 2022, the applicant identified that the previously submitted LGG ORR analyses excluded MR as a response based on FDA's previous recommendation, but the LGG DOR analyses were based on the first occurrence of MR, PR or CR which did not exclude MR as a response. FDA further requested the Applicant to submit all relevant ADAM data that were impacted by this error. The corrected datasets were submitted on March 8, 2022. FDA's assessment in this review was based on the corrected datasets.

8.1.3. Study XUS35T

The Applicant's Description

Study Design

This third-part study (the NCI-sponsored "Molecular Analysis for Therapy Choice (MATCH) Subprotocol H study) is an ongoing open label, Phase II study of dabrafenib and trametinib in subjects with tumors with BRAF V600E/K/R/D mutations. The MATCH master protocol was designed as a precision medicine platform trial with flexibility to open and close subprotocols, and accrual on additional subprotocols is ongoing. To date, the overall study has comprised 37 subprotocols and is open at nearly 1100 centers throughout the United States. Subprotocol-H is one such "basket" study which allows for the simultaneous evaluation of clinical activity and early signals of efficacy in multiple tumor types in a short period and with fewer subjects (Subbiah et al 2018).

Study Population

Adult subjects with solid tumors, lymphoma or multiple myeloma that have a BRAF V600 mutation (V600E, V600K, V600R or V600D mutations). Molecular profiling was performed in a study-specific network of approved Clinical Laboratory Improvement (CLIA)-certified Molecular Characterization Laboratories.

Key Inclusion criteria

• Adults ≥ 18 years of age.

• Subjects with histologically documented solid tumors or histologically confirmed diagnosis of lymphoma or multiple myeloma requiring therapy and meet one of the following criteria:

- Progressed following at least one line of standard systemic therapy and with no other approved/standard therapy available that has been shown to prolong overall survival (i.e. in a randomized trial against another standard treatment or by comparison to historical controls). Subjects who could not receive other standard therapy that was shown to prolong overall survival due to medical issues were eligible, if other eligibility criteria were met. If the subject was receiving therapy, the clinician assessed that the current therapy was no longer benefitting the subject prior to enrolling on MATCH, regardless of whether it was considered standard.

OR

- for whose disease no standard treatment exists that has been shown to prolong overall survival.

• BRAF V600E, V600K, V600R or V600D mutation.
• Measurable disease.
• ECOG performance status ≤ 1 and a life expectancy of at least 3 months.
• Any prior therapy, radiotherapy (except palliative radiation therapy of 30 Gy or less) or major surgery completed at least 4 weeks prior to start of investigational study treatment

Key Exclusion Criteria

• Diagnosis of metastatic melanoma from a cutaneous, acral, mucosal, or unknown primary site
• Diagnosis of papillary thyroid cancer, colorectal adenocarcinoma or non-small cell lung cancer
• Previously received BRAF and MEK inhibitors
• Any history of a RAS mutation positive cancer, active brain metastases, or with left ventricular ejection fraction (LVEF) below the institutional lower limit of normal.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the study design and patient population for study XUS35T. FDA performed the efficacy analysis on patients with solid tumors with a BRAF V600E mutation and excluded patients with NSCLC as this indication is already approved. FDA did not conduct independent analyses to verify the results that are not relevant for inclusion in product labeling.

Study Endpoints

The Applicant's Description:

Study objectives and their respective endpoints are presented in Table 52.

Table 52 Applicant – Study XUS35T Objectives and endpoints

Objective	Endpoint
Primary	

Objective	Endpoint
To evaluate the proportion of subjects with objective response to the investigational treatment	Investigator-assessed, confirmed, objective response rate (either complete or partial response), assessed according to RECIST 1.1 or RANO (2010).
Secondary	
To evaluate the proportion of patients alive and progression free at 6 months of treatment with the investigational product	Proportion of patients alive and progression free at 6 months from start of study treatment
To evaluate time until death or disease progression	Investigator-assessed PFS
To evaluate duration of response	Time from the first documented evidence of response until the time of documented disease progression (investigator-assessed) or death due to any cause
To evaluate overall survival	Time from start of treatment until death from any cause
Exploratory	
Safety and tolerability of the investigational treatment in this patient population	Incidence and severity of AEs

In addition, Novartis undertook independent review of tumor response per FDA request, and this was used in reporting overall response rate, duration of response and progression free survival. The secondary objectives related to predictive biomarkers and radiomic phenotypes were not analyzed or reported at the time of this interim CSR.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of study endpoints. PFS is considered exploratory in this single-arm study.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The statistical reporting and analysis plan for Study XUS35T was finalized on 19-May-2021. Subjects were assigned to one of 3 disease cohorts, based on their primary cancer type: the "Solid Tumor cohort" for solid tumors assessed using RECIST, the "Glioma cohort" for solid tumors assessed using RANO, and the "Myeloma cohort" for subjects with myeloma.

The following data sets were used:

All Treated Set: All subjects in the Solid Tumor and Glioma cohorts who were enrolled and received at least one dose of investigational treatment. This was the primary analysis set for both efficacy and safety analysis.

Supplementary Efficacy Set: All eligible subjects in the Solid Tumor and Glioma cohorts who were enrolled, received at least one dose of investigational treatment and had BRAF V600 mutation confirmed by the MATCH assay (if enrolled based on an outside assay). This set was used for supplementary analyses of ORR, DoR, OS and PFS.

Myeloma Set: This was the analysis set for presenting study data (as listings) for all eligible subjects in the Myeloma cohort.

Efficacy criteria and analysis: The primary endpoint was investigator-assessed ORR, defined as the proportion of subjects achieving a confirmed complete or partial response. Secondary endpoints include median PFS and 6-month PFS rate. DoR and OS were also evaluated although they were not explicitly given in the master protocol. PFS, OS, and DoR were summarized descriptively and graphically using Kaplan-Meier methods. Enrollment into Subprotocol H is continuing, with 35 subjects having completed LPLV as of Feb-2018. Novartis also undertook an independent review of response, in order to conduct additional evaluation of ORR, PFS, and DoR. The Best Overall Response (BOR) was used for each patient as their ORR result.

For investigator assessment: ORR was assessed using RECIST version 1.1 for solid tumor cohorts and the 3 CNS cancers. Two of the CNS cancers were assessed by RANO criteria (Wen et al 2010).

For independent reviewer assessment: ORR was assessed using RECIST version 1.1 for solid tumors, high grade CNS cancers were assessed by (Wen et al 2010), and a modified RANO criteria (Van den Bent et al, 2011) was used for the LGG patient. Independent review of RANO did not include neurological or steroid status as these clinical data were not captured in case report forms, although were available to investigators for their assessment.

The primary analysis set for efficacy is changed from that specified in the protocol. All treated subjects were included in the primary analyses of efficacy endpoints including ORR, using the All Treated Set. This reduced the potential for selection bias.

There were no amendments to the original SAP.

The FDA's Assessment:
FDA agrees with the Applicant's description of the SAP and Amendments.

Protocol Amendments

The Applicant's Description:

The protocol was amended four times and the key reasons are presented in Table 53.

Table 53 Applicant – Study XUS35T Protocol Amendments

Version date	Summary of key changes
Amendment 1 15-Apr-2016.	Use of Strong inducers or inhibitors of CYP2C8 or 3A4 were prohibited.
Amendment 2 09-Sep-2016	Advice women study participants of reproductive potential to use effective contraception while receiving study treatment and for 4 months after the last dose of trametinib
Amendment 3 16-May-2018	Added non-small cell lung cancer as new disease exclusion. Updated the note to state "Patients who interrupt trametinib and dabrafenib for > 2 weeks will be removed from this subprotocol, unless the interruption was for reduction in LVEF, visual changes or RPED with subsequent recovery."

Version date	Summary of key changes
Amendment 4 19-Aug-2020	Expanded the accrual goal to 85 subjects. Updated the exclusion criteria (this study has already enrolled sufficient number of subjects with a diagnosis of cholangiocarcinoma and low grade serous ovarian cancer. To keep a limit on any given histology so that the overall data was not skewed by a predominant histology, these histologies were excluded from further enrollment)

The FDA's Assessment:
FDA agrees with the Applicant's assessment for protocol amendments.

8.1.4. Study CTMT212XUS35T - Results

The Applicant's Position:

Compliance with Good Clinical Practices

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

Financial disclosure

The Applicant's Position:

As pre-agreed with FDA, study XU35T, is considered covered by the "Financial Disclosure for Clinical Investigators" rule.

The FDA's Assessment:
FDA agrees with the Applicant's position and there is no evidence that compliance with good clinical practices was violated during conduct of Study XUS35T. The Applicant's financial disclosure information was reviewed by FDA. Additional information is provided in 19.2.

Patient Disposition

The Applicant's Description:

A total of 33 subjects were treated (1 LGG, 4 HGG and 28 subjects with non-CNS solid tumors). At the time of data cut-off (01-Oct-2020), 4 subjects (12.1%), were continuing treatment and 29 subjects (87.9%) had discontinued treatment (Table 54).

Table 54 Applicant – XUS35T Subject disposition (All Treated set)

		All Subjects N=33
Subjects treated	Treated	33 (100.0)
	Not treated	0
	Treatment ongoing at time of data cut-off (01-Oct-2020)	4 (12.1)
	Completed treatment	0
	Discontinued from treatment	29 (87.9)
Reason for discontinuation	Adverse event	7 (21.2)

		All Subjects N=33
	Death	1 (3.0)
	Other	2 (6.1)
	Progressive disease	15 (45.5)
	Withdrawal by subject	4 (12.1)

Source: Study XUS35T-Table 14.1-1.1a

The FDA's Assessment:

FDA noted that 27 patients had a solid tumor which excluded patients with NSCLC. One patient had a diagnosis of histiocytic sarcoma of the parietal-occipital lobes and was also excluded as this is categorized as a hematologic malignancy.

Protocol Violations/Deviations

The Applicant's Description:

Protocol deviations were reported in 20 subjects (60.6%). In 17 subjects (51.5%), labs/tests/scan/assessments were not obtained as per protocol. Four of the 17 subjects with deviations pertaining to assessments not obtained as per protocol had their baseline scans performed outside of the protocol mandated window (>6 weeks for RECIST or >2 weeks for RANO). Three subjects did not meet all eligibility criteria; one had low CrCL, one had baseline platelet lab tests performed after step 1 registration and one did not meet the baseline measurable disease criteria for RANO (Table 55). Protocol deviations due to Covid-19 pandemic were reported in 3 subjects (9.1%) (Study XUS35T-Table 14.1-1.5).

Table 55 Applicant – Study XUS35T Protocol deviations (All Treated Set)

Category Protocol deviation	All Subjects N=33 n (%)
Any protocol deviation	20 (60.6)
Key procedure not performed as per protocol	17 (51.5)
Late or Missed Study Procedure	2 (6.1)
Subject's labs/tests/scans/assessments were not obtained as required per protocol	17 (51.5)
Treatment deviation	9 (27.3)
Cycle treatment given late	1 (3.0)
Failure to discontinue treatment	3 (9.1)
Treatment was administered/prescribed/modified not in accordance with protocol guidelines	5 (15.2)
Other deviation	5 (15.2)
Other	1 (3.0)
Subject ineligible	3 (9.1)
Phone or Virtual Visit	1 (3.0)

Category Protocol deviation	All Subjects N=33 n (%)
Numbers (n) represent counts of subjects. Source: Study XUS35T-Table 14.1-1.3	

The FDA's Assessment:

FDA agrees with the Applicant's assessment of protocol violations and are unlikely to have had any meaningful impact on the interpretation of the study.

Datasets analyzed

The Applicant's Description:

A total of 35 subjects were enrolled in the study. The All Treated Set (n=33; 94.3%) excluded 2 subjects with multiple myeloma, as hematological malignancies were not in scope of the submission. This set was used for both efficacy and safety analysis. The Supplementary Efficacy Set included the subset of subjects who additionally met all eligibility criteria and had confirmed BRAF V600 mutations; 27 subjects (77.1%) were included in this set (all had confirmed BRAF V600 mutations) and 6 subjects were excluded from the Supplementary Efficacy Set (reasons in one subject each were: biopsy failure, no confirmed measurable disease per protocol (RANO), low CrCl level, no biopsy received, no confirmation of treatment assignment, baseline platelet lab tests performed after first treatment registration) (Study XUS35TSection 10.3).

The FDA's Assessment:

The efficacy analysis used by FDA for study XUS35T included 26 patients (Efficacy Population) with solid tumors to support the proposed indication. A total of six patients with NSCLC and one patient that was reclassified with a hematologic malignancy were excluded.

Demographic Characteristics

The Applicant's Description:

The median age was 63 years (range: 21-85) and 60.6% of subjects were female; 63.6% entered the study with an ECOG PS score of 1 (Table 56).

Table 56 Applicant – Study XUS35T Demographic summary (All Treated set)

Demographic variable		All Subjects N=33
Age (years)	Mean (SD)	58.5 (16.25)
	Median	63.0
	Q1-Q3	45.0-70.0
	Min-Max	21-85
Age category-n (%)	18 to <65 years	19 (57.6)

Demographic variable		All Subjects N=33
	65 to <85 years	12 (36.4)
	≥85 years	2 (6.1)
Sex-n (%)	Female	20 (60.6)
	Male	13 (39.4)
Race-n (%)	White	28 (84.8)
	Not reported	2 (6.1)
	Black or African American	1 (3.0)
	Multiple	1 (3.0)
	Unknown	1 (3.0)
Ethnicity-n (%)	Not Hispanic or Latino	32 (97.0)
	Not reported	1 (3.0)
ECOG performance status-n (%)	1	21 (63.6)
	0	12 (36.4)

Source: Study XUS35T-Table 14.1-1.6a

The FDA's Assessment:

FDA agrees with Applicant's description of the demographic and baseline characteristics described above and has included an analysis set for the population that encompassed the efficacy population (n=26) in Table 57.

Table 57 FDA - Study XUS35T Demographic Summary (Efficacy Population n=26)

Demographic variable		All Subjects N=26 n (%)
Age (years)	Mean (SD)	56
	Median	54
	Min-Max	21-85
Age category-n (%)	18 to <65 years	18 (69)
	65 to <85 years	7 (27)
	≥85 years	2 (8)
Sex-n (%)	Female	17 (65)
	Male	9 (35)
Race-n (%)	White	24 (92)
	Not reported	1 (3.9)
	Black or African American	1 (3.9)
	Multiple	0
	Unknown	0
Ethnicity-n (%)	Not Hispanic or Latino	25 (96)
	Not reported	1 (3.9)
ECOG performance status-n (%)	1	15 (58)
	0	11 (42)

Demographic variable	All Subjects N=26 n (%)

Source: Reviewer Generated Table

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Description:

Primary site of cancer was GI tract in 36.4%, lung in 21.2%, gynecologic in 18.2%, and CNS in 15.2%. The most common tumor histologies (occurring in ≥ 10% subjects) were adenocarcinoma (including adenocarcinoma of anus, pancreas, small intestine, cholangiocarcinoma (intrahepatic /extrahepatic bile ducts (adenocarcinoma)), and mucinous papillary serous adenocarcinoma of peritoneum) (13 subjects, 39.4%), low grade serous ovarian carcinoma (5 subjects, 15.2%), and intrahepatic cholangiocarcinoma (4 subjects, 12.1%). Among the 5 subjects with CNS cancers, the histologies were anaplastic astroblastoma of temporal lobe, epithelioid glioblastoma of corpus callosum, histiocytic sarcoma of parietal-occipital lobes, pleomorphic xanthoastrocytoma of parietal lobe, and pilocytic astrocytoma of optic nerve. Majority of the subjects (24 subjects, 72.7%) had both target and non target lesions at baseline (Table 58).

Table 58 Applicant – Study XUS35T disease history (All Treated Set)

Disease history	All Subjects N=33
Primary site of cancer/Details of tumor histology/cytology-n (%)	
GI Tract	12 (36.4)
Neuroendocrine carcinoma of colon	2 (6.1)
Adenocarcinoma of anus	1 (3.0)
Intrahepatic cholangiocarcinoma	4 (12.1)
Adenocarcinoma of pancreas	3 (9.1)
Mixed ductal/adeneuroendocrine carcinoma	2 (6.1)
Adenocarcinoma of the small intestine	1 (3.0)
Cholangiocarcinoma, intrahepatic and extrahepatic bile ducts (adenocarcinoma)	1 (3.0)
Lung	7 (21.2)
Adenocarcinoma	6 (18.2)
Combined small cell Squamous cell carcinoma	1 (3.0)
Gynecologic	6 (18.2)
Low grade serous ovarian carcinoma	5 (15.2)
Mucinous papillary serous adenocarcinoma of peritoneum	1 (3.0)
CNS	5 (15.2)
Histocytic sarcoma of parietal occipital lobes	1 (3.0)
Pleomorphic xanthoastrocytoma of parietal lobe	1 (3.0)

Disease history	All Subjects N=33
Anaplastic astroblastoma of temporal lobe	1 (3.0)
Epithelioid glioblastoma of corpus callosum	1 (3.0)
Pilocytic astrocytoma of optic nerve	1 (3.0)
Ameloblastoma of mandible	1 (3.0)
Types of lesions at baseline-n (%)	
Both target and non-target	24 (72.7)
Target only	7 (21.2)
Measurable	1 (3.0)
Non-measurable	1 (3.0)
Current extent of disease-n (%) (metastatic sites)	
Lymph Nodes	18 (54.5)
Liver	16 (48.5)
Lung	11 (33.3)
Other	11 (33.3)
Pleura	5 (15.2)
Bone	3 (9.1)
CNS-Brain	3 (9.1)
Large intestine	1 (3.0)

Metastatic sites and number of organs involved are derived from CRF page of diagnosis and extent of cancer if available. Otherwise, they were derived from tumor assessment pages.
[1]One subject in this cohort had cancer with Histocytic sarcoma of parietal occipital lobes.
Source: Study XUS35T-Table 14.1-1.7

The FDA's Assessment:

FDA performed the analysis for disease history based on the Efficacy Population of n=26. A total of 14 (54%) had GI tumors, 6 (23%) had gynecologic tumors, 4 (15%) had CNS tumors. Other enrolled histologies are listed in the table above. The patient with histiocytic sarcoma of the parietal lobe was reclassified by FDA as a hematologic malignancy. A total of 19 (73%) patients had both target and non-target, 5 (19%) patients had target only, and one (3.8%) patient each had measurable or non-measurable lesions at baseline.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Description:

Treatment compliance: Treatment compliance was assessed in Study XUS35T, but results were not presented in the interim CSR.

Prior medications: All subjects (100%) had received at least one type of prior cancer therapy (Table 59). The most frequent prior systemic therapies taken by ≥10% of subjects were carboplatin (36.4%), gemcitabine hydrochloride (30.3%), oxaliplatin (24.2%), paclitaxel (24.2%), cisplatin (21.2%) 5-fluorouracil (21.2%), pemetrexed (18.2%), docetaxel (15.2%), irinotecan (15.2%), and temozolomide (12.1%) (Study XUS35T-Table 14.1-1.11).

Concomitant medications were not collected in the Study XUS35T.

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

Table 59 Applicant – Study XUS35T Prior cancer therapies (All Treated Set)

Characteristic	All Subjects N=33
Any therapy	33 (100.0)
Any medication	31 (93.9)
Chemotherapy multiple agents systemic	27 (81.8)
Chemotherapy single agent systemic	13 (39.4)
Drug and/or immunotherapy	6 (18.2)
Hormonal Therapy	2 (6.1)
Surgery	18 (54.5)
Radiation Therapy	7 (21.2)
Other therapy	2 (6.1)
Therapy (NOS)	1 (3.0)
Vaccine	1 (3.0)
Total number of different therapies received	
1	8 (24.2)
2	11 (33.3)
3	11 (33.3)
4	3 (9.1)

Source : Study XUS35T-Table 14.1-1.10

The FDA's Assessment:

FDA performed the analysis for prior cancer therapies on the Efficacy Population (n=26) which is overall consistent with the Applicant's results for n=33. Table 60 summarizes the prior therapies.

Table 60 FDA - Study XUS35T Prior Cancer Therapies (Efficacy Population n=26)

Characteristic	All Subjects N=26 n (%)
Any therapy	26 (100)
Any medication	24 (92)
Chemotherapy multiple agents systemic	20 (77)
Chemotherapy single agent systemic	10 (39)
Drug and/or immunotherapy	5 (19)
Hormonal Therapy	2 (8)
Surgery	16 (62)
Radiation Therapy	5 (19)
Other therapy	1 (3.8)
Therapy (NOS)	1 (3.8)

Characteristic	All Subjects N=26 n (%)
Vaccine	0
Total number of different therapies received	
1	6 (23)
2	9 (35)
3	9 (35)
4	2 (8)

Source : FDA reviewer's analysis

Efficacy Results

The Applicant's Description:

Primary Endpoint

The study met its primary end point. The ORR was compared against a protocol-specified null benchmark value of 5% and an observed ORR of ≥ 16% was considered sufficiently promising. For both investigator and independent reviewer assessed response in the "All Treated" set, the lower bound of the 95% CI for the estimate of BoR was clearly above the protocol-specified value of 5% (Table 61).

By Investigator: The BoR in the All Treated Set was 39.4% (95% CI: 22.9, 57.9) with complete response in one subject (3.0%) and with partial response in 12 subjects (36.4%). The DCR per Investigator assessment was 81.8%.

By independent review: The BoR was 42.4% (95% CI: 25.5, 60.8) with complete response in one subject (3.0%) and with partial response in 13 subjects (39.4%). The DCR per independent assessment was 81.8%.

The overall concordance rate between Investigator assessment and independent review was 60.6% (Study XUS35T-Table 14.2-1.10c and Study XUS35T-Table 14.2-1.10a).

Table 61 Applicant – Study XUS35T BOR based on investigator assessment across solid tumors and subjects with CNS cancers (All Treated Set)

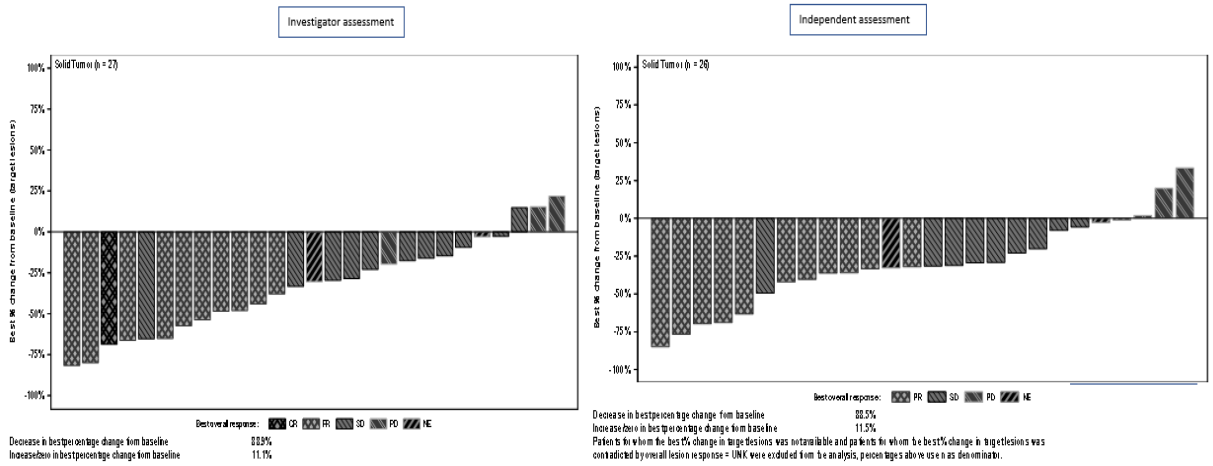
	Investigator assessment All subjects N= 33		Independent review All subjects N= 33	
Best overall response	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Complete Response (CR)	1 (3.0)		1 (3.0)	
Partial Response (PR)	12 (36.4)		13 (39.4)	
Non-CR/Non-PD	0		2 (6.1)	
Stable Disease (SD)	14 (42.4)		11 (33.3)	

	Investigator assessment All subjects N= 33		Independent review All subjects N= 33	
Progressive Disease (PD)	4 (12.1)		3 (9.1)	
Not Evaluable	2 (6.1)		3 (9.1)	
Overall Response Rate (ORR: CR+PR)	13 (39.4)	(22.9, 57.9)	14 (42.4)	(25.5, 60.8)
Disease Control Rate (DCR:CR+PR+SD+Non-CR/Non-PD)	27 (81.8)		27 (81.8)	

N: The total number of subjects in the treatment group. It is the denominator for percentage (%) calculation.
n: Number of subjects who are at the corresponding category. Clopper-Pearson exact 95% CIs.
Source: Study XUS35T-Table 14.2-1.2i, Table 14.2-1.1j

Evidence of efficacy was also seen from reduction of tumor measurement from baseline in the waterfall plot for non-CNS solid tumors (Figure 9).

Figure 9 Applicant - Study XUS35T Investigator and Independent-assessed percent change at maximum reduction from baseline in tumor measurement per RECIST v1.1 criteria for subjects with solid tumors (All Treated Set)



Source: Study XUS35T-Figure 14.2-1.1a and Figure 14.2-1.1b

Best overall response by individual subjects

The BOR for individual subjects by histology are given in the table below (Table 62).

Table 62 Applicant – Study XUS35T BOR by histological type

Primary tumor type	Histology by central review	BoR by Investigator	BoR by Independent review
GI tract	Neuroendocrine carcinoma of colon	PD	PD
GI tract	Neuroendocrine carcinoma of colon	SD	SD
GI tract	Adenocarcinoma of anus	SD	SD
GI tract	Intrahepatic cholangiocarcinoma	SD	SD
GI tract	Intrahepatic cholangiocarcinoma	PR	PR
GI tract	Intrahepatic cholangiocarcinoma	PR	PR

Primary tumor type	Histology by central review	BoR by Investigator	BoR by Independent review
GI tract	Intrahepatic cholangiocarcinoma	PR	SD
GI tract	Mixed ductal/adeneuroendocrine carcinoma	SD	SD
GI tract	Mixed ductal/adeneuroendocrine carcinoma	NE	NE
GI tract	Adenocarcinoma of pancreas	PD	PD
GI tract	Adenocarcinoma of pancreas	PD	PD
GI tract	Adenocarcinoma of pancreas	SD	SD
GI tract	Adenocarcinoma of small intestine	PD	NE
GI tract	Cholangiocarcinoma, intrahepatic and extrahepatic bile ducts (adenocarcinoma)	PR	SD
Lung	Adenocarcinoma	SD	PR
Lung	Adenocarcinoma	PR	SD
Lung	Adenocarcinoma	NE	NE
Lung	Adenocarcinoma	PR	PR
Lung	Adenocarcinoma	SD	SD
Lung	Adenocarcinoma	SD	PR
Lung	Combined small cell Squamous cell carcinoma	SD	PR
Ameloblastoma of mandible	Ameloblastoma of mandible	SD	PR
Gynecologic	Low grade serious ovarian carcinoma	SD	NON-CR/NON-PD
Gynecologic	Low grade serious ovarian carcinoma	CR	CR
Gynecologic	Low grade serious ovarian carcinoma	PR	PR
Gynecologic	Low grade serious ovarian carcinoma	PR	PR
Gynecologic	Low grade serious ovarian carcinoma	PR	PR
Gynecologic	Mucinous papillary seros adenocarcinoma of peritoneum	PR	PR
CNS	Histocytic sarcoma of parietal occipital lobes	PR	NON-CR/NON-PD
CNS	Pleomorphic xanthoastrocytoma of parietal lobe	SD	PR
CNS	Anaplastic astroblastoma of temporal lobe	SD	PR
CNS	Epithelioid glioblastoma of corpus callosum	PR	SD
CNS	Pilocytic astrocytoma of optic nerve	SD	SD

Source: Study XUS35T-Listing 14.2-1.2a, Listing 14.2-1.2b, Listing 14.2-1.4a, Listing 14.2-1.4b

Supportive and Sensitivity analyses

Multiple supportive analyses of the primary endpoint were performed. The results of the supportive and sensitivity analyses of BoR by investigator and independent review were consistent with the results observed for primary analysis and further strengthened the efficacy

of dabrafenib in combination with trametinib in this rare population with solid tumors and CNS cancers with BRAF V600 mutation.

Secondary efficacy results

The Applicant's Description:

All the secondary efficacy parameters (PFS, DoR, and OS) were further corroborated with supportive and sensitivity analysis. A brief summary of the efficacy results are provided in the table below (Table 63).

Table 63 Applicant – Study XUS35T Summary of secondary efficacy results

Efficacy variable	By Investigator	By Independent review
Progression free survival (All treated set)		
Across all subjects (Solid tumors and subjects with CNS cancers) (N=33)	Median PFS was 11.4 months (95% CI: 6.1, 15.7). At the time of data cut-off, 9 subjects were censored (27.3%)	Median PFS was 9.3 months (95% CI: 6.7, 11.5). At the time of data cut-off, 8 subjects were censored (24.2%)
With Solid tumors (N=28)	Median PFS was 9.4 months (95% CI: 4.3, 15.7). At the time of data cut-off, 7 subjects were censored (25.0%)	Median PFS was 9.3 months (95% CI: 4.3, 11.5). At the time of data cut-off, 6 subjects were censored (21.4%)
In subjects with CNS cancers (N=1 in the LGG cohort; N=4 in the HGG cohort)	Median PFS in LGG was 6.1 months (95% CI: NE, NE). Median PFS in HGG was not estimable (95% CI: 7.3, NE).	Median PFS in LGG was not estimable (95% CI: NE, NE). Median PFS in HGG was 11.8 months (95% CI: 3.4, NE).
Duration of response (All treated set)		
Across all subjects (Solid tumors and subjects with CNS cancers) (N=33)	Among the 13 responders, the median DoR was not estimable (95% CI: 7.6, NE). At the time of data cut-off, 7 subjects were censored (53.8%) and 6 subjects had progression events (46.2%). The KM estimate of DoR at 36 months was 50% (95% CI: 20.8, 73.6)	Among the 14 responders, the median DoR was 10.9 months (95% CI: 5.6, 29.7). At the time of data cut-off, 3 subjects were censored (21.4%) and 11 subjects had progression events (78.6%). The KM estimate of DoR at 36 months was 21.4% (95% CI: 5.2, 44.8)
With Solid tumors (N=28)	Among the 11 responders, the median DoR was 16.9 months (95% CI: 7.4, NE). At the time of data cut-off, 5 subjects were censored (45.5%) and 6 subjects had progression events (54.5%)	Among the 12 responders, the median DoR was 10.9 months (95% CI: 5.4, NE). At the time of data cut-off, 3 subjects were censored (25.0%) and 9 subjects had progression events (75.0%)
In subjects with CNS cancers (N=4 in the HGG cohort)	In HGG, among the 2 responders, the median DoR was not estimable (95% CI: NE, NE) as both the subjects were censored at the time of date cut-off.	In HGG, among the 2 responders, the median DoR was 10.1 months (95% CI: 5.6, NE). At the time of date cut-off, both the subjects had PFS events
Overall survival (All treated set)		
Across all subjects (Solid tumors and subjects with CNS cancers) (N=33)	17 subjects (51.5%) died in the study. The median OS was 25.2 month (95% CI: 12.8, NE)	
With Solid tumors (N=28)	16 subjects (57.1%) died in the study. The median OS was 20.8 month (95% CI: 7.4, 29.7)	

Efficacy variable	By Investigator	By Independent review
In subjects with CNS cancers (N=1 in the LGG cohort; N=4 in the HGG cohort)	In LGG: one subject was censored at the time of data cut-off.' In HGG: 1 subject died in the study and the median OS was not estimable (95% CI: 28.4, NE)	
Source: Study XUS35T-Section 11-3		

The FDA's Assessment:

FDA reviewed this section and agreed with the Applicant's analysis results for ORR and DoR. Note that among the 33 treated patients with solid tumors, 6 patients with NSCLC were excluded from the labeling since dabrafenib in combination with trametinib were previously approved for this patient population and 1 patient with histocytic sarcoma of the parietal occipital lobes (this patient was reclassified as having a hematologic malignancy) was also excluded from the analysis. The pooled ORR and DOR results for the 26 patients included in the labeling were summarized in Table 64.

Table 64 FDA – Study XUS35T ORR and DoR (Efficacy Population)

	Independent Review (N=26)
ORR (CR+PR)	
n (%) 95% CI[1]	**11 (42)** (23, 63)
CR (n, %) PR (n, %)	1 (4) 10 (38)
DOR in responder, months	**N=11**
Median[2], 95% CI	14.7 (5.6, NR)
Median follow-up[2]	40.5
Number of patients with DOR ≥ 6[3]	9 (82%)
Number of patients with DOR ≥ 12[3]	7 (64%)
Number of patients with DOR ≥ 24[3]	4 (36%)

[1] *Exact two-sided 95% confidence interval based on Clopper-Pearson method.*
[2] *Based on Kaplan-Meier method.*
[3] *Based on raw data.*
Source: FDA reviewer's analyses.

The PFS and OS data reported by the Applicant are not interpretable in the absence of a comparator arm and are considered exploratory. The analysis of DCR is also considered exploratory since the DCR is not an established measure of clinical benefit.

Data Quality and Integrity

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets.

The details of Audit and HA inspections are presented in Study XUS35T-Appendix 16.1.8. There was no impact of COVID-19 pandemic on the safety and efficacy analysis performed in this study. There were no COVID-19 related AEs, SAEs, deaths during the study.

The FDA's Assessment:
The data quality for this application is acceptable.

8.1.5. Study X2101

Study 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 recommended phase 2 dose (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 LCH).

The FDA's Assessment:
FDA agrees with the Applicant's assessment of the design of study X2101. Only patients in Part C and D with BRAF V600E-positive solid tumors (n=36) were part of the FDA's efficacy analysis to support the indication in the pediatric population.

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 v 4.03) grade 2 or higher from previous anti-cancer therapy, except alopecia.
27. History or evidence of cardiovascular risk

The FDA's Assessment:
FDA agrees with the Applicant's assessment of the eligibility criteria.

Study Endpoints

The Applicant's Description:

The study objectives and their respective endpoints are presented Table 65.

Table 65 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	Adverse events (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	Adverse events (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
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	

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the endpoints in study X2101.

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 best overall response (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 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 all treated population and the response evaluable population,
- Independent reviewer assessed PFS
- Concordance analysis, as applicable.

SAP Amendments

SAP amendments are described in Table 66.

Table 66 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

The FDA's Assessment:

FDA agrees with the Applicant's description of the SAP and SAP amendments.

Protocol Amendments

The Applicant's Description:

The study protocol was amended 9 times. Key amendment features are given in Table 67.

Table 67 Applicant – Study X2101Protocol 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.
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 changed to dabrafenib 10 mg dispersible tablets and trametinib 0.5 mg and 2 mg tablets. 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.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of protocol amendments.

8.1.6. Study CTMT212X2101 - 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 agrees that only patients from Parts C and D with solid tumors were included in the efficacy analysis for study X2101.

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 and there is no evidence that compliance with good clinical practices was violated during conduct of Study X2101.

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:
The Applicant's financial disclosure information was reviewed by FDA. Additional information is provided in 19.2.

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 68.

Table 68 Applicant – Study X2101 Subject disposition (All treated population)

	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 agrees with the Applicant's assessment of patient disposition for Parts C and D.

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 agrees with the Applicant's assessment of protocol violations and are unlikely to have had any meaningful impact on the interpretation of the study.

Analysis Sets

The Applicant's Description:

Definitions of each of the analysis sets are provided in Section 8.1.5. The number of subjects in each of the analysis sets in Part C and D are provided in the Table 69.

Table 69 Applicant – Study X2101 Analysis populations Parts C and D (All treated population)

	Part C	Part D		
	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)

	Part C	Part D		
	All Part C subjects N=18 n (%)	LGG N=20 n (%)	LCH N=10 n (%)	All Part D subjects N=30 n (%)
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

The FDA's Assessment:

FDA agrees with the Applicant's summary of the analysis sets. A total of 36 patients were included in the efficacy analysis form Parts C and D. Patients with LCH (n=2) in Part C and (n=10) in Part D were not included in the efficacy analysis and data were not verified for this patient population.

Table of Demographic Characteristics

The Applicant's Description:

The demographic characteristics of subjects in parts C and D are presented in Table 70.

Table 70 Applicant – Study X2101 Demographics and baseline characteristics Part C and D (All treated population)

	Part C	Part D		
	All Part C subjects N=18 n (%)	LGG N=20 n (%)	LCH N=10 n (%)	All Part D subjects N=30 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)

	Part C	Part D		
	All Part C subjects N=18 n (%)	LGG N=20 n (%)	LCH N=10 n (%)	All Part D subjects N=30 n (%)
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

The FDA's Assessment:

The Applicant's summary of the demographics for Study A2102 was reviewed. FDA did not conduct independent analyses to verify the results that are not relevant for inclusion in product labeling. For patients from Parts C and D (n=36), FDA conducted demographic analyses summarized in Table 71.

Table 71 FDA - Study X2101 Demographics Parts C and D (n=36)

Age (years)	
Mean (SD)	9.8 (4.7)
Median (min-max)	10 (1.4-17)
Age category n (%)	
< 2 years	1 (2.8)
2 - < 6 years	7 (19)
6 - <12 years	12 (33)
≥ 12 years	16 (44)
Sex n (%)	
Female	18 (50)
Male	18 (50)
Karnofsky and Lansky Performance status n (%))	
100	21(58)
90	10 (28)
80	3 (8)
70	1 (2.8)
<70	0

Source: FDA reviewer's analysis

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 low grade gliomas. There were 2 high grade gliomas (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 72).

Table 72 Applicant – Study X2101 Disease characteristics, disease burden at baseline - Part C (All treated population)

	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)

	All part C subjects N=18
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)

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

Disease characteristics - Part D

The disease characteristics were as expected for the enrolled disease cohorts. The primary tumor type was low grade gliomas (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 73).

Table 73 Applicant – Study X2101 Disease characteristics, disease burden at baseline - Part D (All treated population)

	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)

	LGG N=20 n (%)	LCH N=10 n (%)	All subjects N=30 n (%)
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)
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)

* There was no intended distinction in the collected data field for primary tumor type between Brain and CNS.
- Source: Study X2101-Table 14.1-4.1.4

The FDA's Assessment:

The Applicant's summary of the baseline characteristics for Study A2102 was reviewed. FDA did not conduct independent analyses to verify the results that are not relevant for inclusion in product labeling. FDA For patients from Parts C and D (n=36), FDA conducted baseline characteristics analyses summarized in Table 74.

Table 74 FDA - Study X2101 Disease Characteristics, Disease Burden at Baseline - Parts C and D (n=36)

	Parts C and D N=36 n (%)
Primary tumor type n (%)	
LGG	34 (94)
HGG	2 (6)
Metastatic disease at Screening	
Yes	0
No	36 (100)
Type of lesion at baseline based on investigator assessment per RANO-n (%)	
Measurable only	24 (67)
Both Measurable and Non-Measurable	8 (22)
Non-Measurable only	4 (11)
Type of lesion at baseline based on independent reviewer assessment per RANO 2010-n (%)	
Measurable only	6 (17)
Non-Measurable only	19 (53)
Both Measurable and Non-Measurable	6 (17)
Unknown	5 (14)
Type of lesion at baseline based on independent reviewer assessment per RANO 2017-n (%)	
Measurable only	32 (89)
Non-Measurable only	1 (2.8)
Both Measurable and Non-Measurable	3 (8)

Source: FDA reviewer's analysis

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:

For Patients in Parts C and D (n=36), prior anti-cancer treatments included surgery (83%), and external beam radiotherapy (2.8%), and systemic therapy (92%).

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:

There were no clinically significant issues relating to treatment compliance or need for concomitant or rescue medication that could impact the results of the trial or warrant discussion.

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 agrees with the Applicant's assessment of the primary objective.

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 75).

Table 75 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)

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

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 76). 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 76 Applicant – Study X2101 Secondary efficacy endpoints and supportive analyses

Parameter	LGG BRAF V600 mutation		LCH BRAF V600 mutation
	trametinib	dabrafenib+trametinib	dabrafenib+trametinib
	N=13	N=36	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)	

[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).

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

The FDA's Assessment:

The Applicant's summary of the efficacy results for Study X2101 was reviewed. FDA did not conduct independent analyses to verify the results that are not relevant for inclusion in product labeling. Of the 36 patients, 2 were treated below the RP2D. The ORR was 25% (95% CI: 12%, 42%). For the 9 patients who responded, DoR was ≥6 months for 78% of patients, ≥12 months for 56% of patients, and ≥24 months for 44% of patients. Results for PFS are not interpretable in a single-arm study and are considered exploratory.

Pediatric glioma response determinations are challenging for multiple reasons (e.g., presence of cystic cavities with nodules, post-surgical changes, etc.). pLGG response determinations are additionally challenging due to their typical absence of gadolinium enhancement, making margin definition less distinct (Warren 2013). The accepted RANO response criteria changed during the course of study X2101 conduct with the introduction of RANO 2017 criteria based on RAPNO 2013 criteria. This change resulted in emphasis on lesion measurements based on T2 FLAIR. Novartis reports both the 2010 and 2017 RANO criteria for the independent review of tumor response for patients with LGG. Investigator determined RANO responses were performed by institutional radiologists using RANO criteria with the 2010 criteria noted in the

protocol and without mandating any retrospective re-determination of response assessment upon the publication of the RAPNO (Warren 2013) or RANO 2017 criteria. With these challenges in response determination, discordance was observed even within the independent review process, where concordance calculated between the two independent response determinations (one using 2010 and the other using 2017) for BOR was 66.7 % (X2101 table 14.2-1.3.5). The concordance between investigator determined BOR and independent review using RANO 2017 criteria was 69.4% (T14.2-1.3.3). The difference in ORR (CR+PR) between investigator (19/36 or 52.7%) and independent review (9/36 or 25%) is partially due to the independent review downgrading 3 CRs due to absence of measurable disease and 4 of 6 PRs who approached but did not meet the defined 50% reduction in sum of products of perpendicular diameters necessary for this response determination.

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:
The data quality for this application is acceptable.

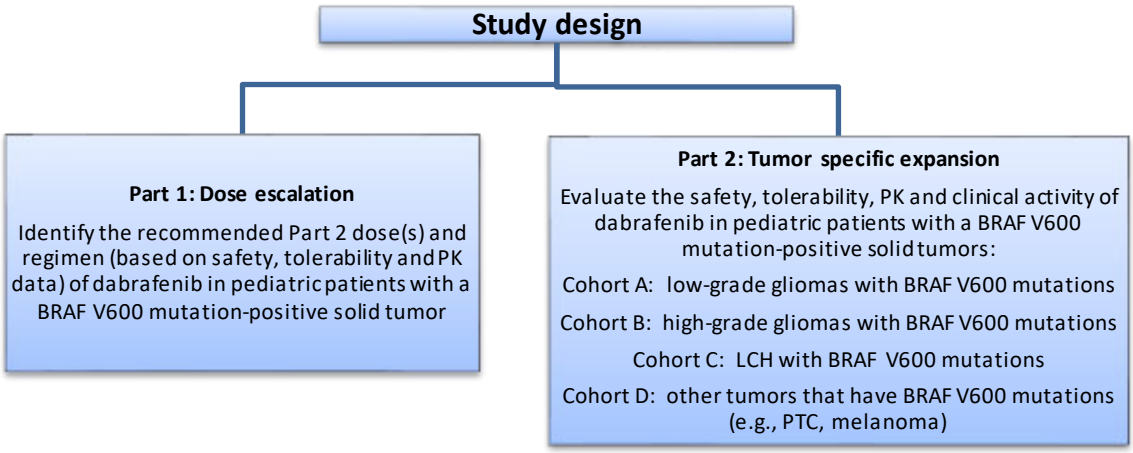
8.1.7. Study A2102

Study 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 10).

Figure 10 Applicant - Study A2101 Study design



Part 1: Dose escalation: this was a repeat dose, dose escalation study. The RSD (Skolnik et al 2008) 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 low grade glioma; pediatric high grade glioma; 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 RSD was employed to determine the MTD. If dose de-escalation had occurred (due to the occurrence of DLTs) 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 assessment of the design study A2102.

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 77.

Table 77 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

Objectives	Endpoints
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

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the population and endpoints for 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 (PK) 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 Dose Limiting Toxicity (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 overall response rate (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. Time to response (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). Duration of response (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 agrees with the Applicant's description of the SAP and Amendments.

Protocol Amendments

The Applicant's Description:

The study protocol was amended 11 times. Key amendment features are given in Table 78.

Table 78 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 7.1.1; 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 10mg 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
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.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the protocol amendments for study A2102.

8.1.1. Study CDRB436A2102 - 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 and there is no evidence that compliance with good clinical practices was violated during conduct of Study A2102.

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:

The Applicant's financial disclosure information was reviewed by FDA. Additional information is provided in 19.2.

Patient Disposition

The Applicant's Description:

Table 79 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 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 (%)**
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)

- 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.
- Source: Study A2102-Table 14.1-1.1

The FDA's Assessment:

The Applicant's summary of the patient disposition for Study A2102 was reviewed. FDA did not conduct independent analyses to verify the results that are not relevant for inclusion in product labeling.

Protocol Violations/Deviations

The Applicant's Description:

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 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:

The Applicant's summary of the protocol deviations for Study A2102 was reviewed. FDA did not conduct independent analyses to verify the results that are not relevant for inclusion in product

labeling.

Analysis sets

The Applicant's Position:

Analysis sets for part 1, part 2 and pooled disease cohorts are shown in Table 80.

Table 80 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)
Part 2 Analysis set	**LGG N=17 n (%)**	**HGG N=28 n (%)**	**LCH N=11 n (%)**	**Other N=2 n (%)**	**All subjects N=58 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)
Pooled disease cohort Analysis set	**LGG BRAF V600 N=33 n (%)**	**HGG BRAF V600 N=35 n (%)**	**LCH BRAF V600 N=13 n (%)**	**Other N=4 n (%)**	**All subjects N=85 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

The FDA's Assessment:

The Applicant's summary of the analysis population for Study A2102 was reviewed. FDA did not conduct independent analyses to verify the results that are not relevant for inclusion in product labeling.

Table of Demographic Characteristics

The Applicant's Description:

Demographic characteristics of both the parts are presented in Table 81.

Table 81 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)

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
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)

- A patient may be represented in more than one race category due to multiple races.
- Source: Study A2102-Table 14.1-3.1

The FDA's Assessment:

The Applicant's summary of the demographics and baseline characteristics for Study A2102 was reviewed. FDA did not conduct independent analyses to verify the results that are not relevant for inclusion in product labeling.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline characteristics

The Applicant's Description:

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:
The Applicant's summary of the demographics and baseline characteristics for Study A2102 was reviewed. FDA did not conduct independent analyses to verify the results that are not relevant for inclusion in product labeling.

Prior anti-cancer therapy, radiotherapy and related surgeries

The Applicant's Description:

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 (Study A2102Table 14.1-3.7). All except one patient received chemotherapy as their prior therapy (Study A2102-Table 14.1-3.5). Ten subjects underwent prior radiotherapy with intent to provide local/regional control (N=4) or with curative intent (N=5) (Study A2102-Table 14.1-3.6). In Part 2, the majority of subjects (47, 81.0%) received chemotherapy as prior therapy (Study A2102-Table 14.1-3.5). At least 31 subjects underwent prior radiotherapy (11 local/regional, 20 curative) (Study A2102Table 14.1-3.6). 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 (Study A2102-Table 14.1-3.7).

The FDA's Assessment:
The Applicant's summary of prior therapies for Study A2102 was reviewed. FDA did not conduct independent analyses to verify the results that are not relevant for inclusion in product labeling.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
The Applicant's Description:

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:
There were no clinically significant issues relating to treatment compliance or need for concomitant or rescue medication that could impact the results of the trial or warrant discussion.

Efficacy Results

The Applicant's Description:

Best overall response (Secondary efficacy endpoint)

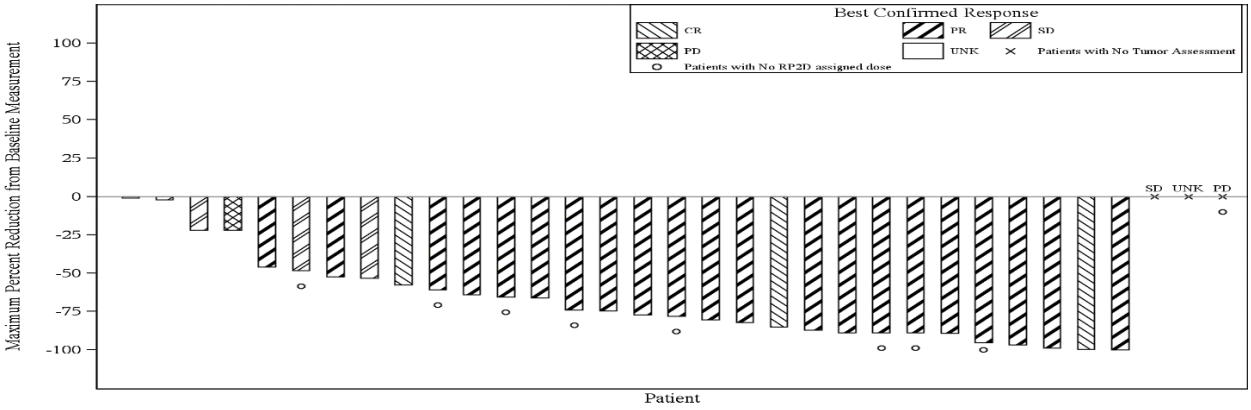
LGG (based on investigator assessment): ORR based on investigator assessment was achieved in 70.8% (95% CI: 48.9, 87.4) of all 24 LGG subjects at RP2D; 3 subjects (12.5%) achieved CR and 14 subjects (58.3%) achieved PR. Among the 33 LGG subjects, the ORR was 72.7% (95% CI: 54.5, 86.7) with CR in 3 subjects, PR in 21 subjects and SD in 5 subjects (15.2%) (Table 82). Percentage reduction from baseline sum of the products of perpendicular diameters for LGG subjects is presented in Figure 11.

Table 82 Applicant – Study A2102 BOR based on investigator assessment per RANO criteria for LGG subjects (All treated population)

Disease: LGG	Part 1 3.75 mg/kg N=4 n (%)	Part 1 4.5 mg/kg N=6 n (%)	Part 1 5.25 mg/kg N=6 n (%)	Part 2 LGG N=17 n (%)	All LGG subjects at RP2D* N=24 n (%)	All LGG subjects N=33 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)

- * 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.
- Source: Study A2102-Table 14.2-1.1a

Figure 11 Applicant - Study A2102 Investigator-assessed percent change at maximum reduction from baseline in tumor measurement per RANO criteria for LGG subjects (All treated population)



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.
Source: Study A2102-Figure 14.2-1.1a

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 83) and the RANO criteria (2017): 41.7% (95% CI: 22.1, 63.4) with 10 subjects (41.7%) achieving PR (Study A2102-Table 14.2 1.1b).

Table 83 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)
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)

- 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.
- Source: Study A2102-Table 14.2 1.1b

The concordance between 2010 and 2017 RANO criteria based on independent reviewer assessment of response for LGG subjects was 60.6% (Study A2102-Table 14.2-1.7). Concordance between investigator and independent reviewer assessment of BOR for LGG subjects was 48.5% for both 2010 and 2017 RANO criteria (Study A2102-Table 14.2-1.8).

HGG: The ORR based on investigator assessment was 25% (95% CI: 10.7, 44.9) for 28 HGG subjects treated at the 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 84). 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 12.

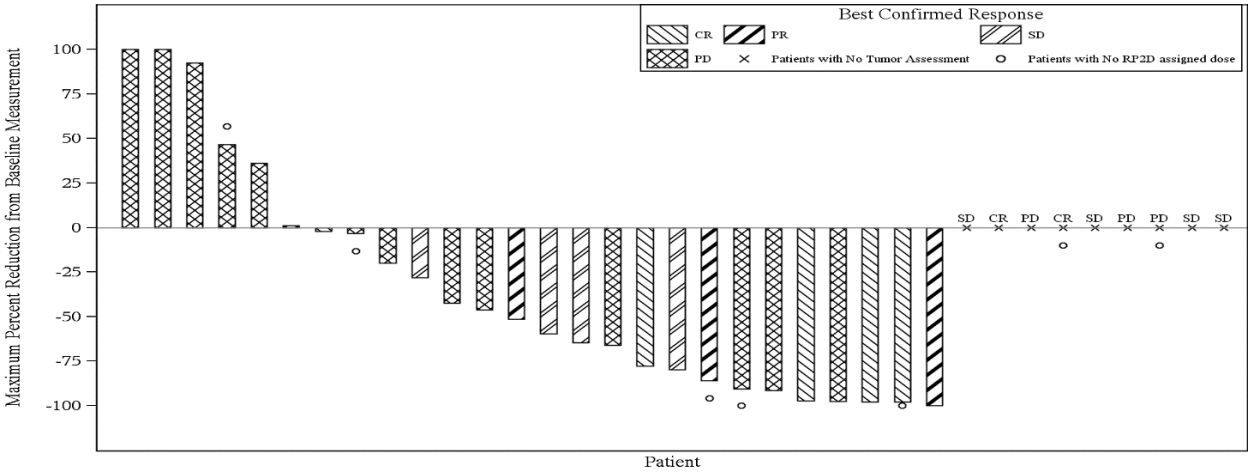
Table 84 Applicant – Study A2102 BOR based on investigator assessment per RANO 2010 criteria for HGG subjects (All treated population)

	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)					

Disease: HGG	Part 1 3 mg/kg N=3 n (%)	Part 1 3.75 mg/kg N=4 n (%)	Part 2 HGG N=28 n (%)	All HGG at RP2D* N=28 n (%)	All HGG N=35 n (%)
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)
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)

* 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.
- Source: Study A2102-Table 14.2 1.2a

Figure 12 Applicant - Study A2102 Investigator-assessed percent change at maximum reduction from baseline in tumor measurement per RANO criteria for HGG subjects (All treated population)



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.
Source: Study A2102-Figure 14.2-1.2a

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 85). Nine of the 10 responses were ongoing at study completion and 12 of the 13 subjects overall were progression free at study completion (Study A2102-Table 11-6).

Table 85 Applicant – Study A2102 Response rate of LCH subjects based on investigator assessment (All treated population)

Disease: LCH	Part 1		Part 2	All LCH subjects	All LCH subjects
	3.75 mg/kg N=1 n (%)	4.5 mg/kg N=1 n (%)	LCH N=11 n (%)	at RP2D* N=11 n (%)	N=13 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)

- * 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.
- Source: Study A2102-Table 14.2-1.3a

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).

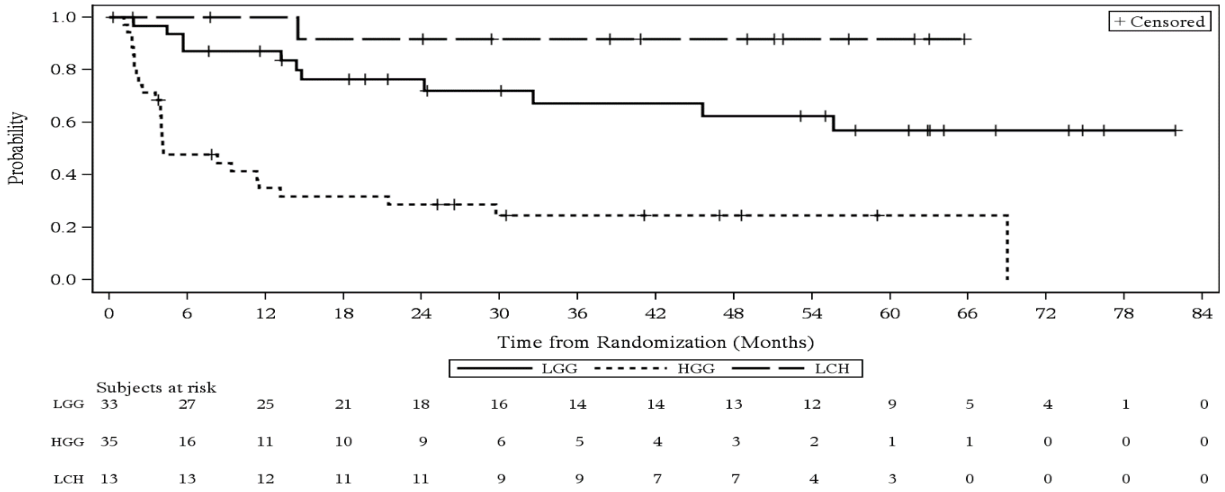
The ORR based on investigator assessment in all 21 response-evaluable HGG subjects at RP2D was 28.6% (95% CI: 11.3, 52.2) and in all 27 response-evaluable HGG subjects at any dose was 33.3% (95% CI: 16.5, 54.0). The BOR of CR and PR was reported in 6 subjects (22.2%) and 3 subjects (11.1%), respectively 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 13).

Figure 13 Applicant - Study A2102 Kaplan-Meier PFS curves by Investigator assessment by cohort - pooled disease cohorts (All treated population)

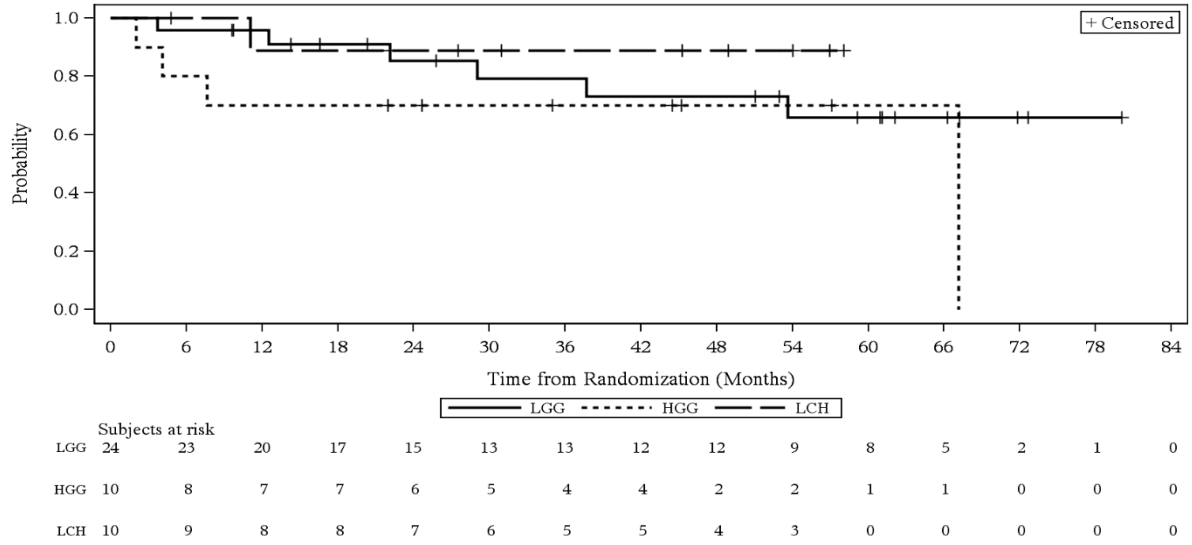


Source: Study A2101-Figure 14.2-1.4.1

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 14).

Figure 14 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

The FDA's Assessment:

The Applicant's summary of the efficacy results for Study A2102 was reviewed. FDA acknowledges the primary analysis results for ORR and DoR but did not conduct independent analyses to verify the rest of the summary since the results are not considered relevant for inclusion in product labeling.

Data Quality and Integrity

The Applicant's Description:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets. The details of Audit and HA inspections are presented in Study A2102-Appendix 16.1.8. 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.

8.1.2. Integrated Review of Effectiveness

The FDA's Assessment:

Study X2201 is the primary study supporting the efficacy claims in adult patients and study X2101 is the primary study supporting efficacy claims in the pediatric population. Studies XUS35T in adults and A2102 in pediatrics were submitted. Refer to the Section 8.1.4 for FDA's

overall comments regarding efficacy.

8.1.3. Assessment of Efficacy Across Trials

Primary Endpoints

The Applicant's Position:

The information on the primary endpoints is presented under each study mentioned in the section above. This needs a statement of how information across all available sources supports an agnostic indication

The FDA's Assessment:

FDA's assessment of efficacy is based primarily on Studies X2201 and X2101. FDA considered Studies XUS35T and A2101 separately as a supportive trials. In the overall assessment of efficacy for the indication, FDA also considered results of Trials COMBI-d, COMBI-v, and BRF113928. These results have been previously reviewed and supported approvals in melanoma and NSCLC. The results (also previously reviewed and in labeling) in patients with ATC also supported the broader tissue agnostic claim.

Comparisons between the trials were not performed due to the limitations of cross trial comparisons. FDA requested that the Applicant provide a breakdown of the histologic subtypes of CNS tumors from studies X2201 and XUS35T to evaluate the response rates across the different CNS subtypes. Table 86summarizes the efficacy results for CNS tumors across the two studies. It is difficult to make any conclusion across studies and with several subtypes enrolling only 1 or 2 patients, no meaningful conclusion can be extrapolated to the broader histologic subtypes.

Table 86 FDA - Efficacy Results for CNS Tumors Across Studies X2201 and XUS35T

Tumor Type	N	Objective Response Rate (ORR)		Duration of Response (DoR)
		%	95% CI	Range (months)
High grade glioma[a]	48	33	(20, 48)	3.9, 44
Glioblastoma	32	25	(12, 43)	3.9, 27
Anaplastic pleomorphic xanthoastrocytoma	6	67	(22, 96)	6, 43
Anaplastic astrocytoma	5	20	(0.5, 72)	15
Astroblastoma	2	100	(16, 100)	15, 23[b]
Undifferentiated	1	PR	(2.5, 100)	6
Anaplastic ganglioglioma	1	0	NA	NA
Anaplastic oligodendroglioma	1	0	NA	NA

Tumor Type	N	Objective Response Rate (ORR)		Duration of Response (DoR)
		%	95% CI	Range (months)
Low grade glioma	14	50	(23, 77)	6, 29[b]
Astrocytoma	4	50	(7, 93)	7, 23
Ganglioglioma	4	50	(7, 93)	6, 13
Pleomorphic xanthoastrocytoma	2	50	(1.3, 99)	6
Pilocytic astrocytoma	2	0	NA	NA
Choroid plexus papilloma	1	PR	(2.5, 100)	29[d]
Gangliocytoma/Ganglioglioma	*1*	*PR*	*(2.5, 100)*	*18[d]*

[a]Median DoR 13.6 months (95% CI: 5.5, 26.7).
[b]Denotes a right-censored DoR.
Source: IR response from the Applicant

Secondary and Other Endpoints

The Applicant's Position:

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

The FDA's Assessment:
FDA's assessment of efficacy is based primarily on Studies X2201 and X2101. FDA considered Studies XUS35T and A2101 separately as a supportive trials. Comparisons between the trials were not performed due to the limitations of cross trial comparisons.

Subpopulations

The Applicant's Position:

No formal subgroup analyses were conducted for the population as a whole. However, subgroup analysis in studies included in this report are based on demographic and disease factors and presented in this section below. Nevertheless, it should be noted that the available data do not indicate a difference in efficacy for demographic subgroups in general: responses were observed in males and females, in subjects older as well as younger than 65 years, pediatric subjects (infants, children and adolescents) and in whites as well as Asians.

The FDA's Assessment:
FDA cautions against cross-study comparisons due to limitations inherent in such comparisons and the potential impact of differences between the studies.

8.1.4. Integrated Assessment of Effectiveness

The Applicant's Position:

The data collected in clinical trial participants with rare BRAF V600 mutated locally advanced or metastatic solid tumors from the 4 clinical trials, across more than 15 tumor types compiled in this application, provide evidence of efficacy of targeted therapy with dabrafenib and trametinib in patients that have exhausted all other available treatment options. The reported endpoints of ORR and DoR can be considered as direct clinical benefit in molecularly defined subsets of rare cancers. The ORR and DoR data, along with data from the managed access program, from IITs and from a comprehensive literature review, suggest that the oncogenic BRAF V600E is a tissue-independent actionable driver mutation.

In Study X2201, dabrafenib + trametinib combination therapy demonstrated robust and durable anti-tumor activity in adult subjects with BRAF V600E mutation-positive advanced solid tumors who had exhausted prior therapies or who progressed on standard of care therapies. A total of 141 subjects representing 6 major tumor types (ATC, BTC, HGG, LGG, ASI and GIST) were included. Clinically significant reductions in tumor size and improvement in ORR were observed compared to historic control rates in unselected population in all tumor types where at least 3 subjects were enrolled. This represents an important clinical benefit. A supportive analysis of ORR by independent radiology review showed that the ORR was consistent with investigator assessed responses documenting similar response rates. The responses were also durable with encouraging PFS and overall survival in most cohorts. These results represent a significant improvement over existing salvage therapy. Subgroup analysis by grade (grade 3 vs Grade 4) and age (18–39 years vs ≥ 40 years) in HGG cohort showed clinical benefits in all subgroups. The efficacy results seen in this study (141 subjects) are also corroborated by the results from Study XUS35T in 33 subjects with refractory BRAF V600 mutated solid tumors and including CNS cancers. The efficacy endpoints indicated a robust and durable clinical activity in this population. A supportive analysis by independent review further corroborated the efficacy conclusions. Durable responses were seen across a variety of tumor types including CNS, GI tract, histiocytic disorders, ameloblastoma, gynecologic and lung cancers. Overall, this Study XUS35T revealed similar efficacy across several histologies studied in Study X2201 and similar objective responses were seen in some additional histologic categories such as LGSOC, mucinous-papillary serous adenocarcinoma of the peritoneum, histiocytic sarcoma of the brain, and ameloblastoma of mandible.

Dabrafenib + trametinib combination therapy provided greater than expected efficacy in 22 distinct histologic types of pediatric tumors bearing the BRAFV600 driver mutation compared to available non-targeted therapies. Dabrafenib + trametinib combination therapy demonstrated higher ORR in relapsed or refractory LGG and LCH subjects with BRAFV600-mutation compared to trametinib monotherapy. DoR and PFS are immature from Study X2101 but appear favorable.

A review of Individual Patient Requests for dabrafenib+trametinib combination therapy received in the Novartis Managed Access Program (MAP) identified 263 patients across 25

countries, with the vast majority of requests (255) for the treatment of solid tumors (CNS, thyroid, histiocytic disorders, biliary tract and GI tumors, gynecological cancers, ameloblastoma and other rare tumors); approximately half were for pediatric patients. While no formal efficacy evaluation was performed in the MAP, the resupply requests (for which the requesting physician has to confirm continued clinical benefit) and the supply duration provide a surrogate measure of the potential benefit across these rare tumor types in patients that have exhausted available standard treatment options. The estimated overall median duration of combination therapy for solid tumor patients was 6.0 months; the estimated duration was similar for the subset of pediatric patients < 18 years of age (8.0 months). The longest estimated exposure duration was 67 months in adults and 35 months in pediatric patients aged ≥6 to < 18 years. More than half of patients had their status recorded as "Treatment ongoing" at the time of the data cut-off (Nov-2020).

In the medical literature, clinical benefits of dabrafenib and trametinib have been reported in individual cases reports in a wide variety of tumors. A literature review identified a total of 126 relevant cases across 13 tumor categories (CNS cancers: 56, histiocytic disorders: 38, BTC: 9, ameloblastoma: 4, pancreatic cancer: 4, Gynecologic cancers 3, Papillary thyroid cancer 3, renal tumors 3, sarcomas 2, GIST 1, pituitary cancers 1, breast cancer 1, salivary duct cancer 1). These case reports comprise of 76 cases treated with dabrafenib in combination with trametinib, 50 with dabrafenib monotherapy (mostly in gliomas and histiocytic disorders); 39 cases were in pediatric patients.

In addition, 3 investigator-sponsored clinical studies evaluating dabrafenib + trametinib combination therapy in Erdheim-Chester Disease, PTC and DTC, respectively and 2 clinical studies evaluating dabrafenib monotherapy (in thyroid cancer and LCH) reported favorable efficacy.

The clinical benefit reported in tumor types such as ameloblastoma and histiocytic sarcomas that are exceedingly rare with no defined standard therapy, highlight the important unmet medical need in rare tumor types. While acknowledging the selection bias of investigators reporting mostly successful outcomes, clinical evidence seen in PTC, pancreatic cancer, gynecological cancer, renal tumors, sarcomas, pituitary tumors, breast cancer, and salivary duct cancer further extends the breadth of histologies where therapy directed at the oncogenic BRAFV600 mutation provides clinical benefit.

There has also been a demonstrated interest in the use of dabrafenib + trametinib combination therapy in a variety of BRAF V600E mutation-positive tumor types through independent clinical research in investigator-initiated trials (IITs). In the US, 8 IITs evaluating dabrafenib+trametinib across a wide variety of BRAF V600E mutation-positive tumor types (thyroid cancer, ameloblastoma, glioma, ECD, multiple myeloma and general solid tumors) were identified. The 2 completed IITs investigated the use in thyroid cancer and provide evidence of efficacy in a tumor known to have a high BRAF V600 mutation frequency: the study by Shah et al (2017) in papillary thyroid cancer (n=53) investigated combination therapy and dabrafenib monotherapy

and determined an ORR of 54% and a PFS of 15.1 months for combination therapy (the corresponding monotherapy results of 50% ORR and 11.4 months PFS were moderately lower). The study by Leboulleux et al 2021 in adult patients with BRAF V600E mutation-positive radio-iodine refractory metastatic differentiated thyroid carcinoma (n=21, evaluable) reported an ORR of 38%.

Histology, demography and duration of treatment data collected in the MAP program and a literature review of cases reports of clinical activity in various tumor types treated with the combination of dabrafenib and trametinib indicate clinical activity in adult and pediatric subjects with additional tumor types not tested in clinical trials. Published data from investigator initiated trials in differentiated thyroid cancers including PTC also provide evidence of efficacy in this tumor type with high BRAF v600 rate.

Overall, the accumulated evidence for clinical efficacy and a positive benefit-risk balance in the approved BRAF V600 mutation-positive adult indications (melanoma, NSCLC and ATC), the magnitude and consistency of the clinically meaningful responses observed across a broad range of additional histologies in the adult and pediatric studies included in this submission, and the supportive evidence from IPR (individual patient requests), IITs (investigator initiated trials), and the literature confirms that dabrafenib + trametinib combination therapy is a viable treatment option in BRAF V600E mutation-positive advanced solid tumors.

The FDA's Assessment:

The analysis of effectiveness of dabrafenib in combination with trametinib for this indication was based on data submitted from 105 adult patients enrolled on study X2201 and 36 pediatric patients enrolled on study X2101. FDA agrees that dabrafenib in combination with trametinib demonstrated clinically meaningful efficacy across multiple tumor types and showed durable response rates. Anti-tumor effects were observed in patients with disparate cancers including biliary tract cancers, multiple glioma subtypes with different biology (aside from BRAF-mutation-positivity), low grade ovarian carcinoma, and small intestinal carcinoma. Responses were also observed in individual patients with ameloblastoma of the mandible, combined small cell-squamous carcinoma of the lung, and mucinous-papillary serous adenocarcinoma of the peritoneum. Importantly, although the sponsor did not seek claims for dabrafenib and trametinib in hematological malignancies, anti-tumor activity has also been observed in patients with hairy cell leukemia, LCH, and multiple myeloma (providing support for extended activity amongst tumor types).

In the overall assessment of efficacy for the indication, FDA also considered results of Trials COMBI-d, COMBI-v, and BRF113928. These results have been previously reviewed and supported approvals in melanoma and NSCLC. Improvements in outcomes in randomized controlled trials in melanoma have been observed (and described in labeling) supporting the overall risk benefit among tumors where meaningful anti-tumor response have bene observed.

The results (also previously reviewed and in labeling) in patients with ATC also supported the broader tissue agnostic claim.

When hematological malignancies (HCL, MM, LCH), melanoma, ATC, and NSCLC are considered in the context of the anti-tumor responses observed in biliary tract cancers, multiple glioma subtypes with different biology (aside from BRAF-mutation-positivity), low grade ovarian carcinoma, and small intestinal carcinoma, a tissue agnostic claim can be supported. Importantly, CRC is known to be less responsive to BRAF inhibition (at least in the absence of blocking the EGFR pathway), and a limitation of use will be included in product labeling. Although the potential also exists that one or more individual tumor types may not respond, it is expected that identification of such patients would be very rare, and in the absence of available effective therapies, it is reasonable to attempt to treat a patient with a BRAF V600E mutation given the overall evidence among patients with BRAF-positive tumors (excluding CRC). Novartis will enroll 80 patients under a PMR to further refine the treatment effect in patients with BRAF-positive tumors. If it appears that an individual tumor is resistant to treatment, the potential exists to further refine the indication (e.g., by expanding the limitation of use) in product labeling. In the absence of a tissue agnostic claim, use of dabrafenib and trametinib in rare patient groups, such as BRAF-positive small intestinal cancer, ovarian cancer, or ameloblastoma would have otherwise been delayed for decades.

8.2. Review of Safety

The Applicant's Position:

The safety profile of dabrafenib in combination with trametinib has been well established in adult subjects in the currently approved indications (melanoma, NSCLC and ATC), with the most common AEs including pyrexia, fatigue, nausea, headache, asthenia, chills, and diarrhea.

The FDA's Assessment:

FDA agrees with the above. This submission is based mainly on the results from 4 clinical studies: Study CDRB436X2201 (Study BRF117019; the ROAR study) in adults, Study CTMT212XUS35T (NCI code: EAY131-H; the NCI-MATCH subprotocol H study) in adults, Study CTMT212X2101 (Study MEK116540) in pediatric patients, and Study CDRB436A2102 (Study BRF116013), in pediatric patients, referred to as X2201, XUS35T, X2101 and A2102 respectively.

8.2.1. Safety Review Approach

The Applicant's Position:

The safety profile in rare BRAF V600E mutation-positive solid tumors was assessed in the context of the established safety profile of the dabrafenib + trametinib combination therapy in the currently approved solid tumor indications (melanoma, NSCLC, and ATC). Safety data stem

mainly from four clinical studies (Table 24 and Table 25). Study X2201 was the main source of new safety data in adult subjects with rare tumor types; Study XUS35T is included as supportive safety data in adult subjects, and studies X2101 and A2102 contributed pediatric safety data. Safety data were not pooled across studies due to differences in safety data collection methodology (Study X2201 was conducted by Novartis and Study XUS35T was conducted by NCI), populations (adult vs pediatric) and treatments (monotherapy vs combination). Limited additional safety data from the MAP program are presented in Section 8.2.10.

The FDA's Assessment:

FDA agrees with the above, and in this section will comment on the safety population in adults mainly in Study X2201 (safety dataset n=206), the pivotal trial in adult patients with BRAF V600E mutated tumors. Study XUS35T was reviewed and comments regarding the safety data will be included where relevant. Pediatric study X2101 (safety dataset n=48) was considered to be the main source of data to assess the safety of dabrafenib in combiantion with trametinib in pediatric patients, with Study A2102 as supportive data as pediatric patients were treated with dabrafenib monotherapy only. FDA agrees with not pooling safety data across the 4 studies (or 2 within the adult and pediatric populations, respectively) due to differences in safety data collection methodology, in addition to differences in study populations, and dose levels, which was agreed to at the administrative pre-NDA meeting.

The FDA safety review focused on analyses of the incidences of key adverse event (AE) categories including fatal and nonfatal SAEs, AEs resulting in permanent discontinuation of one or more of the study drugs, AEs requiring dose-modifications, common AEs, Grade > 3 AEs, and AESIs in both adult and pediatric patients receiving dabrafenib + trametinib. FDA agrees with the Applicant's position regarding the general safety review approach.

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

The duration of exposure for all four clinical studies is presented in Table 87.

Table 87 Applicant - Duration of exposure by study (all subjects)

Studies		Dabrafenib		Trametinib	
Adult subjects		N	Median (range), months	N	Median (range), months
Study X2201		N=206	12.5 (1 to 72)	N=206	12.0 (1 to 72)
Study XUS35T		N=33	8.2 (0 to 50)	N=33	9.2 (0 to 50)
Pediatric subjects		**N**	Median (range), months	**N**	Median (range), months
Study A2102	Part 1	N=27	20.8 (1.3 to 81.9)	-	-
	Part 2	N=58	19.7 (0.07 to 68.1)	-	-
Study X2101	Part A	-	-	N=50	24.4 (0.6 to 63.6)

Part B	-	-	N=41	19.1 (0.33 to 55.2)
Part C	N=18	20.8 (1.9 to 52.5)	N=18	20.8 (1.8 to 52.5)
Part D	N=30	24.9 (2.1 to 38.7)	N=30	24.4 (2.1 to 38.7)

Source: Study X2201 IA#16-Section 10.6.1, Study XUS35T – Section 10.6.1, Study A2102-Section 10.6.1, and Study X2101-Section 10.6.1.

The FDA's Assessment:

FDA has reviewed the exposure table and agrees with the presentation of the data, and has validated the findings. Parts A and B of Study X2101 were not included in Table 87 as the population enrolled was not applicable to the indicated population. Study A2101 was a study that administered dabrafenib as a single agent in pediatric patients, and therefore was not included in Table 87 above. The overall exposure to dabrafenib in combination with trametinib across Studies X2201, XUS35T, A2102, and X2101 is considered adequate to support characterization of the safety profile of this drug regimen in the intended patient population.

Relevant characteristics of the safety population:

The Applicant's Position:

Studies in adults: Study X2201 enrolled 206 subjects with rare and ultra-rare, advanced cancers with BRAF V600E mutations (ATC, BTC, GIST, LGG, HGG, ASI, HCL and GIST). Study XUS35T enrolled 33 patients with a broad range of tumor histologies.

Pediatric studies: Data from Study X2101 in pediatric subjects served to characterize the pediatric safety profile of dabrafenib+trametinib combination therapy in pediatric subjects. Additionally, monotherapy data from studies X2101 and A2102 are discussed. Of note, while data from all age groups (1 month to 17 years of age) are presented, (b) (4)

The FDA's Assessment:

FDA agrees with the Applicant's position. Given the rarity of patients with solid tumors with BRAF V600E mutations, FDA considered the safety database to be adequate with respect to enrolling population populations sufficiently diverse to represent the expected population who would be treated with dabrafenib in combination with trametinib in the postmarket setting.

Subgroup safety analyses to evaluate the impact of age on frequency of AEs across adults and pediatric patients is challenging due to differences in study methodology, endpoints, and doses. Additional exploratory subgroup analyses based on gender, race, performance score, and tumor type are limited due to the small sample size and lack of internal control in all studies.

Adequacy of the safety database:

The Applicant's Position:

The safety profile of trametinib and dabrafenib has been extensively characterized in clinical trials (since 2008 and 2009 respectively) and in the marketed setting (since 2013), with a total cumulative patient exposure of over 55,000 patient-treatment years (PTY) for each compound.

This submission presents data from 465 subjects in four clinical trials including 224 pediatric subjects aged as low as 1 month old. The clinical trial data was collected in over 15 tumor types across a broad range of tumor histologies. The clinical trial safety data was complemented by a report of adverse events from the MAP program (which involved 263 patients including 79 pediatric patients). These safety data in subjects with rare BRAF V600 mutation positive solid tumors are considered adequate for the proposed sNDA.

The FDA's Assessment:

Overall, the safety database submitted by the Applicant was adequate. No major deficiencies were identified. Given the rarity of solid tumors with a BRAF V600E mutation and the observed adverse reaction profile in the context of the dabrafenib in combination with trametinib exposure achieved in the safety population, FDA considered the safety database sufficient to characterize the safety profile of dabrafenib in combination with trametinib and identify AEs that occur at an incidence of approximately 1%. The FDA agrees that the safety database supporting the application was adequate.

8.2.3. 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 details of Audit and HA inspections are presented in Appendix 16.1.8 of the respective CSRs.

The FDA's Assessment:

FDA review did not uncover any data integrity issues related to safety.

Categorization of Adverse Events

The Applicant's Position:

Safety was evaluated in subjects who received at least one dose of study treatment and summarized according to the treatment received. No additional safety analysis were conducted

for this submission besides the analysis reported in individual Clinical Study Reports. Safety assessments in the Novartis-sponsored studies X2201, X2101 and A2102 included monitoring and documenting all AEs and SAEs with severity and relationship to study drug noted. AEs were coded to the preferred term (PT) level by different MedDRA versions and assessment of the intensity of AEs had different CTCAE grading for different studies are presented in Table 88.

Table 88 Applicant - MedDRA version and CTCAE coding

Studies	MedDRA versions	CTCAE grading
X2201	23.0	4.0
A2102	23.1	4.0
X2101	23.1	4.03

AEs were summarized by presenting the number and percentage of subjects having at least one AE by primary SOC and PT. A subject with multiple occurrences of an AE was only counted once in the AE category using the worst severity grade for that AE and for that subject. 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. Adverse events of special interest are summarized by AESI categories, PT, and maximum toxicity grade.

Safety data collection in Study XUS35T was limited to AEs. AEs were coded using MedDRA version 23.0 and CTCAE v5.0 was used for grading of AEs.

An overview of AEs was produced displaying the number and percentage of subjects with any AEs and those with AEs with grade ≥3, and summaries of treatment-related AEs were also produced. SAEs were not recorded in the study, however AEs which required expedited reporting were flagged, and these were also summarized. If an event fit the criteria for SAE, it was also reported in the CTEP-AERs database. The AEs that required expedited reporting were specified in the protocol. The requirements were:

- LVEF changes: If any of the following circumstances occur, the event(s) must be reported via CTEP-AERS (Adverse Event Reporting System). Asymptomatic: Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN and LVEF does not recover within 4 weeks. Symptomatic: Grade 3-4 LVEF.

- Visual changes: RPED (retinal pigment epithelial detachments) or RVO (retinal vein occlusion

- Liver chemistry: ALT >/= 3xULN and bilirubin ≥ 2x ULN or > 35% direct bilirubin ALT > /=3xULN and INR ≥ 1.5, if INR measured (INR threshold does not apply if subject is on anticoagulant)

- Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the subject is on dabrafenib or trametinib, or within 28 days of the subject's last dose of Dabrafenib or Trametinib.

It was not possible to identify AEs leading to study discontinuation. However, the number and percentage of subjects discontinuing the study due to an AE were summarized.

Groupings of AEs of special interest consisted of adverse events for which there is a specific clinical interest in connection with dabrafenib and trametinib treatment. A comprehensive list of MedDRA terms based on clinical review was used to identify each type of event.

All deaths (on-treatment and post-treatment) were tabulated and listed. Post treatment deaths were also flagged.

The FDA's Assessment:
FDA agrees with the Applicant's description of methods for coding and grading AEs and the procedures for interrogating the safety data. AE of special interest (AESI) were summarized by AESI categories, PT, and maximum toxicity grade.

Routine Clinical Tests

The Applicant's Position:

Safety monitoring in studies X2201, X2101 and A2102 included regular monitoring of hematology and blood chemistry (including liver function test). All laboratory values in CTCAE were graded using CTCAE v4.0 (study X2201) or CTCAE v 4.03 (studies A2102 and X2101). Parameters for which a grading did not exist were classified into low or high group by means of laboratory normal ranges.

The FDA's Assessment:
FDA agrees with the Applicant's description of the routine clinical and laboratory assessments obtained.

8.2.4. Safety Results

The Applicant's Position:

In view of the well-established safety profile of dabrafenib and trametinib for the treatment of adjuvant and advanced melanoma, NSCLC and ATC in adults with a BRAF V600 mutation, only a brief summary of safety data from the two adult studies is provided, whereas the safety data in the pediatric population is discussed in greater detail. Of note, the source of pediatric safety data from pediatric studies included in this submission also contain safety data in trametinib or dabrafenib monotherapy, and in subjects younger than 6 years of age. Study X2201 also included safety data obtained in subjects with hematological malignancies (HCL and MM) and in subjects with non-BRAF mutated tumors. However, for the purposes of this submission, the review and analysis will focus on the data supporting the proposed use of dabrafenib +

trametinib combination therapy for the treatment of rare BRAF V600E mutation-positive advanced solid tumors in patients 6 years of age and older.

Safety in adult subjects (studies X2201 and XUS35T)

In the pivotal adult study X2201 (N=206), the median duration of exposure to dabrafenib and trametinib was ≥12 months (range: 1-72 months) with two-thirds of the subjects receiving dabrafenib and trametinib for over 6 months. The safety profile of the combination therapy was consistent with the known safety profile of dabrafenib + trametinib and with previously reported studies in the currently approved indications, both in terms of event categories and of common adverse events, which included pyrexia, fatigue, nausea, chills, headache, constipation, vomiting, diarrhea, cough, and rash. The safety information collected in Study XUS35T with 8-9 months of median exposure to dabrafenib and trametinib was also consistent

Safety in pediatric subjects (studies X2101 and A2102)

The pediatric studies used oral liquid formulations in addition to the currently marketed (adult) formulations. Pediatric subjects received study treatment based on their body weight and age. The median duration of exposure was 20.81 to 24.89 months for dabrafenib + trametinib combination therapy, 19.06 to 24.38 months for trametinib monotherapy, and 19.76 to 20.77 months for dabrafenib monotherapy.

The incidence of AEs leading to discontinuation of dabrafenib and/or trametinib and AEs leading to dose interruption/delay was slightly higher in pediatric subjects (21% and 73%, respectively) treated with combination therapy as compared with adult subjects with NSCLC (19% and 65%) and melanoma (12% and 55%) (Table 98). This may be attributed to a small sample size and higher duration of exposure in pediatric subjects (20 to 25 months) as compared with Study X2201 (12.5 months), NSCLC indication (7.59 months) and metastatic melanoma indication (10 months), all treated with combination therapy.

Deaths

One on-treatment death (defined as occurring within 28 days after last dose of study treatment) and 2 post-treatment deaths were reported. None were considered related to study drug. The on-treatment death was reported in a 10-year-old subject with glioma on dabrafenib monotherapy in Study A2102 due to depressed level of consciousness concurrent with disease progression 2 weeks after the last dose of the study medication (Study A2102 Section 14.3.3). The 2 post-treatment deaths occurred in a 3-year-old subject with treated with trametinib monotherapy in Study X2101 (due to massive lung aspiration, with a history of neurologic deficits and requirement for enteral feedings), and in a 17-year-old subject with anaplastic ganglioglioma treated with dabrafenib monotherapy in Study A2102 (due to disease progression).

Serious adverse events

Study X2101: SAEs were reported in 45.8% subjects (22/48) treated with dabrafenib+ trametinib. The most commonly reported (≥5%) SAEs were pyrexia (25%), and ejection fraction decreased (6.3%). Treatment-related SAEs that occurred in at least 2 subjects were pyrexia (7 subjects) and ejection fraction decreased (2 subjects).

SAEs were reported for 50.5% subjects (46/91) treated with trametinib monotherapy. The most commonly reported (≥5%) SAEs were pyrexia (11%), vomiting (5.5%), and pneumonia (5.5%). Treatment-related SAEs that occurred in at least 2 subjects were hypernatremia, hyponatremia, and pyrexia (2 subjects each only in Part A).

Study A2102: SAEs were reported in 48.1% (13/27) in Part 1 and 44.8% subjects (26/58) in Part 2 subjects treated with dabrafenib monotherapy. The most commonly reported (≥5%) SAEs in Part 1 were pyrexia (14.8%), seizure (11.1%), pneumonia (11.1%), hypoxia (7.4%), and headache (7.4%). The most commonly reported (≥5%) SAEs in Part 2 were pyrexia (17.2%), headache (8.6%), blood culture positive, device related infection, and vomiting (5.2% each). Pyrexia was the only SAE reported in at least 2 subjects and had a suspected relationship with dabrafenib.

Dropouts and/or Discontinuations Due to Adverse Effects

Study X2101: AEs leading to treatment discontinuation occurred in 22.2% subjects in Part C and 20% subjects in Part D. All these AEs occurred in 1 subject each (Part C: ALT increased, ejection fraction decreased, and Part D: ALT increased, ejection fraction decreased, AST increased, GGT increased, and transaminases increased).

AEs leading to trametinib discontinuation occurred in 24% subjects in Part A and 26.8% subjects in Part B. All the AEs occurred in 1 subject each except for dermatitis acneiform, rash, and nausea (Part A: 3 subjects each and Part B: 2 subjects each).

Study A2102: AEs leading to dabrafenib discontinuation occurred in total 6 subjects (Part 1 and 2) and all these AEs occurred in 1 subject each (Part 1: Epstein-Barr virus associated lymphoma, hemorrhage intracranial, Part 2: hypersensitivity, tumor hemorrhage, increased blood creatinine, same subject had arthralgia and erythema nodosum).

Dose interruptions/reductions due to Adverse Effects

Study X2101: AEs requiring dose interruption of study treatment (dabrafenib or trametinib) were reported 61.1% subjects in Part C and 80% subjects in Part D. The most frequently reported AEs (≥5%) were ejection fraction decreased, neutrophil count decreased, pyrexia, diarrhea, neutropenia, rash maculopapular, and vomiting. AEs requiring dose interruptions of trametinib monotherapy were reported in 64% subjects in Part A and 58.5% subjects in Part B. The most frequently reported AEs (≥5%) were dermatitis acneiform, mucosal inflammation, edema peripheral, paronychia, pyrexia, seizure, and rash-maculopapular. AEs requiring dose reduction of study treatment (dabrafenib or trametinib) were reported 27.8% subjects in Part C and 23.3% subjects in Part D. The most frequently reported AEs (≥5%) were pyrexia, ejection fraction decreased, and pyrexia. AEs requiring dose reduction of trametinib monotherapy were

reported in 46.0% subjects of Part A and 39% subjects in Part B. The most frequently reported AEs (≥5%) were rash maculopapular, dermatitis acneiform, paronychia, edema peripheral, dermatitis acneiform, mucosal inflammation, edema peripheral, and rash.

Study A2102: AEs requiring dose interruptions of dabrafenib were reported in 63% subjects and the most frequent (≥5%) events were pyrexia, vomiting, influenza, blood creatinine increased, and headache. AEs requiring dose reductions of dabrafenib were reported in 22.2% subjects. All these AEs occurred in 1 subject each in both Parts 1 and 2 except pyrexia (2 subjects).

Significant Adverse Events

Study X2101: Grade ≥3 AEs in subjects treated with dabrafenib+trametinib occurred in 66.7% subjects in Part C and 63.3% subjects in Part D. Frequent grade ≥3 AEs (>2 subjects) were pyrexia (Part C: 3 subjects, 16.7% and Part D: 5 subjects, 16.7%) and neutrophil count decreased (Part C: 2 subjects, 11.1% and Part D: 4 subjects, 13.3%).

Grade ≥3 AEs in subjects treated with trametinib monotherapy occurred in 50% subjects in Part A and 65.9% subjects in Part B. Frequent grade ≥3 AEs (>2 subjects) were pyrexia (Part A: 2 subjects, 4% and Part B: 3 subjects, 3.7%), weight increased (Part A: 3 subjects, 6% and Part B: 3 subjects, 7.3%), hyponatremia (Part A: 3 subjects, 6% and Part B: 0 subject), pneumonia (Part A: 3 subjects, 6% and Part B: 2 subjects, 4.9%), anemia (Part A: 1 subject, 2% and Part B: 4 subjects, 9.8%), paronychia (Part A: 1 subject, 2% and Part B: 3 subjects, 7.3%), device related infection (Part A: 1 subject, 2% and Part B: 3 subjects, 7.3%), and rash maculo-papular (Part A: 3 subjects, 6% and Part B: 0 subject).

Study A2102: Grade ≥3 AEs in subjects treated with dabrafenib monotherapy occurred in 63% subjects in Part 1 and 58.6% subjects in Part 2. All the grade ≥3 AEs occurred in 1 or 2 subjects treated with dabrafenib monotherapy (in either Part 1 or Part 2) except pyrexia (Part 1: 4 subjects, 14.8% and Part 2: 5 subjects, 8.6%) and weight increased (Part 1: 3 subjects, 11.1% and Part 2: 2 subjects, 3.4%).

Treatment Emergent Adverse Events

The most commonly reported AEs in pediatric subjects (vomiting, diarrhea, dry skin, paronychia, and headache) were in line with the known safety profile of dabrafenib+trametinib combination therapy.

Study X2101: All subjects had at least one AE. The most commonly (≥ 50%) reported AEs in subjects treated with dabrafenib+trametinib included pyrexia (75%) and vomiting (52.1%). The most commonly (≥ 50%) reported AEs in subjects treated with trametinib monotherapy included diarrhea (65.9%), paronychia (61.5%), pyrexia (58.2%), and dry skin (56%).

Study A2102: All subjects in Part 1 and 96.6% subjects in Part 2 had at least 1 AE. The most commonly (≥ 50%) reported AEs in subjects treated with dabrafenib monotherapy included pyrexia (74.1%), vomiting (59.3%), dry skin and headache (each in 51.9%) in Part 1 and pyrexia (53.4%) in Part 2.

Laboratory findings

Hyponatremia

In Study X2101, 5 pediatric subjects treated with trametinib monotherapy had AEs of hyponatremia ≥ grade 3; 4 of which were early in their course of treatment. One subject in Part C, combination therapy had a lab value of grade 3 decreased sodium on study day 30, however no AE was reported. One subject had panhypopituitarism, another had a history of sodium homeostasis issues. Each recovered and remained on treatment. No hyponatremia events were reported in pediatric subjects treated with dabrafenib+trametinib combination therapy. Hyponatremia was reported 4 subjects treated with dabrafenib monotherapy (one of which was grade 3) in study A2102.

Liver chemistry assessments

No confirmed Hy's law cases were reported in either of the pediatric studies.

Other laboratory findings

No additional clinically significant changes in hematological or clinical chemistry parameters were observed in pediatric subjects.

Weight and Vital signs

Study X2101: Weight increases by > 10% were noted in >70% of subjects. While marked as notable, this is expected over time for pediatric subjects.

Study A2102: The median heart rate decreased slightly over time in Part 1. This trend was not seen in Part 2. The significance of this finding is not known.

Electrocardiogram

Study X2101: Clinically significant abnormal ECG findings occurred for 1 subject treated with dabrafenib+trametinib (Part C) with QTcB > 500 ms and was reported as grade 2 and grade 3 AEs of ECG QT prolonged. This subject had several significant confounding clinical features, including electrolyte abnormalities. During trametinib monotherapy, new clinically significant abnormal ECG findings were reported for 2 subjects (11-12 days after the last dose of trametinib monotherapy). For 1 of the subjects, a grade 1 AE of ECG QT prolonged was reported 12 days after discontinuing treatment for lack of efficacy and observed at the end of study visit. in total, 5 subjects had new QTcB value of > 500 ms.

Study A2102: no subject had a new QTcB value of ≥ 501 ms in any of the treatment groups. 4 out of 13 (30.8%) subjects in Part 1 and 5 out of 30 (16.7%) subjects in Part 2 had an CTcB increase of > 60 ms from baseline.

Immunogenicity

Immunogenicity was not assessed nor expected with small molecule therapy.

Adverse drug reactions

No new safety signals were identified in any of the 4 studies. The ADRs are consistent with the previously reported ADRs with dabrafenib and trametinib.

The FDA's Assessment:

The FDA agrees with a focused review and analysis on the data supporting the proposed use of dabrafenib in combination with trametinib combination therapy for the treatment of BRAF V600E mutation-positive advanced solid tumors in patients 6 years of age and older, including pivotal Study X2201, supportive Study XUS35T, and pertinent parts of pediatrics studies X2101 and A2012.

FDA agrees that there is a well-established adverse event profile of dabrafenib and trametinib for the treatment of adult patients, as described in labelling for adjuvant and advanced melanoma, NSCLC, and ATC in adults with a BRAF V600 mutation. FDA therefore will comment on appropriate safety signals if/when applicable in the indicated adult population, and describes the safety in pediatrics in greater detail below (for additional details refer to Section 10).

Study X2201

FDA performed a high-level analysis of safety for study X2201. Among the 206 patients, the median age was 60 years (range: 18 to 89); 56% were male; 79% were white; and 34% had baseline ECOG performance status 0 and 60% had ECOG performance status 1.

The most common ARs occurring in ≥20% of patients were pyrexia, fatigue, nausea, rash, chills, headache, hemorrhage, cough, vomiting, constipation, diarrhea, myalgia, arthralgia, and edema. Serious ARs occurred in 45% of patients who received dabrafenib in combination with trametinib. Serious ARs occurring in >5% of patients included pyrexia (11%) and pneumonia (6%). Fatal ARs occurred in 3.9% of patients who received dabrafenib in combination with trametinib. Specific fatal events included sepsis (1.9%), pneumonia (1%), diverticulitis (0.5%), general physical health deterioration (0.5%), hemorrhage (0.5%), pleural effusion (0.5%) and pulmonary embolism (0.5%). Given the single arm nature of the trial, determination of attribution of specific events to the drugs (versus underlying life-threatening cancers) is difficult. Permanent treatment discontinuation due to an AR occurred in 13% of patients. ARs which resulted in permanent treatment discontinuation in >1% of patients included nausea (1.5%). Dosage interruptions due to an AR occurred in 55% of patients. ARs which required dosage interruption in >5% of patients included pyrexia (22%), chills (9%), fatigue (6%), neutropenia, (6%), and nausea (5%). Dose reductions due to an AR occurred in 44% of patients. ARs which required dose reductions in 5% of patients included pyrexia (18%), chills (8%), and fatigue (6%).

FDA agrees that the safety data from adult patients enrolled in study X2201 are consistent with

the well-characterized safety profile for dabrafenib in combination with trametinib and no new safety signals were identified.

Study X2101

FDA performed a safety analysis for the 48 patients enrolled on study X2101 Parts C and D. A more detailed analysis was performed as dabrafenib in combination with trametinib in pediatric patients has not previously been reported. The median duration of exposure to dabrafenib in Parts C (dose escalation) and D (cohort expansion) was 20.8 and 24.9 months, respectively. The median duration of exposure to trametinib in Parts C and D was 20.8 and 24.4 months, respectively. The median age of pediatric patients who received dabrafenib in combination with trametinib was 9 years (range: 1 – 17 years).

Deaths

There were no deaths attributed to an AR within 28 days of treatment with dabrafenib in combination with trametinib. There was a post-treatment death (death that occurred post-28 days after the last dose of study treatment). FDA agrees with the attribution of death from the narratives, and therefore, there were no deaths related to drug in either pediatric study.

SAE

FDA has reviewed the SAEs and has included Table 89 from the pivotal pediatric Study X2102. The most common SAEs occurring in ≥5% of patients were pyrexia (25%) and ejection fraction decreased (6%).

Table 89 FDA - Summary of Pediatric Serious Adverse Events from Study X2101 Parts C and D

	PART C TMT 0.025 + 100% DRB RP2D N = 9 N (%)	PART C TMT 0.025 + 50% DRB RP2D N = 3 N (%)	PART C TMT 0.032 + 100% DRB RP2D (EXT) N = 6 N (%)	PART D TMT 0.025 + 100% DRB RP2D N = 22 N (%)	PART D TMT 0.032 + 100% DRB RP2D N = 8 N (%)	Total N = 48 N (%)
All	**5 (56)**	**1 (33)**	**2 (33)**	**10 (45)**	**4 (50)**	**22 (46)**
General Disorders And Administration Site Conditions						
Pyrexia (GT)	3 (33)	0	1 (17)	5 (23)	3 (38)	12 (25)
Investigations						
Ejection Fraction Decreased	2 (22)	0	0	1 (4.5)	0	3 (6)
C-reactive Protein Increased	1 (11)	0	0	0	0	1 (2.1)
Weight Decreased	0	0	0	1 (4.5)	0	1 (2.1)
White Blood Cell Count Decreased	0	0	0	1 (4.5)	0	1 (2.1)

	PART C TMT 0.025 + 100% DRB RP2D N = 9 N (%)	PART C TMT 0.025 + 50% DRB RP2D N = 3 N (%)	PART C TMT 0.032 + 100% DRB RP2D (EXT) N = 6 N (%)	PART D TMT 0.025 + 100% DRB RP2D N = 22 N (%)	PART D TMT 0.032 + 100% DRB RP2D N = 8 N (%)	Total N = 48 N (%)
Alanine Aminotransferase Increased	0	0	0	0	1 (13)	1 (2.1)
Aspartate Aminotransferase Increased	0	0	0	0	1 (13)	1 (2.1)
Gastrointestinal Disorders						
Vomiting (GT)	2 (22)	0	0	0	0	2 (4.2)
Nausea	1 (11)	0	0	0	0	1 (2.1)
Injury, Poisoning And Procedural Complications						
Upper Limb Fracture	1 (11)	0	0	0	0	1 (2.1)
Metabolism And Nutrition Disorders						
Dehydration	1 (11)	0	1 (17)	0	0	2 (4.2)
Hyperglycemia	0	0	0	1 (4.5)	0	1 (2.1)
Nervous System Disorders						
Ataxia	1 (11)	0	0	0	0	1 (2.1)
Balance Disorder	1 (11)	0	0	0	0	1 (2.1)
Dysarthria	1 (11)	0	0	0	0	1 (2.1)
Brain Oedema	0	1 (33)	0	0	0	1 (2.1)
Posterior Reversible Encephalopathy Syndrome	0	0	0	1 (4.5)	0	1 (2.1)
Seizure	0	0	0	1 (4.5)	0	1 (2.1)
Infections And Infestations						
Upper Respiratory Tract Infection	0	0	1 (17)	1 (4.5)	0	2 (4.2)
Varicella	0	0	1 (17)	0	0	1 (2.1)
Adenovirus Infection	0	0	0	1 (4.5)	0	1 (2.1)
Parotitis	0	0	0	1 (4.5)	0	1 (2.1)
Pharyngitis Streptococcal	0	0	0	0	1 (13)	1 (2.1)
Tonsillitis	0	0	0	0	1 (13)	1 (2.1)
Respiratory, Thoracic And Mediastinal Disorders						
Cough (GT)	0	0	1 (17)	0	0	1 (2.1)
Lung Disorder	0	0	0	1 (4.5)	0	1 (2.1)
Respiratory Distress	0	0	0	1 (4.5)	0	1 (2.1)
Blood And Lymphatic System Disorders						
Neutropenia	0	0	0	1 (4.5)	0	1 (2.1)

	PART C TMT 0.025 + 100% DRB RP2D N = 9 N (%)	PART C TMT 0.025 + 50% DRB RP2D N = 3 N (%)	PART C TMT 0.032 + 100% DRB RP2D (EXT) N = 6 N (%)	PART D TMT 0.025 + 100% DRB RP2D N = 22 N (%)	PART D TMT 0.032 + 100% DRB RP2D N = 8 N (%)	Total N = 48 N (%)
Musculoskeletal And Connective Tissue Disorders						
Musculoskeletal Pain (GT)	0	0	0	1 (4.5)	0	1 (2.1)
Psychiatric Disorders						
Restlessness	0	0	0	1 (4.5)	0	1 (2.1)
Vascular Disorders						
Hypertension (GT)	0	0	0	1 (4.5)	0	1 (2.1)
Hypotension (GT)	0	0	0	1 (4.5)	1 (13)	2 (4.2)
Cardiac Disorders						
Tachycardia	0	0	0	0	1 (13)	1 (2.1)

Source: FDA reviewer's analysis: ADSL (Subject-Level Analysis Dataset) - 2021-09-22, ADAE (Adverse Events Analysis Dataset) - 2021-09-22. Variables used: USUBJID, TRT01A, SAFFL, COHORT, TRTEMFL, AEDECOD, AETOXGR, AEBODSYS, AESER
Group Pyrexia (GT) includes PT terms PYREXIA,
Group Vomiting (GT) includes PT terms VOMITING,
Group Hypotension (GT) includes PT terms HYPOTENSION,
Group Musculoskeletal Pain (GT) includes PT terms BACK PAIN,
Group Cough (GT) includes PT terms COUGH,
Group Hypertension (GT) includes PT terms HYPERTENSION

FDA analyzed cardiac toxicity related to the cardiac SAE signal (See 8.2.5). According to the label for both drugs, there is a known risk of cardiomyopathy defined as a decrease in left ventricular ejection fraction (LVEF) ≥ 10% from baseline and below the institutional lower limit of normal (LLN), and QT prolongation in patients treated with dabrafenib in combination with trametinib. (U.S. package insert, Mekinist, Tafinlar, accessed on 26 Feb 2022). The pediatric study had provisions for stopping rules and dose modifications for LVEF that were adequate. The warnings and precautions of both dabrafenib in combination with trametinib list the incidence of cardiomyopathy of 6% in patients, and although cross trial comparisons are challenging, this is consistent with the incidence of 6% of the SAE of decreased ejection fraction in study X2101.

Dropouts and/or Discontinuations, Dose interruptions/reductions due to Adverse Effects

According to FDA's assessment as portrayed in Table 90, and Table 91, the incidence of AEs leading to discontinuation of dabrafenib and/or trametinib (21% in pediatrics vs 13% in adults) and AEs leading to dose interruption/delay (73% in pediatrics vs 55% in adults) was higher in pediatric patients on Study X2102 treated with combination therapy as compared with adult patients in Study X2201, and with the safety reference populations in patients with NSCLC and melanoma (Table 92). The difference in incidences between adult and pediatrics patients may be attributed to a small sample size. Some reasons for discontinuation and dose

interruptions/reductions were similar, such as liver function abnormalities, decreased LVEF, or rash, while other AEs such as EBV, varicella, or adenovirus, and tonsillectomy are expected to occur predominantly in pediatric patients. Given the single arm design of clinical studies of dabrafenib in combination with trametinib, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether differences in the incidence of discontinuations, dose interruptions, and reductions to dabrafenib + trametinib are related to patient age or other factors.

Table 90 FDA - Summary of Pediatric Drug Discontinuations from Study X2101 Parts C and D

	PART C TMT 0.025 + 100% DRB RP2D N = 9 N (%)	PART C TMT 0.025 + 50% DRB RP2D N = 3 N (%)	PART C TMT 0.032 + 100% DRB RP2D (EXT) N = 6 N (%)	PART D TMT 0.025 + 100% DRB RP2D N = 22 N (%)	PART D TMT 0.032 + 100% DRB RP2D N = 8 N (%)	Total N = 48 N (%)
ALL	**3 (33)**	**0**	**1 (17)**	**5 (23)**	**1 (13)**	**10 (21)**
Ejection Fraction Decreased	1 (11)	0	0	1 (4.5)	0	2 (4.2)
Iridocyclitis	1 (11)	0	0	0	0	1 (2.1)
Panniculitis	1 (11)	0	0	0	0	1 (2.1)
Vomiting (GT)	1 (11)	0	0	0	0	1 (2.1)
Alanine Aminotransferase Increased	0	0	1 (17)	0	1 (13)	2 (4.2)
Gamma-glutamyltransferase Increased	0	0	0	1 (4.5)	0	1 (2.1)
Paronychia	0	0	0	1 (4.5)	0	1 (2.1)
Pyrexia (GT)	0	0	0	1 (4.5)	0	1 (2.1)
Rash (GT)	0	0	0	1 (4.5)	0	1 (2.1)
Transaminases Increased	0	0	0	1 (4.5)	0	1 (2.1)
Aspartate Aminotransferase Increased	0	0	0	0	1 (13)	1 (2.1)

Source: FDA reviewer generated table from Palintir; ADSL (Subject-Level Analysis Dataset) - 2021-09-22, ADAE (Adverse Events Analysis Dataset) - 2021-09-22. Variables used: USUBJID, TRT01A, SAFFL, COHORT, TRTEMFL, AEDECOD, AETOXGR, AEACN, AEACN1, AEACN2, AEACN3, AEACN4, AEBODSYS, AESER
Group Pyrexia (GT) includes PT terms PYREXIA,
Group Vomiting (GT) includes PT terms VOMITING, RETCHING,
Group Rash (GT) includes PT terms DERMATITIS ACNEIFORM, RASH, RASH MACULO-PAPULAR, ECZEMA, RASH PAPULAR, RASH PUSTULAR, RASH ERYTHEMATOUS, RASH MACULAR, SKIN EXFOLIATION, RASH FOLLICULAR, PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME, DERMATITIS

Table 91 FDA - Summary of Pediatric Drug Interruptions/delays from Study X2101 Parts C and D

	PART C TMT 0.025 + 100% DRB RP2D N = 9 N (%)	PART C TMT 0.025 + 50% DRB RP2D N = 3 N (%)	PART C TMT 0.032 + 100% DRB RP2D (EXT) N = 6 N (%)	PART D TMT 0.025 + 100% DRB RP2D N = 22 N (%)	PART D TMT 0.032 + 100% DRB RP2D N = 8 N (%)	Total N = 48 N (%)
All	**6 (67)**	**1 (33)**	**4 (67)**	**18 (82)**	**6 (75)**	**35 (73)**
Pyrexia (GT)	5 (56)	0	3 (50)	13 (59)	6 (75)	27 (56)
Neutrophil Count Decreased	2 (22)	0	0	0	1 (13)	3 (6)
Arrhythmia (GT)	1 (11)	0	0	0	0	1 (2.1)
Ejection Fraction Decreased	1 (11)	0	0	1 (4.5)	0	2 (4.2)
Nausea	1 (11)	0	0	1 (4.5)	0	2 (4.2)
Seizure	1 (11)	0	0	0	0	1 (2.1)
Upper Limb Fracture	1 (11)	0	0	0	0	1 (2.1)
Vomiting (GT)	1 (11)	0	2 (33)	5 (23)	1 (13)	9 (19)
Uveitis	0	1 (33)	0	0	0	1 (2.1)
Rash (GT)	0	0	2 (33)	3 (14)	0	5 (10)
Acne	0	0	1 (17)	0	0	1 (2.1)
Tonsillectomy	0	0	1 (17)	0	0	1 (2.1)
Diarrhea (GT)	0	0	0	2 (9)	0	2 (4.2)
Neutropenia	0	0	0	2 (9)	1 (13)	3 (6)
Adenovirus Infection	0	0	0	1 (4.5)	0	1 (2.1)
Hypersensitivity	0	0	0	1 (4.5)	0	1 (2.1)
Influenza Like Illness	0	0	0	1 (4.5)	0	1 (2.1)
Iridocyclitis	0	0	0	1 (4.5)	0	1 (2.1)
Lung Disorder	0	0	0	1 (4.5)	0	1 (2.1)
Malaise	0	0	0	1 (4.5)	0	1 (2.1)
Parotitis	0	0	0	1 (4.5)	0	1 (2.1)
Pharyngitis	0	0	0	1 (4.5)	0	1 (2.1)
Posterior Reversible Encephalopathy Syndrome	0	0	0	1 (4.5)	0	1 (2.1)
Respiratory Distress	0	0	0	1 (4.5)	0	1 (2.1)
Skin Mass	0	0	0	1 (4.5)	0	1 (2.1)
Stomatitis (GT)	0	0	0	1 (4.5)	0	1 (2.1)
Upper Respiratory Tract Infection	0	0	0	1 (4.5)	0	1 (2.1)

	PART C TMT 0.025 + 100% DRB RP2D N = 9 N (%)	PART C TMT 0.025 + 50% DRB RP2D N = 3 N (%)	PART C TMT 0.032 + 100% DRB RP2D (EXT) N = 6 N (%)	PART D TMT 0.025 + 100% DRB RP2D N = 22 N (%)	PART D TMT 0.032 + 100% DRB RP2D N = 8 N (%)	Total N = 48 N (%)
Urticaria	0	0	0	1 (4.5)	0	1 (2.1)
Weight Decreased	0	0	0	1 (4.5)	0	1 (2.1)
Blood Creatinine Increased	0	0	0	0	1 (13)	1 (2.1)
Gastroenteritis	0	0	0	0	1 (13)	1 (2.1)
Lethargy	0	0	0	0	1 (13)	1 (2.1)
Tonsillitis	0	0	0	0	1 (13)	1 (2.1)

Source: FDA reviewer generated table from Palintir; ADSL (Subject-Level Analysis Dataset) - 2021-09-22, ADAE (Adverse Events Analysis Dataset) - 2021-09-22. Variables used: USUBJID, TRT01A, SAFFL, COHORT, TRTEMFL, AEDECOD, AETOXGR, AEACN, AEACN1, AEACN2, AEACN3, AEACN4, AEBODSYS, AESER
Group Pyrexia (GT) includes PT terms PYREXIA,
Group Vomiting (GT) includes PT terms VOMITING, RETCHING,
Group Diarrhea (GT) includes PT terms DIARRHOEA,
Group Rash (GT) includes PT terms RASH, RASH MACULO-PAPULAR, DERMATITIS ACNEIFORM, ECZEMA, RASH PUSTULAR, RASH PAPULAR, RASH ERYTHEMATOUS, RASH MACULAR, SKIN EXFOLIATION, PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME, RASH FOLLICULAR, DERMATITIS,
Group Arrhythmia (GT) includes PT terms SINUS TACHYCARDIA, SINUS BRADYCARDIA, ELECTROCARDIOGRAM QT PROLONGED, ATRIOVENTRICULAR BLOCK FIRST DEGREE,
Group Stomatitis (GT) includes PT terms STOMATITIS, MUCOSAL INFLAMMATION, CHEILITIS

Table 92 FDA - Summary of Pediatric Drug Reductions from Study X2101 Parts C and D

	PART C TMT 0.025 + 100% DRB RP2D N = 9 N (%)	PART C TMT 0.025 + 50% DRB RP2D N = 3 N (%)	PART C TMT 0.032 + 100% DRB RP2D (EXT) N = 6 N (%)	PART D TMT 0.025 + 100% DRB RP2D N = 22 N (%)	PART D TMT 0.032 + 100% DRB RP2D N = 8 N (%)	Total N = 48 N (%)
All	**3 (33)**	**1 (33)**	**1 (17)**	**6 (27)**	**1 (13)**	**12 (25)**
Ejection Fraction Decreased	2 (22)	0	0	0	0	2 (4.2)
Pyrexia (GT)	2 (22)	0	0	3 (14)	1 (13)	6 (13)
Panniculitis	1 (11)	0	0	0	0	1 (2.1)
Uveitis	0	1 (33)	0	0	0	1 (2.1)
Blood Alkaline Phosphatase Increased	0	0	1 (17)	0	0	1 (2.1)
Rash (GT)	0	0	0	2 (9)	0	2 (4.2)
Hyperglycemia	0	0	0	1 (4.5)	0	1 (2.1)
Paronychia	0	0	0	1 (4.5)	0	1 (2.1)

	PART C TMT 0.025 + 100% DRB RP2D N = 9 N (%)	PART C TMT 0.025 + 50% DRB RP2D N = 3 N (%)	PART C TMT 0.032 + 100% DRB RP2D (EXT) N = 6 N (%)	PART D TMT 0.025 + 100% DRB RP2D N = 22 N (%)	PART D TMT 0.032 + 100% DRB RP2D N = 8 N (%)	Total N = 48 N (%)
Visual Field Defect	0	0	0	1 (4.5)	0	1 (2.1)
Hypotension	0	0	0	0	1 (13)	1 (2.1)

Source: FDA reviewer generated table from Palintir; ADSL (Subject-Level Analysis Dataset) - 2021-09-22, ADAE (Adverse Events Analysis Dataset) - 2021-09-22. Variables used: USUBJID, TRT01A, SAFFL, COHORT, TRTEMFL, AEDECOD, AETOXGR, AEACN, AEACN1, AEACN2, AEACN3, AEACN4, AEBODSYS, AESER
Group Pyrexia (GT) includes PT terms PYREXIA,
Group Rash (GT) includes PT terms RASH, DERMATITIS ACNEIFORM, RASH MACULO-PAPULAR, ECZEMA, RASH ERYTHEMATOUS, RASH PUSTULAR, RASH PAPULAR, RASH MACULAR, PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME, SKIN EXFOLIATION, RASH FOLLICULAR, DERMATITIS,

Significant Adverse Events

There was an incidence of 65% for Grades 3-4 events on Study X2101 Parts C and D (Table 93). FDA notes that the incidence of Grades 3-4 events on adult Study X2201 was 58%. However, cross study comparisons between adult and pediatric patients administered dabrafenib in combination with trametinib are challenging to interpret due to differences amongst clinical trial methodologies.

Table 93 FDA - Summary Table of Grade 3-4 Adverse Events in Pediatric Patients for Study X2101 Parts C and D

	PART C TMT 0.025 + 100% DRB RP2D N = 9 N (%)	PART C TMT 0.025 + 50% DRB RP2D N = 3 N (%)	PART C TMT 0.032 + 100% DRB RP2D (EXT) N = 6 N (%)	PART D TMT 0.025 + 100% DRB RP2D N = 22 N (%)	PART D TMT 0.032 + 100% DRB RP2D N = 8 N (%)	Total N = 48 N (%)
Patients with Grade 3-4 TEAEs	**6 (67)**	**3 (100)**	**3 (50)**	**14 (64)**	**5 (63)**	**31 (65)**
Gastrointestinal Disorders						
Vomiting (GT)	2 (22)	0	0	0	0	2 (4.2)
Nausea	1 (11)	0	0	0	0	1 (2.1)
Abdominal Pain (GT)	1 (11)	0	0	1 (4.5)	0	2 (4.2)
Abdominal Distension	1 (11)	0	0	0	0	1 (2.1)
Dental Caries	0	0	1 (17)	0	0	1 (2.1)
Stomatitis (GT)	0	0	0	1 (4.5)	0	1 (2.1)
Diarrhea (GT)	0	0	0	1 (4.5)	0	1 (2.1)
General Disorders And Administration Site Conditions						
Pyrexia (GT)	2 (22)	0	1 (17)	4 (18)	1 (13)	8 (17)
Investigations						

	PART C TMT 0.025 + 100% DRB RP2D N = 9 N (%)	PART C TMT 0.025 + 50% DRB RP2D N = 3 N (%)	PART C TMT 0.032 + 100% DRB RP2D (EXT) N = 6 N (%)	PART D TMT 0.025 + 100% DRB RP2D N = 22 N (%)	PART D TMT 0.032 + 100% DRB RP2D N = 8 N (%)	Total N = 48 N (%)
Neutrophil Count Decreased	2 (22)	0	0	1 (4.5)	3 (38)	6 (13)
Blood Alkaline Phosphatase Increased	1 (11)	0	1 (17)	0	1 (13)	3 (6)
Gamma-glutamyltransferase Increased	0	1 (33)	0	1 (4.5)	1 (13)	3 (6)
Alanine Aminotransferase Increased	0	1 (33)	1 (17)	0	1 (13)	3 (6)
Weight Increased	0	0	0	2 (9)	0	2 (4.2)
Transaminases Increased	0	0	0	1 (4.5)	0	1 (2.1)
Lymphocyte Count Decreased	0	0	0	0	1 (13)	1 (2.1)
Aspartate Aminotransferase Increased	0	0	0	0	1 (13)	1 (2.1)
Injury, Poisoning And Procedural Complications						
Upper Limb Fracture	1 (11)	0	0	0	0	1 (2.1)
Skin And Subcutaneous Tissue Disorders						
Panniculitis	1 (11)	0	0	0	0	1 (2.1)
Rash (GT)	0	0	0	1 (4.5)	0	1 (2.1)
Vascular Disorders						
Hypotension (GT)	1 (11)	0	0	1 (4.5)	1 (13)	3 (6)
Hypertension (GT)	0	0	0	1 (4.5)	0	1 (2.1)
Flushing	0	0	0	1 (4.5)	0	1 (2.1)
Blood And Lymphatic System Disorders						
Febrile Neutropenia	1 (11)	0	0	0	0	1 (2.1)
Neutropenia	0	0	0	3 (14)	1 (13)	4 (8)
Anemia	0	0	0	1 (4.5)	1 (13)	2 (4.2)
Metabolism And Nutrition Disorders						
Dehydration	1 (11)	0	0	0	0	1 (2.1)
Hyperglycemia	0	0	0	1 (4.5)	0	1 (2.1)
Cardiac Disorders						
Arrhythmia (GT)	1 (11)	0	0	0	0	1 (2.1)
Eye Disorders						
Uveitis	0	1 (33)	0	0	0	1 (2.1)

	PART C TMT 0.025 + 100% DRB RP2D N = 9 N (%)	PART C TMT 0.025 + 50% DRB RP2D N = 3 N (%)	PART C TMT 0.032 + 100% DRB RP2D (EXT) N = 6 N (%)	PART D TMT 0.025 + 100% DRB RP2D N = 22 N (%)	PART D TMT 0.032 + 100% DRB RP2D N = 8 N (%)	Total N = 48 N (%)
Nervous System Disorders						
Brain Oedema	0	1 (33)	0	0	0	1 (2.1)
Posterior Reversible Encephalopathy Syndrome	0	0	0	1 (4.5)	0	1 (2.1)
Infections And Infestations						
Varicella	0	0	1 (17)	0	0	1 (2.1)
Upper Respiratory Tract Infection	0	0	1 (17)	0	0	1 (2.1)
Cellulitis	0	0	1 (17)	0	0	1 (2.1)
Parotitis	0	0	0	1 (4.5)	0	1 (2.1)
Adenovirus Infection	0	0	0	1 (4.5)	0	1 (2.1)
Tonsillitis	0	0	0	0	1 (13)	1 (2.1)
Epstein-barr Virus Infection	0	0	0	0	1 (13)	1 (2.1)
Psychiatric Disorders						
Restlessness	0	0	0	1 (4.5)	0	1 (2.1)
Respiratory, Thoracic And Mediastinal Disorders						
Respiratory Distress	0	0	0	1 (4.5)	0	1 (2.1)
Lung Disorder	0	0	0	1 (4.5)	0	1 (2.1)
Apnea	0	0	0	1 (4.5)	0	1 (2.1)

Source: FDA reviewer generated table using Palantir; ADSL (Subject-Level Analysis Dataset) - 2021-09-22, ADAE (Adverse Events Analysis Dataset) - 2021-09-22. Variables used: USUBJID, TRT01A, SAFFL, COHORT, TRTEMFL, AEDECOD, AETOXGR, AEBODSYS, AESER
Group Pyrexia (GT) includes PT terms PYREXIA,
Group Hypotension (GT) includes PT terms HYPOTENSION,
Group Abdominal Pain (GT) includes PT terms ABDOMINAL PAIN,
Group Vomiting (GT) includes PT terms VOMITING,
Group Stomatitis (GT) includes PT terms MUCOSAL INFLAMMATION,
Group Hypertension (GT) includes PT terms HYPERTENSION,
Group Rash (GT) includes PT terms RASH,
Group Diarrhea (GT) includes PT terms DIARRHOEA,
Group Arrhythmia (GT) includes PT terms ELECTROCARDIOGRAM QT PROLONGED

On Study X2210, Grade 3-4 AEs $\geq$ 5% incidence included neutropenia, anemia, pneumonia, fatigue while on pediatric Study X2101, Grade 3-4 AEs $\geq$ 5% incidence included pyrexia, neutropenia, liver abnormalities, and hypotension. There was also AEs that are seen often in pediatric patients without cancer such as AE of dental caries, and as described previously above

in "Dropouts And/or Discontinuations, Dose interruptions/reduction," varicella, adenovirus, tonsillectomy, and EBV. Due to the small number of pediatric patients, the single arm design of clinical studies of dabrafenib in combination with trametinib, difference of study methodology and endpoints, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether differences in the incidence of adverse reactions to dabrafenib in combination with trametinib are related to patient age or other factors. Summary of Pediatric Adverse Events from Study X2101 Parts C and D

Adverse Events

A high-level overview of the safety analysis for study X2101 Parts C and C is provided in **Error! R eference source not found.**.

Table 94 FDA - Summary of Pediatric Adverse Events from Study X2101 Parts C and D

	PART C TMT 0.025 + 100% DRB RP2D N = 9 N (%)	PART C TMT 0.025 + 50% DRB RP2D N = 3 N (%)	PART C TMT 0.032 + 100% DRB RP2D (EXT) N = 6 N (%)	PART D TMT 0.025 + 100% DRB RP2D N = 22 N (%)	PART D TMT 0.032 + 100% DRB RP2D N = 8 N (%)	Total N = 48 N (%)
All-Grade AEs	9 (100)	3 (100)	6 (100)	22 (100)	8 (100)	48 (100)
Grade 3-5 AEs	6 (67)	3 (100)	3 (50)	14 (64)	5 (63)	31 (65)
Grade 3-4 AEs	6 (67)	3 (100)	3 (50)	14 (64)	5 (63)	31 (65)
Grade 3	6 (67)	3 (100)	3 (50)	12 (55)	3 (38)	27 (56)
Grade 4	0	0	0	2 (9)	2 (25)	4 (8)
Grade 5 (Deaths)	0	0	0	0	0	0
SAEs	5 (56)	1 (33)	2 (33)	10 (45)	4 (50)	22 (46)
Drug interrupted	6 (67)	1 (33)	4 (67)	18 (82)	6 (75)	35 (73)
Dose reduced	3 (33)	1 (33)	1 (17)	6 (27)	1 (13)	12 (25)
Drug withdrawn	3 (33)	0	1 (17)	5 (23)	1 (13)	10 (21)

Source: FDA reviewer generated table using Palantir; ADSL (Subject-Level Analysis Dataset) - 2021-09-22, ADAE (Adverse Events Analysis Dataset) - 2021-09-22. Variables used: USUBJID, TRT01A, SAFFL, COHORT, TRTEMFL, AETOXGR, AESER, AEACN, AEACN1, AEACN2, AEACN3, AEACN4
TMT=trametinib, DRB=dabrafenib, RP2D-recommended phase 2 dose, EXT-extension arm.

The most common AEs occurring in ≥20% of patients in study X2101 were pyrexia, rash, vomiting, fatigue, dry skin, cough, diarrhea, dermatitis acneiform, headache, abdominal pain, nausea, hemorrhage, constipation, and paronychia. The majority of AEs that occurred more

commonly in pediatric patients compared to adults are common sequalae of viral illnesses that occur frequently during childhood. Pediatric patients are prone to seasonal illnesses such upper respiratory infections and the symptoms that accompany them such as pyrexia. Table 95 summarized the most common AEs in study X2101 Parts C and D.

Table 95 FDA - Summary of Adverse Reactions (>20%) in Pediatric Patients Treated on Study X2101 Parts C and D

Adverse Reactions	Dabrafenib plus Trametinib (n=48)	
	All Grades (%)	Grade 3 or 4 (%)
General		
Pyrexia	75	17
Fatigue[b]	48	0
Skin		
Rash[c]	73	2.1
Dry skin	48	0
Dermatitis acneiform[d]	40	0
Gastrointestinal		
Vomiting	52	4.2
Diarrhea	42	2.1
Abdominal pain[e]	33	4.2
Nausea	33	2.1
Constipation	23	0
Respiratory		
Cough	44	0
Nervous system		
Headache	35	0
Vascular disorders		
Hemorrhage[f]	33	0
Infections		
Paronychia	23	0

Source: FDA reviewer generated table: ADSL (Subject-Level Analysis Dataset) - 2021-09-22, ADAE (Adverse Events Analysis Dataset) - 2021-09-22. Variables used: USUBJID, TRT01A, SAFFL, COHORT, TRTEMFL, AEDECOD, AETOXGR, AEACN, AEACN1, AEACN2, AEACN3, AEACN4, AEBODSYS, AESER

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[b] *Includes fatigue, asthenia and malaise.*

[c] *Includes rash, rash maculo-papular, rash erythematous, rash papular, rash pustular, and rash macular.*

[d] *Includes dermatitis acneiform and acne.*

[e] *Includes abdominal pain and abdominal pain upper.*

[f] *Includes epistaxis, hematuria, contusion, hematoma, petechiae, rectal hemorrhage, and red blood cell count decreased.*

Laboratory Findings

The laboratory abnormalities associated with dabrafenib in combination with trametinib experienced by pediatric patients was similar to adult patients treated with dabrafenib in

combination with trametinib (**Error! Reference source not found.**). Pediatric patients enrolled o n Study X2101 experienced laboratory abnormalities that are clinically relevant with the potential for intervention, including hyperglycemia (65%), anemia (60%), increased LFT's (ALT 40%, AST 55%), and hypernatremia (27%). FDA does not agree that "no additional clinically significant changes in hematological or clinical chemistry parameters were observed in pediatric" patients as hypoalbuminemia was experienced by 48%. Grade 3-4 laboratory AEs that were potentially clinically relevant included anemia (6%), increased AST/ALT (4.2% and 6%, respectively), and hyperkalemia (4.2%). The laboratory abnormalities experienced by pediatric patients are consistent with the reference population (incidence of 25% in the dabrafenib in combination with trametinib COMBI-AD Study) or are anticipated in children with cancer and can be managed by a pediatric oncologist (NSCLC, melanoma; see U.S. package insert, Tafinlar, and Mekinist, accessed on 19 Feb 2022).

Table 96 FDA - Laboratory Abnormalities (>20%) That Worsened from Baseline in Pediatric Patients in Study X2101 Parts C and D

Laboratory Abnormality	Dabrafenib plus Trametinib[a]	
	All Grades (%)	Grade 3 or 4 (%)
Chemistry		
Hyperglycemia	65	2.2
Hypoalbuminemia	48	2.1
Hypocalcemia	40	2.1
Decreased phosphate	38	0
Decreased magnesium	33	2.1
Hypernatremia	27	0
Hypokalemia	21	2.1
Hepatic		
Increased AST	55	4.2
Increased ALT	40	6
Increased alkaline phosphatase	28	6
Increased total bilirubin	21	2.1
Hematology		
Decreased hemoglobin	60	6
Decreased neutrophils	49	28

[a] The denominator used to calculate the rate varied from 39 to 48 based on the number of patients with a baseline value and at least one post-treatment value.

Source: FDA reviewer generated table.

Weight and Vital Signs

The FDA agrees with Novartis's analysis of vital signs. There were no notable changes in vital signs in pediatric patients according to the Applicant on Study X2101 aside from weight increased by > 10% in >70% of patients. FDA assessed the incidence of the AE of decreased weight at 2.1% on Study X2101 Parts C and D, with the laboratory dataset incidence of 4.2%,

and no Grade 3-4 toxicity. The incidence of increased weight assessed the laboratory dataset was 19%, with Grade 3-4 of 4.2%.

ECG

The FDA agrees with Novartis's assessment of ECG changes. FDA agrees that the significance of the decreased heart rate over time in pediatric patients is unknown, and that a better assessment might be made by analyzing serial ECGs.

Additionally, FDA reviewed any patient narrative that had QTcB >500 ms or a "clinically significant ECG abnormality" defined by investigative staff as those that "contain abnormalities that, in the opinion of the investigator, or other suitably qualified clinical staff, are considered significant in relation to the patient's health status."

On Study X2101, at baseline, 3 (17%) patients had abnormal but not clinically significant ECG findings. In Part A-B (trametinib monotherapy), 2 patients had prolonged QTc 11-12 days after the last dose. Patient (b) (6) had an AE of QTc prolongation but no corresponding supportive ECG data (baseline QTcB 449ms and 453 ms on day of AE report), but trametinib had been discontinued due to "lack of efficacy" at the same time. Patient (b) (6) had ECG results from the end of study reported by the investigator as clinically significant without further information or apparent QTcB abnormality (QTcB 379 ms). One patient required a drug interruption/delay due to ECG QT prolongation (other patients were with concurrent LVEF).

Two patients had a new QTcB value of >500 ms on Parts C-D. Prolongation of QTcB interval was detected through routine protocol-specified local ECG monitoring.

For additional details including cardiac toxicity, see 8.2.5.

FDA Summary review of Pediatric Safety

The review of safety for dabrafenib in combination with trametinib in pediatric patients has been described within the subsections above. Dabrafenib in combination with trametinib in pediatric patients was reasonably tolerated, and consistent with AEs and irAEs experienced by adults in the reference population (NSCLC, melanoma; see Table 98). The adverse drug reactions in pediatric patients can be managed by an oncologist who is well trained in monitoring and treatment of the adverse reactions to anti-cancer therapeutics. While drug discontinuation, interruption, or delays may appear higher on the pediatric Study X2102 compared to the adult pivotal study X2201, due to the small number of pediatric and adult patients, the single arm design of clinical studies of dabrafenib in combination with trametinib, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether differences in the incidence of adverse reactions to dabrafenib in combination with trametinib are related to patient age or other factors. Additionally, standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs, drug class, and oncologists are generally experienced in the monitoring and management of serious risks.

For additional information regarding the review of dabrafenib + trametinib in the pediatric safety population, see Section 10.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

Adverse events of special interest (AESI)

This section provides AESI summaries for the two pediatric studies, followed by a discussion of individual AESI topics by study (for both adult and pediatric studies).

Study X2101

No new primary or secondary malignancy events, pancreatitis events, venous thromboembolism, pre-renal and intrinsic renal failure events were reported. Except pyrexia, hepatic disorders, and neutropenia events in Part D (dabrafenib+trametinib), all other AESI events occurred in less than 5 subjects (Table 97).

Table 97 Applicant - Study X2101 AESIs (Safety population)

	Trametinib monotherapy				Dabrafenib+Trametinib			
	Part A N=50		Part B N=41		Part C N=18		Part D N=30	
Safety Topic	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
-Total	**13 (26.0)**	**6 (12.0)**	**13 (31.7)**	**6 (14.6)**	**9 (50.0)**	**7 (38.9)**	**16 (53.3)**	**14 (46.7)**
Skin toxicity	4 (8.0)	4 (8.0)	4 (9.8)	4 (9.8)	0	0	1 (3.3)	1 (3.3)
Pyrexia	0	0	0	0	3 (16.7)	3 (16.7)	5 (16.7)	5 (16.7)
Hepatic disorders	1 (2.0)	1 (2.0)	1 (2.4)	1 (2.4)	2 (11.1)	2 (11.1)	3 (10.0)	3 (10.0)
Neutropenia	0	0	0	0	2 (11.1)	2 (11.1)	8 (26.7)	8 (26.7)
Bleeding events	3 (6.0)	0	2 (4.9)	0	0	0	0	0
Hyperglycemia	0	0	0	0	0	0	1 (3.3)	1 (3.3)
Ocular events	1 (2.0)	0	2 (4.9)	0	1 (5.6)	0	0	0
New primary or secondary malignancy	0	0	0	0	0	0	0	0
Hypertension	0	0	1 (2.4)	1 (2.4)	0	0	1 (3.3)	1 (3.3)
Cardiac related events	2 (4.0)	0	4 (9.8)	0	2 (11.1)	0	2 (6.7)	0
Hypersensitivity	2 (4.0)	0	3 (7.3)	0	0	0	2 (6.7)	0
Venous thromboembolism	0	0	0	0	0	0	0	0
Pre-renal and intrinsic renal failure	0	0	0	0	0	0	0	0
Pancreatitis	0	0	0	0	0	0	0	0

	Trametinib monotherapy				Dabrafenib+Trametinib			
	Part A N=50		Part B N=41		Part C N=18		Part D N=30	
Safety Topic	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Pneumonitis and interstitial lung disease	1 (2.0)	1 (2.0)	1 (2.4)	1 (2.4)	0	0	0	0
Uveitis	0	0	0	0	2 (11.1)	1 (5.6)	1 (3.3)	0

A subject with multiple occurrences of an AESIs under one treatment is counted only once in the AESIs category for that treatment. A subject with multiple AESIs is counted only once in the total row. Only AEs occurring during treatment or within 30 days of the last dose of study drug are included.
Source: Study X2101-Table 12-26, Table 12-27, Table 12-28, and Table 12-29

Study A2102

The AESIs reported in this study were: pyrexia in 9 subjects (all grade ≥3), uveitis (grade 2) in 1 subject, new primary or secondary malignancy (grade 2 lip neoplasm and grade 2 neoplasm skin) in 1 subject, pre-renal and intrinsic renal failure (grade 2 renal failure) in 1 subject, pancreatitis (grade 4 lipase increased) (Study A2102-Table 14.3.1-1.24). In addition to the AESI, there was one subject who had EBV associated lymphoma as a new malignancy which was not suspected to be related to the study drug and resulted in discontinuation of study dabrafenib (Study A2102-Listing 16.2.7-1.1).

8.2.5.1 Skin related events

Grade 4 skin related events were not observed in any of the 4 studies. The incidence of grade 3 skin toxicity events was low:

- Study X2201 in adult subjects: 6 subjects (2.9%, of which 4 subjects were in the HCL cohort) rash, rash maculo-papular, and dermatitis acneiform
- Study XUS35T in adult subjects: 1/33 subjects with grade 3 rash maculo-papular
- Study X2101 in pediatric subjects: 1/48 subjects treated with dabrafenib+trametinib therapy reported grade 3 rash and urticaria, and 8/91 subjects treated with trametinib monotherapy reported grade 3 skin toxicity (rash, rash maculo-papular, eczema, and dermatitis acneiform)
- Study A2102 in pediatric subjects: 3/85 subjects treated with dabrafenib monotherapy reported grade 3 rash maculo-papular and 1 subject had grade 3 hyperkeratosis.

8.2.5.2 New primary or secondary malignancy

In Study X2201, 25 adult subjects (12.1%) across all cohorts had new primary or secondary malignancies of any grade (20 of the 25 subjects were in HCL cohort). One subject had grade 5 event of adenocarcinoma pancreas; no grade 4 events were noted. Grade 3 new primary or

secondary malignancy events were reported in total in 11 (5.3%) adult subjects (of which 9 were in the HCL cohort). The two events in the solid tumor cohorts were invasive breast carcinoma (1 subject in the HGG cohort) and bladder transitional cell carcinoma (1 subject in the ATC cohort).

In pediatric subjects, no grade ≥3 new primary or secondary malignancy events were reported in subjects treated with dabrafenib+trametinib and trametinib monotherapy. One case of grade 2 lip neoplasm and grade 2 neoplasm skin and one case of EBV associated lymphoma as a new malignancy were reported on dabrafenib monotherapy.

8.2.5.3 Cardiac related events (ejection fraction decreased)

In Study X2201, cardiac-related events were reported in 18 adult subjects (8.7%; 17 with ejection fraction decreased and 1 with left ventricular dysfunction). None of the subjects had grade 4 events, grade 3 ejection fraction decreased was reported in 3 (1.5%) subjects (1 subject each from ATC, HGG and MM). The 2 events in HGG and MM were suspected to be related to dabrafenib and trametinib.

In Study XUS23T, cardiac related events were reported in 6 subjects (18.2%). None of the subjects had grade 4 events, grade 3 ejection fraction decreased and left ventricular dysfunction was reported in the same 1 subject.

All events of decreased ejection fraction reported in pediatric subjects were grade 1 or 2 (dabrafenib+trametinib: 1 subject with left ventricular dysfunction and 3 subjects with ejection fraction decreased; monotherapy: 6 subjects treated with trametinib monotherapy and 3 subjects treated with dabrafenib monotherapy with ejection fraction decreased).

8.2.5.4 Pyrexia

In the adult studies, pyrexia events were reported in 117 subjects (56.8%), of which 10 (4.9%) had grade 3 events, in Study X2201, and in 21 subjects (63.6%, all grade 1 or 2) in Study XUS35T; none of the subjects had grade 4 pyrexia event.

Pediatric studies: In subjects treated with dabrafenib+trametinib, pyrexia events (all grade ≥3) were reported in 8 subjects. Under trametinib monotherapy, no pyrexia grade ≥3 was reported. Under dabrafenib monotherapy, 9 subjects reported grade ≥3 pyrexia events. Pyrexia was mostly managed by dose interruption/dose adjustment (Study X2201- Table 1431.1060, Study A2102-Table 14.3.1-1.24, and Table 2-10).

8.2.5.5 Melanocytic nevus

In the adult studies, melanocytic nevi were reported in 5/206 subjects (all were either of grade 1 or 2) in Study X2201, and in none of subjects in study XUS35T. In pediatric subjects treated with dabrafenib+trametinib, melanocytic nevus was reported in 2/48 subjects. In pediatric subjects treated with trametinib monotherapy, melanocytic nevus was reported in 3/91

subjects. In pediatric subjects treated with dabrafenib monotherapy, melanocytic nevus was reported in 22 subjects (7/27 in Part 1 and 15/58 in Part 2; 25.9% subjects in each part). All events were non-serious and grade 1 or 2 in severity.

The higher incidence of melanocytic naevus in subjects treated with dabrafenib monotherapy relative to those treated with trametinib monotherapy or with dabrafenib + trametinib combination therapy is consistent with the known paradoxical stimulation of MAPK pathway signaling by dabrafenib monotherapy in tissues with wild type BRAF, and with the mitigating impact of adding trametinib.

The FDA's Assessment:

FDA agrees with the AESI identified and discussion above regarding adult and pediatric patients treated with dabrafenib + trametinib. According to prescribing information (U.S. package insert, Tafinlar, Mekinist, accessed on 5 March 2022) the warnings and precautions identified most of these AEOSI including: New Primary Malignancies, Cutaneous, and Non-cutaneous, Cardiomyopathy: Assess left ventricular ejection fraction (LVEF), uveitis or ocular toxicity, Serious Skin Toxicities, Hyperglycemia.

Skin Related Events

On Study X2101, 60% of patients experienced skin toxicity, of which 6 patients with Grade 3 events consisting of rash, maculopapular rash, and dermatitis acneiform. One pediatric patient (3.3%) enrolled on Study X2101 across Part C – D had a Grade 3 event of skin toxicity.

New primary or secondary malignancy

On Study 2201, a total of 12% of adults had secondary malignancies including: 1 patient with invasive breast carcinoma in the HGG cohort, 1 patient with bladder transitional cell carcinoma in the ATC cohort, basal cell carcinoma and squamous cell carcinoma of skin, squamous cell carcinoma, bladder neoplasm, Bowen's disease, chronic lymphocytic leukemia, colon cancer, Hodgkin's disease, lymphoma, and metastatic squamous cell carcinoma (9 patients in HCL cohort). Grade 5 event of adenocarcinoma of the pancreas was experienced in 1 patient of the HCL cohort. Given that the trial was a single arm trial, it is unclear as to the magnitude of the increased risk in Study 2201, as secondary malignancies have been reported to occur at an increased rate in patients with HCL (e.g., WY Au et al., Blood, 1998; R Kurzrock et al., JCO, 1997; Cornet et al., BJ Haem 2014; J Pailassa et al., BCJ, 2020; M Wiber et al., Cancer Treatment and Research Communications, 2020; and M Hisada, JNCI, 2007). Nevertheless, given the prior experience of dabrafenib + trametinib, an increased risk of secondary malignant events can occur; this is described in product labeling.

None of the pediatric patients treated with either trametinib monotherapy or combination dabrafenib + trametinib had new primary or secondary malignancy events.

Cardiac related events (ejection fraction decreased)

Cardiac related events were identified in 17 pediatric patients (12% across all pediatric patients enrolled on Study X2102 Parts A-D) as decreases in LVEF of more than 20% and/or an AE of decreased ejection fraction. Transient and reversible decrease in LVEF is a known side effect of trametinib treatment (Banks, 2017). Management of this side effect is outlined in prescribing information (U.S. package insert, Mekinist, accessed on 5 March 2022) and in Novartis-sponsored clinical trials. Decreases in LVEF were detected through routine ECHO monitoring procedures in 11 patients ((b) (6)). Each of these patients were asymptomatic (i.e., no other associated AEs reported) and the LVEF decreases were transient and reversible. In 2 patients ((b) (6)), recurrent decrease in LVEF identified by ECHO was the primary reason for discontinuation of trametinib treatment, with subsequent recovery of LVEF.

Five of the 17 patients had prolongation of QTcB interval detected through routine protocol specified local ECG monitoring (b) (6) , see FDA's discussion on "Weight changes and Vital Signs" and "ECG" above.

Cardiac events were observed in 9% of patients enrolled on Study X2201, with Grade 3 events in 3 patients (decreased ejection fraction). LVEF decreases in both adults and pediatric patients were similar in incidence, were managed by dose modification guidance provided per protocol, and were reversible. See FDA discussion of "Dropouts and/or Discontinuations Due to Adverse Effects" and "Dose interruptions/reductions due to Adverse Effects."

Pyrexia

In adult patients enrolled on Study X2201, 57% had pyrexia, and $\geq$ Grade 3 events were experienced in 10 patients (5%). In pediatric patients enrolled across Parts C-D on Study X2101, 17% experienced pyrexia all of whom had $\geq$ Grade 3. AEs such as pyrexia are common in pediatric patients compared to adults as sequalae of viral illnesses that occur frequently during childhood.

Melanocytic nexus

FDA notes that in Study X2201, melanocytic nevi were reported in 2.4% of patients, all were $\leq$ Grade 2, and in Study X2201 Parts C-D, melanocytic nevus was reported in 4.2% of patients.

FDA assessed the following AEOSI based on safety signals documented in previous labels for Mekinist and Tafinlar, in addition to the above in which Novartis outlined:

Hepatic Disorders

There was an incidence of 34% of hepatic disorders in adults enrolled on Study X2201, including Grade 3 in 9%, defined as increased AST, ALT, GGT, or bilirubin, or hepatocellular injury. On Study X2102, there was 11% of patients enrolled on Part C and 10% on Part D with $\geq$ Grade 3

hepatic disorders.

Hypertension

On Study X2201, there was an incidence of hypertension of 11%, and Grade 3 events in 3.8% of adult patients, and no hypotension. There was only 1 patient enrolled on Study X2101 with Grade 3 hypertension, and no hypotension events.

Hyperglycemia

There was an incidence of hyperglycemia of 24% on Study X2201. There was 1 patient enrolled on Study X2101 who also had Grade 3 hyperglycemia.

Uveitis

There were 24% ocular events identified on Study X2201, and uveitis had an incidence of 1.9%, which was ≥ Grade 3 in 1 patient. There was 1 patient enrolled on Study X2101 with uveitis and it was ≤ Grade 3.

While cross trial comparisons are challenging, the incidence of AEOSI are generally similar between adult and pediatric patients treated with dabrafenib + trametinib, and do not warrant additional labelling (i.e. the information is described in Warnings and Precautions).]

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

The Applicant's Position:

Patient related outcome (PRO) data was collected in Study X2201 however, no analysis was performed for this submission.

The FDA's Assessment:

FDA agrees with the Applicant's position. It would be difficult to analyze PRO information given that patients with multiple tumor types were enrolled with differences in baseline symptoms, different age categories (which may necessitate different instruments), and given that the studies were single arm.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Combination therapy (dabrafenib+trametinib), study X2101

Number of subjects treated: <2 years: N=1; 2-<6 years: N=15; 6-<12 years : N=15; 12-<18 years: N=17.

The incidence of vomiting was lower in the age group 12-<18 years (41.2%) as compared to 2-<6 years (66.7%), and 6-<12 years (53.3%). The incidence of pyrexia was lower in the age group of 12-<18 years (64.7%) and 6-<12 years (66.7%) than the age group of 2-<6 years (100%) (Study X2101-Table 14.3.1-2.3.6). The number of subjects reporting SAEs was varied across age groups. The 1 subject in <2 years age group did not report an SAE. SAEs reported in 12-<18 years age group were lower (29.4%) than other age groups of 2-<6 years (53.3%) and 6-<12 years (60%). The incidence of serious pyrexia was higher in the age group 2-<6 years (40%) as compared with 6-<12 years (20%) and 12-<18 years (17.6%) age group. Ejection fraction decreased was reported only in age group of 12-<18 years (3 subjects, 6.3%) (Study X2101-Table 14.3.1-2.3.8).

Trametinib monotherapy, study X2101

Number of subjects treated: <2 years of age (N=9), 2-<6 years of age (N=33), 6-<12years of age (N=28), 12-<18 years of age (N=21).

The incidence of pyrexia and dry skin in subjects treated with trametinib monotherapy was lower in age group 12-<18 years (28.6% and 42.9%) as compared to other age groups < 2 years (66.7% and 55.6%), 2-<6 years (66.7% and 60.6%), and 6-<12 years (67.9% and 60.7%) (Study X2101-Table 14.3.1-2.3.5). The number of subjects reporting SAEs was evenly distributed across age groups (42.9% of subjects 12<18 years to 66.7% of subjects <2 years). Serious vomiting only occurred in subjects less than 6 years (4 subjects of 2-<6 years and 1 subject <2 years of age) (Study X2101-Table 14.3.1-2.3.7).

Dabrafenib monotherapy, study A2102

Number of subjects treated: <2 years: N=3; 2-<6 years: N=17; 6-<12years: N=28; 12-<18 years: N=35.

Clinically meaningful conclusions regarding age- and dose-specific frequency of AEs could not be drawn due to small sample size across multiple dose levels. AEs were reported in almost all subjects across different age groups and disease cohorts. Except for nervous system AEs such as headache (75%) and paresthesia (37.5%) that were reported at a higher frequency in adolescent subjects in the LGG cohort, no major differences were observed (Study A2102-Table 14.3.1-1.3). No clinically meaningful differences were observed in the frequency of SAEs reported across different age groups, dose levels and disease cohorts (Study A2102-Table 14.3.1-1.12).

The FDA's Assessment:

FDA agrees with the Applicant's position. Cross trial comparisons are difficult due to subtle differences between the trials conducted in adult and pediatric patients. Small sample size precludes statistically sound conclusions regarding age- and dose-specific frequency of AEs. Informative language regarding pediatrics will be included in Section 6 and Section 8.4 of the label.

8.2.8. 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 position that this section is not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicant's Position:
No carcinogenicity studies were conducted for this submission. The safety topic "new primary or secondary malignancy" is discussed in section 1768.2.5.

The FDA's Assessment:
FDA agrees with the Applicant's position that this section is not applicable.

Human Reproduction and Pregnancy
The Applicant's Position:

No new pregnancy cases have been reported. The information on pregnancy and lactation is adequately described in the label.

The FDA's Assessment:
FDA agrees with the Applicant's position that this section is not applicable.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Height and weight: Height and weight were monitored over time for study participants to delineate possible impact of the diseases under study, and their treatment, on the gain in height and weight. These were compared with expected normal changes in height and weight for individuals of that age and presented as standard deviations from expected normal values.

In Study X2101, no large differences in height and weight changes were observed overall compared to a normal population of similar ages. In most cohorts, the median gain in weight and height within one standard deviation of the expected gain, at the 18 month time point (Study X2101-Section 12.5.6).

In Study A2102, the velocity of height changes and weight changes were slightly above that of a normal population (SDS ranged between 0 to 2) in different dose groups across Part 1 and Part

2. With few exceptions, these changes were not clinically meaningful (Study A 2102-Section 12.6).

Skeletal changes in Study X2101: Growth plates were open at baseline and remained open throughout treatment for most subjects. Several subjects did have closure of their growth plates at age appropriate times. Exceptions were noted for 2 subjects. A 9 year old male in Part B with NF-1 with PN, had Tanner stage 1 at baseline and throughout the study, showed growth plate was open at Week 9, and reported closed growth plate at Week 145. An 8 year old male in Part D with LGG, had Tanner stage 1 throughout the study, showed growth plate open at Week 9, but closed at Week 25 and Week 49 (Study X2101-12.5.7).

Sexual maturity in Study X2101: Tanner stage of development was assessed every 6 months as a measure of sexual maturation. No stage changes were recorded for subjects during study participation (Study X2101-Section 12.5.8). The expected progression through Tanner stages was not noted for subjects during study participation but it is unclear if this might be due to incomplete assessments rather than treatment effect.

The FDA's Assessment:
FDA agrees with the Applicant's analysis. See 8.2.4 "Weight and Vital Signs" for further FDA discussion regarding weight and vital sign changes.

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 position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Safety data from Managed access program (MAP)

A total of 275 patients with BRAF V600 mutated tumors other than those currently approved received access to dabrafenib+trametinib combination therapy via individual patient requests in the Novartis Managed Access Program (MAP). Safety case reports received for these patients were retrieved from the company global safety database; as of the cut-off date of 19-Nov-2020, 223 cases were identified and reviewed. The most frequent serious AEs included malignant neoplasm progression (36 events; of note, the term included the progression of underlying disease in anaplastic astrocytoma, glioblastoma and glioma), pyrexia (24 events), seizure (8 events), headache (7 events), rash (6 events), pneumonia and death (each 5 events). Overall, the data were consistent with the know safety profile of dabrafenib + trametinib combination therapy in the approved indications.

The FDA's Assessment:
FDA agrees with the Applicant's position. The MAP has limitations because it was not a clinical trial and did not have prespecified endpoints. Furthermore, duration on therapy is not a surrogate for response as patients could stay on trial for non-progression. Although limited, FDA reviewed the available safety data; FDA did not identify any new safety signal based on the MAP.

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 position.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

Dabrafenib + trametinib combination therapy demonstrated an acceptable safety profile in adult subjects with rare BRAF V600E mutation-positive advanced solid tumors that was consistent with previous observations in the approved indications (Table 98).

No significant new safety signals were observed in the pediatric population and the safety was consistent with the previously established safety profile in adult subjects.

Table 98 Applicant - Overview of AEs with dabrafenib+trametinib combination across indications

	Proposed indication		Previously approved indication	
	Adult X2201	Pediatric X2101 Parts C and D	Metastatic NSCLC	Unresectable or metastatic melanoma
	N=206 n (%)	N=48 n (%)	N=93 n (%)	N=559 n (%)
Any AE	201 (98)	48 (100)	91 (98)	546 (98)
Related to study treatment	181 (88)	48 (100)	83 (89)	501 (90)
Leading to permanent discontinuation of any study treatment	26 (13)	10 (21)	18 (19)	68 (12)
Leading to dose reduction	91 (44)	12 (25)	33 (35)	174 (31)
Leading to dose interruption/delay	113 (55)	35 (73)	60 (65)	310 (55)
Any SAE	92 (45)	22 (46)	52 (56)	219 (39)
Related to study treatment	46 (22)	11 (23)	35 (38)	154 (28)
Fatal	9 (4)	0	6 (6)	8 (1)
Fatal and related to study treatment	0	0	0	0

Table 99 Applicant - Frequent AEs by SOC (>10% in study X2201) with dabrafenib + trametinib combination across indications

	Proposed indication		Previously approved indication	
	Adult X2201	Pediatric X2101 Parts C and D	Metastatic NSCLC	Unresectable or metastatic melanoma
System organ class	N=206 n (%)	N=48 n (%)	N=93 n (%)	N=559 n (%)
Any event	201 (98)	48 (100)	91 (98)	546 (98)
General disorders and administration site conditions	162 (79)	43 (90)	78 (84)	439 (79)
Gastrointestinal disorders	157 (76)	41 (85)	66 (71)	366 (65)
Investigations	138 (67)	36 (75)	43 (46)	239 (43)
Skin and subcutaneous tissue disorders	135 (66)	46 (96)	66 (71)	364 (65)
Infections and infestations	125 (61)	36 (75)	40 (43)	294 (53)
Metabolism and nutrition disorders	118 (57)	27 (56)	43 (46)	157 (28)
Musculoskeletal and connective tissue disorders	112 (54)	21 (44)	42 (45)	283 (51)
Nervous system disorders	110 (53)	29 (60)	43 (46)	284 (51)
Respiratory, thoracic and mediastinal disorders	105 (51)	28 (58)	50 (54)	209 (37)
Blood and lymphatic system disorders	78 (38)	18 (38)	32 (34)	124 (22)
Eye disorders	65 (32)	16 (33)	29 (31)	119 (21)
Vascular disorders	53 (26)	7 (15)	28 (30)	202 (36)
Psychiatric disorders	51 (25)	13 (27)	20 (22)	73 (13)
Cardiac disorders	46 (22)	11 (23)	14 (15)	66 (12)
Injury, poisoning and procedural complications	40 (19)	12 (25)	15 (16)	65 (12)

	Proposed indication		Previously approved indication	
	Adult X2201	Pediatric X2101 Parts C and D	Metastatic NSCLC	Unresectable or metastatic melanoma
System organ class	N=206 n (%)	N=48 n (%)	N=93 n (%)	N=559 n (%)
Renal and urinary disorders	38 (18)	11 (23)	14 (15)	53 (9)
Neoplasms benign, malignant and unspecified	36 (18)	5 (10)	14 (15)	76 (14)
Ear and labyrinth disorders	21 (10)	3 (6)	11 (12)	36 (6)

Table 100 Applicant - Most common AEs with dabrafenib + trametinib combination across indications (>10% in study X2201)

	Proposed indication		Previously approved indication	
	Adult X2201	Pediatric X2101 Parts C and D	Metastatic NSCLC	Unresectable or metastatic melanoma
Preferred term	N=206 n (%)	N=48 n (%)	N=93 n (%)	N=559 n (%)
Any event	201 (98)	48 (100)	91 (98)	546 (98)
Pyrexia	113 (55)	36 (75)	51 (55)	303 (54)
Fatigue	86 (42)	20 (42)	22 (24)	182 (33)
Nausea	83 (40)	16 (33)	42 (45)	193 (35)
Chills	61 (30)	6 (13)	21 (23)	174 (31)
Headache	61 (30)	17 (35)	14 (15)	170 (30)
Constipation	56 (27)	11 (23)	15 (16)	72 (13)
Vomiting	56 (27)	25 (52)	31 (33)	153 (27)
Cough	54 (26)	21 (44)	20 (22)	113 (20)
Diarrhea	54 (26)	20 (42)	30 (32)	175 (31)
Rash	52 (25)	16 (33)	21 (23)	132 (24)
Anemia	49 (24)	11 (23)	15 (16)	39 (7)
AST increased	48 (23)	14 (29)	9 (10)	68 (12)
Arthralgia	46 (22)	9 (19)	15 (16)	138 (25)
Hyperglycemia	46 (22)	8 (17)	5 (5)	25 (4)
Myalgia	44 (21)	5 (10)	11 (12)	85 (15)
Edema peripheral	43 (21)	4 (8)	22 (24)	86 (15)
Decreased appetite	40 (19)	5 (10)	27 (29)	68 (12)
Alanine aminotransferase increased	39 (19)	7 (15)	8 (9)	76 (14)
Blood alkaline phosphatase increased	36 (18)	7 (15)	10 (11)	42 (8)
Dermatitis acneiform	32 (16)	16 (33)	0	42 (8)
Dizziness	32 (16)	8 (17)	13 (14)	63 (11)
Dyspnea	32 (16)	3 (6)	19 (20)	36 (6)
Dry skin	31 (15)	23 (48)	29 (31)	55 (10)
Dry mouth	27 (13)	0	6 (6)	41 (7)
Pain in extremity	27 (13)	8 (17)	4 (4)	65 (12)
Rash maculo-papular	27 (13)	14 (29)	1 (1)	25 (4)

	Proposed indication		Previously approved indication	
	Adult X2201	Pediatric X2101 Parts C and D	Metastatic NSCLC	Unresectable or metastatic melanoma
Preferred term	**N=206 n (%)**	**N=48 n (%)**	**N=93 n (%)**	**N=559 n (%)**
Abdominal pain	26 (13)	15 (31)	4 (4)	58 (10)
White blood cell count decreased	26 (13)	7 (15)	1 (1)	18 (3)
Neutropenia	25 (12)	4 (8)	13 (14)	52 (9)
Urinary tract infection	25 (12)	0	8 (9)	42 (8)
Insomnia	22 (11)	3 (6)	8 (9)	29 (5)
Pneumonia	22 (11)	0	3 (3)	11 (2)
Pruritus	22 (11)	8 (17)	14 (15)	55 (10)
Vision blurred	22 (11)	3 (6)	1 (1)	21 (4)
Back pain	21 (10)	3 (6)	9 (10)	53 (9)
Blood creatinine increased	21 (10)	6 (13)	5 (5)	19 (3)
Hypertension	21 (10)	1 (2)	9 (10)	144 (26)
Nasal Congestion	21 (10)	11 (23)	1 (1)	13 (2)
Neutrophil count decreased	21 (10)	11 (23)	1 (1)	18 (3)
Thrombocytopenia	21 (10)	0	5 (5)	20 (4)
Upper respiratory tract infection	21 (10)	14 (29)	1 (1)	27 (5)

The FDA's Assessment:

In general, FDA agrees with Novartis's integrated assessment of safety. Overall, the safety profile for dabrafenib in combination trametinib is consistent with the types of AEs expected from previous clinical trials in NSCLC, melanoma, and ATC. No new safety signals associated with dabrafenib in combination with trametinib were observed. There was a similar incidence of AEs in adult and pediatric patients treated with dabrafenib in combination with trametinib. Oncologists are well versed in the management of AEs. FDA proposes to update Section 6 as well as Section 8.4 of the product label to address pediatric patients.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There are no major statistical issues that impact the interpretation of the study results.

8.4. Conclusions and Recommendations

The FDA's Assessment:

FDA agrees that the results of studies X2201 and XUS35T in adults and study X2101 in pediatric patients with BRAF V600E mutation positive solid tumors provides clinically meaningful responses and durability of responses across a wide variety of tumor types for patients that have no satisfactory alterative treatment options.

The primary safety review consisted of data based on the results from 4 clinical studies: Study X2201, and Study US35T, both in adults, and Study X2101, and Study A2102, both in pediatric patients. The safety profile in both adult and pediatric patients who received dabrafenib in combination with trametinib is generally consistent with the established safety profile. The overall AE profile, including AEOSI and irAEs, is generally consistent with the established safety profile of dabrafenib in combination with trametinib. Dabrafenib in combiantion with trametinib has a clinically manageable safety profile that is acceptable given the effects on response rate (as well as effects on PFS/OS in trials in patients with metastatic melanoma). Based on the types, frequencies, and severity of the AEs observed in the patient population enrolled across Studies X2201, XUS35T, X2101, and A2102, there was no important clinical change of the safety profile of dabrafenib + trametinib. No new safety concerns were identified. Overall, a review of the safety profile of the dabrafenib in combination with trametinib safety dataset did not reveal unexpected safety events.

X X

Mengdie Yuan , PhD
Primary Statistical Reviewer

Joyce Cheng, PhD
Statistical Team Leader

X X

Leslie Doros, MD
Primary Clinical Reviewer

Leslie Doros, MD
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The Division did not refer the application to the Oncologic Drug Advisory Committee (ODAC) or seek input from Special Government Employees (SGEs) for this NDA as no significant review issues were identified during the review of this application.

10 Pediatrics

The Applicant's Position:
All relevant information from the pediatric population is presented in prior sections.

The FDA's Assessment:

The safety and effectiveness of dabrafenib in combination with trametinib in pediatric patients was established based upon data from two multicenter, open-label, single-arm clinical trials, X2101 and A2102. For information regarding the review of the pharmacokinetics, efficacy and safety of dabrafenib in combination with trametinib in pediatric patients, see Section 6 (Clinical Pharmacology), and Section 8 (Statistical and Clinical Evaluation).

As part of the Agreed iPSP, the Applicant will be submitting data (post market) to support the pediatric formulation for patients <6 years of age and additional safety and efficacy data from an ongoing study in pediatric patients with LGG and HGG receiving dabrafenib in combination with trametinib.

11 Labeling Recommendations

The Applicant's Position:

Summary of Significant Labeling Changes for TAFINLAR and/or MEKINIST		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
Highlights	Section updated in alignment with the individual changes described below	FDA revised this section according to the changes made in the rest of the USPI.
1. Indication and Usage	New indication added: (b) (4) Limitations of Use revised to include colorectal cancer and any wild-type BRAF solid tumors.	Indication revised to describe use in patients without satisfactory alternative treatment options
2. Dose and Administration	Patient selection information for solid tumors added. Adult posology consolidated across indications for legibility. Information on pediatric (6 to 17 years) weight-based dosing added. Dose reduction table for adverse reactions in pediatric patients added.	FDA updated dosing information in pediatric patients as described above.
6. Adverse Reactions	Study X2201 summary expanded to include all solid tumor cohorts.	In addition to safety information in adults, safety data from Study X2101 also included in the labeling to describe safety experience in children.
8. Use in Specific Populations	Pediatric Use section updated to include safety and efficacy data in pediatric patients from studies (b) (4) X2101.	FDA added statements pertaining to age (less than 6) and use of Tafinlar as a single agent).
12. Pharmacokinetics	Pharmacokinetic information on pediatric population added.	Statement was added about resistance to BRAF inhibition in CRC.
14. Clinical Studies	Efficacy results of adult studies (b) (4)	Section was extensively re-edited. Table combined responses for individual tumor types in MATCH and ROAR. Granular

		information by CNS histology were provided. Reference to melanoma, NSCLC, ATC data provided.
Medication guide	Updated to reflect the new indication and age range	Changes were made to reflect the revised PK.

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	See above
1 Indication and Usage	New indication added: (b) (4) Limitations of Use revised to include colorectal cancer and any wild-type BRAF solid tumors	See above
2. Dose and administration	Patient selection information for solid tumors was added. Adult posology consolidated across indications for legibility. Information on pediatric (6 to 17 years) weight-based dosing added. Dose reduction table for adverse reactions in pediatric patients added.	See above
6 Adverse reactions	(b) (4) summary expanded to include all solid tumor cohorts	See above
8 Use in Specific population	Pediatric Use section updated to include safety and efficacy data in pediatric patients (b) (4)	See above
12. Pharmacokinetics	Pharmacokinetic information on pediatric population added.	See above
14 Clinical Studies	Efficacy results of adult studies (b) (4)	See above
Medication guide	Updated to reflect the new indication and age range	See above

The FDA's Assessment:

The table above summarizes changes to the proposed prescribing information (PI) made by FDA. See the final approved prescribing information for dabrafenib and trametinib accompanying the approval letter for more information.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The safe use of dabrafenib in combination with trametinib can be adequately implemented in the postmarketing setting without issuing a REMS for this drug product. The product label for dabrafenib in combination with trametinib includes information on common and clinically significant adverse reactions that have been observed across the drug class. Product labeling also includes dose modification and management guidelines for these events. Risk management based on labeling and routine pharmacovigilance is expected to ensure the safe use of dabrafenib in combination with trametinib.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The clinical review team recommends issuing the following postmarketing requirements (PMRs) and postmarketing commitment (PMC).

Clinical PMR:

1. Conduct a clinical trial(s) in at least 80 patients with solid tumors with a BRAF V600E mutation to verify and describe the clinical benefit of dabrafenib in combination with trametinib, through more precise estimation of the overall response rate and mature response duration. Include patients with unresectable or metastatic solid tumors with a BRAF V600E mutation from the ongoing trial and from a prospectively conducted trial (which will exclude patients with melanoma, non-small cell lung cancer, anaplastic thyroid cancer, biliary tract cancer, gliomas and colorectal cancer). Follow all patients for at least 6 months from the onset of response to characterize the response rate and duration.

2. Develop age appropriate pediatric formulations (dabrafenib dispersible tablets for oral suspension, and trametinib powder for oral solution), and evaluate these in Study CDRB436G2201 ("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)").

3. Conduct Study CDRB436G2201 ("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]) to confirm safety and efficacy in pediatric patients with glioma one year of age and above.

Clinical/CDRH PMC:

1. Commitment to establish, through the use of clinical trial data, an in-vitro diagnostic device that is essential to the safe and effective use of dabrafenib and trametinib for patients with BRAF V600E mutations in solid tumor specimens, excluding colorectal cancer.

14 Division Director (Clinical)

I agree with the review teams' recommendations regarding the approvability of this application. As stated in Section 1 and Section 8.1.4, the recommendation considers treatment effects observed to-date not just in the trials submitted for this application, but also previous trials conducted (and reviewed) in patients with melanoma, lung cancer, and thyroid cancer. Anti-tumor activity has also been observed in different hematological malignancies (which were not included in this application).

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 _____

15 Office Director (or designated signatory authority)

Not applicable for this efficacy supplement.

X

16 Appendices

16.1. References

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16.2. Financial Disclosure

The Applicant's Position:

As pre-agreed with FDA, studies A2102, X2101 and XUS35T 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. Certification was provided for 628/642 (97.8%) investigators in Study X2201; one investigator (0.2%) had financial information to disclose (summarized in Table 101); this investigator constituted 1 of the total 206 enrolled patients in the trial (0.5%). Certification was provided for 257/259 (99.2%) investigators listed in Study A2102, for 252/253 (99.2%) investigators listed in Study X2101 and for all 55 investigators (100%) listed in Study XUS35T. No investigators from studies A2102, X2101 and XUS35T had financial arrangements or interests to disclose.

Table 101 Applicant - Summary of Financial Disclosures from Study BRF117019 (X2201)

(b) (6)

The FDA's Assessment:

There were 642 Investigators, 265 Investigators, 259 Investigators, and 55 Investigators at studies X2201, A2102, X2101, and XUS35T, respectively, at sites that enrolled patients. FDA agrees with the Applicant's assessment as stated above.

Covered Clinical Study (Name and/or Number):* DRB436X2201

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 642		
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): 1		
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: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 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):* DRB436A2102

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

		Applicant)
Total number of investigators identified: 259		
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)

Covered Clinical Study (Name and/or Number):* TMT212X2101

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: 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)

Covered Clinical Study (Name and/or Number):* TMT212XUS35T

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 55		
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: NCI, GSK, 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)

16.3. Nonclinical Pharmacology/Toxicology

Data:
No new information is provided in the current submission.

16.4. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

19.4.1. Pharmacometrics Assessment

The PopPK models for dabrafenib and trametinib were previously established based on both monotherapy and combination treatment in adult population. The Applicant updated the PopPK models with the PK data from pediatric patients ages 6 to 17 years old from the 3 clinical studies of dabrafenib and trametinib in pediatric patients (Table 102).

Table 102 FDA – Pediatric studies included in PopPK analysis for dabrafenib and trametinib

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 63 pediatric 6 to 17 year old patients	Dabrafenib and its metabolites	D1: 0.5, 2, 4 h after dose; D15: predose, 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 trametinib+dabrafenib combination (N ~ 18); Part D: expansion with trametinib+dabrafenib combination (N ~ 20 with LGG and 10 with LCH)	N=133, with 21 older than 12 years receiving trametinib alone 28 subjects between 6 and 11 year olds receiving trametinib alone; 17 older than 12 years receiving combination, and 15 between 6 and 11 year olds receiving combination	dabrafenib and its metabolites, trametinib	D1: 0.5, 2, 4 h after dose; D15: predose, 0.5, 1, 2, 3, 4, 6, 8 h after dose; D22: predose
CDRB436G2201	trametinib+dabrafenib combination (N ~ 40);	N=13 older than 12 years with PK, N=1 between 6 and 11 years old	dabrafenib and its metabolites, trametinib	D1: 0.5, 2, 4 h after dose; D15: predose, 0.5, 1, 2, 3, 4, 6, 8 h after dose; D22: predose

*: The most detailed schedule is listed when multiple schedules were present in the design.

Source: Applicant's PopPK analysis report. Table 5-2, page 15.

The previously established adult PopPK final models served as the base models. For both pediatric PopPK analyses for dabrafenib, and trametinib, the Applicant utilized a Bayesian approach to estimate PK parameters for the pediatric patients leveraging the previous knowledge of dabrafenib and trametinib PopPK obtained from a large adult dataset. For model development, PK data from both liquid and solid formulations of dabrafenib and trametinib were used. The detailed review for each drug is in following sections.

16.4.1.1. Dabrafenib PopPK Analysis for Pediatric Patients

Applicant's PopPK analysis for Dabrafenib

Previous PopPK model based on adult data: Dabrafenib PK was described using 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). Accounting for the autoinduction of the metabolism of dabrafenib via CYP2C8 and CYP3A4, the CL_{ind}/F is described using an empirical exponential function of time governed by two parameters, maximum inducible clearance (CLind,ss/F) and time to reach 50% (T_{50}) of CLind,ss/F.

$$CL/F = CL_0/F + CL_{ind}/F$$, where

$$\frac{CL_{ind}}{F} = \frac{CL_{ind,ss}}{F} \times \left(\frac{DOSE \times F_1}{150}\right)^{\alpha} \times \left(1 - e^{-\frac{ln2}{T_{50}} \times t}\right)$$, where t stands for time elapsed from the 1st dose of dabrafenib. Term α represents the power of dependence of $CL_{ind,ss}/F$ on absorbed dose (DOSE× F1), where F1= relative bioavailability of gelatin capsule to HPMC

capsule which were used for the adult model development. Sex and weight (reference value is 80 kg) were significant covariates on the CL/F, and dose was a significant covariate on $CL_{ind,ss}$/F. Weight was also a significant covariate on the central volume (Vc/F) and intercompartmental clearance (Q/F). Use of trametinib was a covariate on CLind,ss/F.

Pediatric PopPK analysis*:* A Bayesian approach was used to estimate PK parameter for dabrafenib in the pediatric patients ages 6 to 17 years old from the three pooled studies. For the parameters that were included in the previous PopPK models, the previous estimates were used as weakly informative priors (with assuming ~50% [%CV]). In general, for those parameters that were newly incorporated to represent covariate effects, noninformative priors were assumed (Table 103). The relative BA (rBA) of liquid formulation with the solid dabrafenib was set to 0.8, which was estimated from the ratio of AUC from the clinical study report [CDRB436G2101].

Table 103 FDA – Priors used in the Bayesian modeling for the PopPK for dabrafenib

Parameter	Notation	Prior	Variance to prior fixed effect	Degree of freedom to prior of random effect	Informativeness of prior and rationale
Fixed effects					
Apparent base clearance	CL_0/F (L/h)	16.7	69.72	NA	Moderate (50% CV)
Apparent central volume	Vc/F (L)	58.5	855.56	NA	Moderate (50% CV)
Apparent intercompartmental clearance	Q/F (L/h)	4.63	5.36	NA	Moderate (50% CV)
Apparent peripheral volume	Vp/F (L)	197	1	NA	High
Absorption lag time	ALAG1 (h)	0.415	0.04	NA	Moderate (50% CV)
Absorption rate constant	Ka (1/h)	1.22	0.37	NA	Moderate (50% CV)
Apparent maximum inducible clearance at steady state	$CL_{ind,ss}$/F (L/h)	18.6	86.49	NA	Moderate (50% CV)
Power of dependence of $CL_{IND,SS}$/F on absorbed dose	Alpha	1.02	0.26	NA	Moderate (50% CV)
Time to reach 50% of $CL_{ind,ss}$/F	T_{50} (h)	60.7	921.12	NA	Moderate (50% CV)
Relative bioavailability of liquid formulation vs. capsule formulation	F (-)	0.8	0.001	NA	High
Effect of weight on total apparent clearance	CLWT	0.300	0.02	NA	Moderate (50% CV)
Effect of sex on total apparent clearance	CLSEX	0.899	0.01	NA	High
Effect of weight on Vc/F	VcWT	0.593	0.09	NA	Moderate (50% CV)
Effect of weight on Q/F	QWT	1.06	0.28	NA	Moderate (50% CV)
Effect of combination with trametinib on $CL_{IND,SS}$/F	CL_{COMBO}	0.625	0.098	NA	Moderate (50% CV)
Random effects					
Variance of CL_0/F	ω^2_{CL}	0.362	NA	4	Weak
Variance of Vc/F	ω^2_{Vc}	0.298	NA	4	Weak
Covariance of CL_0/F and Vc/F	$\omega_{CL}\omega_{Vc}$	0.304	NA	4	Weak
Variance of Q/F	ω^2_{Q}	0.760	NA	4	Weak
Variance of Ka	ω^2_{Ka}	1.18	NA	4	Weak

Source: Applicant's PopPK analysis report. Table 6-5, page 25.

Data: A total of 1161 dabrafenib PK observations across 109 patients (32 patients in X2101, 14 patients in G2201, and 63 patients in A2102) were used for the model development. Mean (range) of body weight and age were 51.3 (15, 155.6) kg and 12.2 (6, 17) years old. A total of 63

patients (58%) received dabrafenib as monotherapy, and 46 patients (42%) received dabrafenib in combination with trametinib. Concentrations below the limit of quantification were not used in modeling (3.38% of concentrations in X2101, 2.58% of concentrations in G2201, and 0.59% of concentrations in A2102).

Covariates: The following pre-specified covariates and covariate-parameter relations to be evaluated or reevaluated: 1) the effect of body weight (WT) on apparent central volume, total apparent clearance, and apparent intercompartmental clearance; 2) the effect of combination with trametinib on apparent maximum inducible clearance at steady state; and 3) the effect of sex on total apparent clearance was kept fixed to the values from the adult model.

Results: The parameters updated by the PopPK model with the data from the three pediatric studies are listed in Table 104. Three Markov chain Monte Carlo (MCMC) chains were run with different sets of initial values for fixed effect parameters and the trace plots for the 3 chains show that the three chains were adequately mixed. In Gelman-Rubin test, the point estimates and corresponding upper confidence boundaries of potential scale reduction factor (PSRF) were close to 1. Standard goodness of fit (GOF) plots for all dabrafenib PK, GOF plots stratified by combination and formulation type, and visual predictive check (VPC) plots are presented in Figure 15, Figure 16, and Figure 17, respectively.

Table 104 FDA – Dabrafenib parameter posteriors updated by the pediatric PopPK model

Parameter Name	Mean	SD	Naive SE	Time-series SE	2.5%	25%	50%	75%	97.5%	Effective N	95% Confidence Interval
VP (L)	5.28	Fixed	NA	NA	NA	NA	NA	NA	NA	NA	NA
CLSEX (-)	0.899	Fixed	NA	NA	NA	NA	NA	NA	NA	NA	NA
Formulation (-)	0.8	Fixed	NA	NA	NA	NA	NA	NA	NA	NA	NA
CLbase (L/h)	14.077	1.411	0.007	0.046	11.465	13.095	14.029	14.999	16.966	962	(11.465- 16.966)
VC (L)	48.079	4.730	0.022	0.14	39.433	44.763	47.844	51.158	57.932	1152	(39.433– 57.932)
Q (L/h)	5.303	0.921	0.004	0.024	3.692	4.653	5.237	5.873	7.3	1488	(3.692 - 7.3)
KA (1/h)	1.194	0.094	0	0.002	1.021	1.128	1.189	1.255	1.391	1486	(1.021 - 1.391)
ALAG1 (h)	0.41	0.002	0	0	0.405	0.409	0.411	0.412	0.414	2299	(0.405 - 0.414)
CLindmax (L/h)	19.413	1.304	0.006	0.03	16.893	18.521	19.4	20.284	22.006	1865	(16.893 – 22.006)
Alpha (-)	1.018	0.01	0	0	0.998	1.011	1.018	1.025	1.038	7848	(0.998 - 1.038)
T50 (h)	42.233	17.714	0.084	0.283	15.194	28.914	39.967	52.939	82.848	3920	(15.194 - 82.848)
WT_CL (-)	0.221	0.081	0	0.002	0.066	0.165	0.221	0.276	0.381	1120	(0.066 - 0.381)
WT_Q (-)	1.277	0.222	0.001	0.006	0.834	1.128	1.281	1.428	1.705	1496	(0.834 - 1.705)
WT_VC (-)	0.662	0.126	0.001	0.003	0.419	0.578	0.662	0.747	0.912	1330	(0.419 – 0.912)
Combo_CLind (-)	0.716	0.066	0	0.001	0.592	0.67	0.714	0.76	0.849	2035	(0.592 - 0.849)
ω^2_{CL}	0.441	0.084	0	0.001	0.301	0.381	0.432	0.491	0.63	3388	(0.301 - 0.63)
ω^2_{Vc}	0.262	0.064	0	0.002	0.16	0.217	0.254	0.299	0.409	1559	(0.16 - 0.409)
$\omega_{CL}\omega_{Vc}$	0.317	0.065	0	0.001	0.208	0.271	0.311	0.356	0.463	2368	(0.208 - 0.463)
ω^2_{Q}	0.668	0.143	0.001	0.002	0.432	0.567	0.653	0.753	0.986	5828	(0.432 – 0.986)
ω^2_{Ka}	0.961	0.175	0.001	0.002	0.668	0.837	0.944	1.066	1.352	6961	(0.668– 1.352)
SIGMA.1.1.	0.314	0.018	0	0	0.28	0.302	0.313	0.326	0.352	11839	(0.28 - 0.352)
MCMCOBJ	13185.531	51.498	0.243	1.06	13086.816	13150.505	13184.967	13219.783	13289.075	2406	(13086.816 – 13289.075)
Model#	runA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

‡: statistics summarized (using the coda package) from pooled Bayesian posterior samples from 3 chains with 15000 samples per chain. SD, standard deviation; naïve SE, standard error without consideration of autocorrelation within a chain; time-series SE, standard error with consideration of autocorrelation; effective N, posterior sample size void of autocorrelation; 95% CI, 2.5th – 97.5th percentiles of the posterior samples.

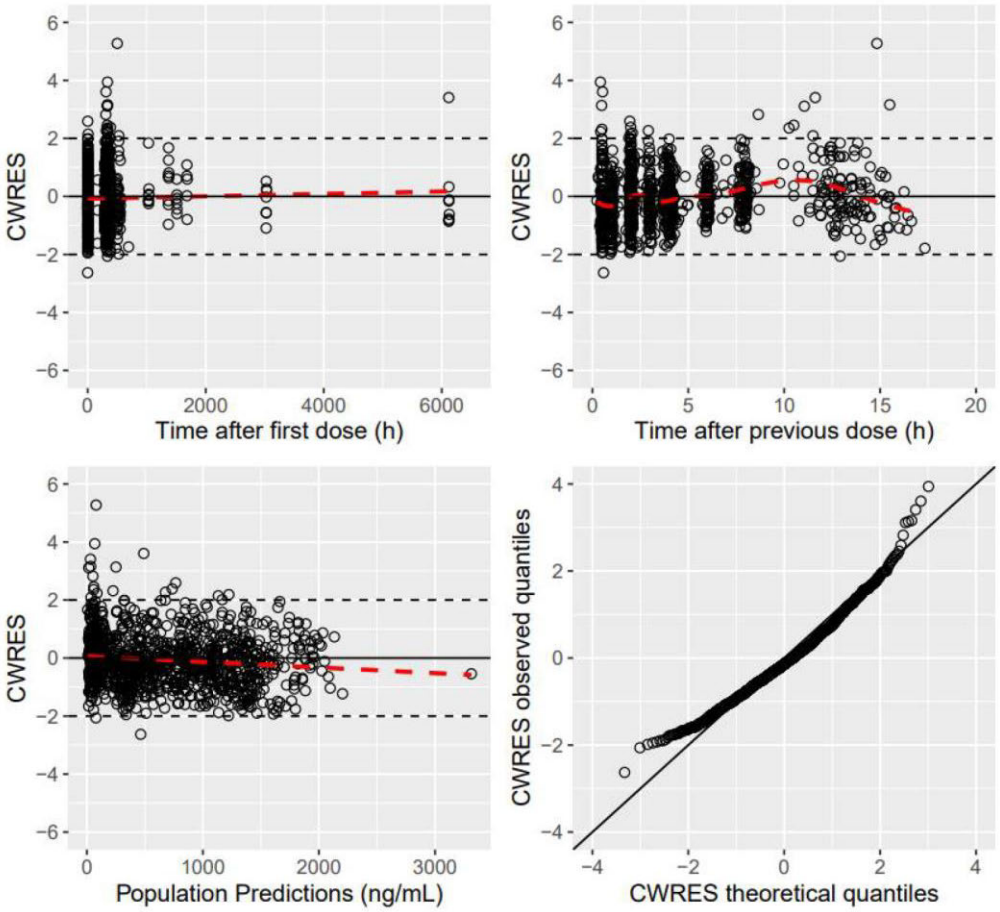
#: parameter estimate statistically insignificant, i.e., 95% CI includes the null value;

SIGMA.1.1. is for proportional error

All parameters in the form of covariate_PK parameter are parameters representing covariate effects. The dashes in parentheses indicate the related parameters are unitless.

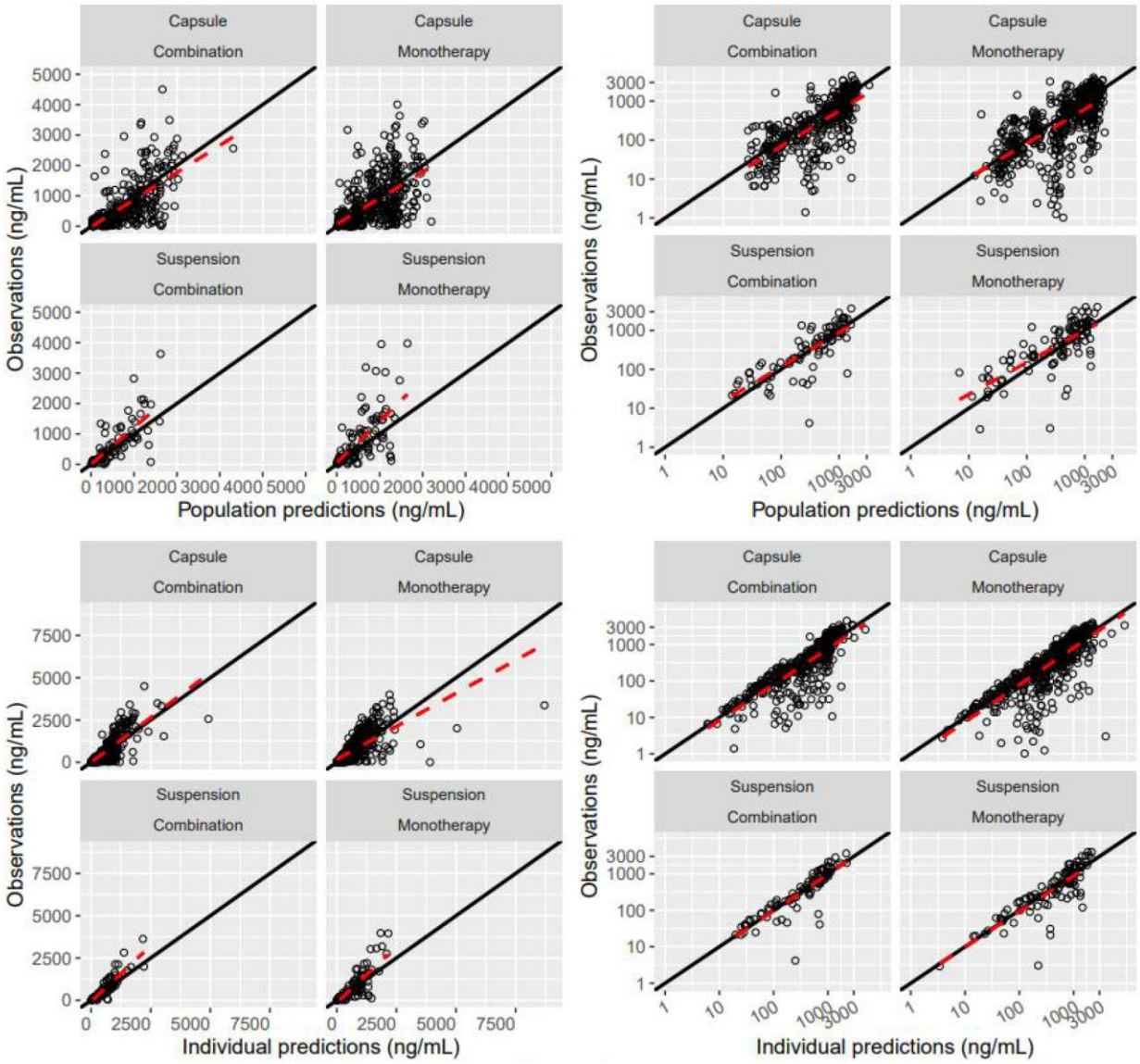
Source: Applicant's PopPK analysis report. Table 7-3, page 41-42.

Figure 15 FDA - Residual Based GOF Plots of Dabrafenib Final PopPK Model



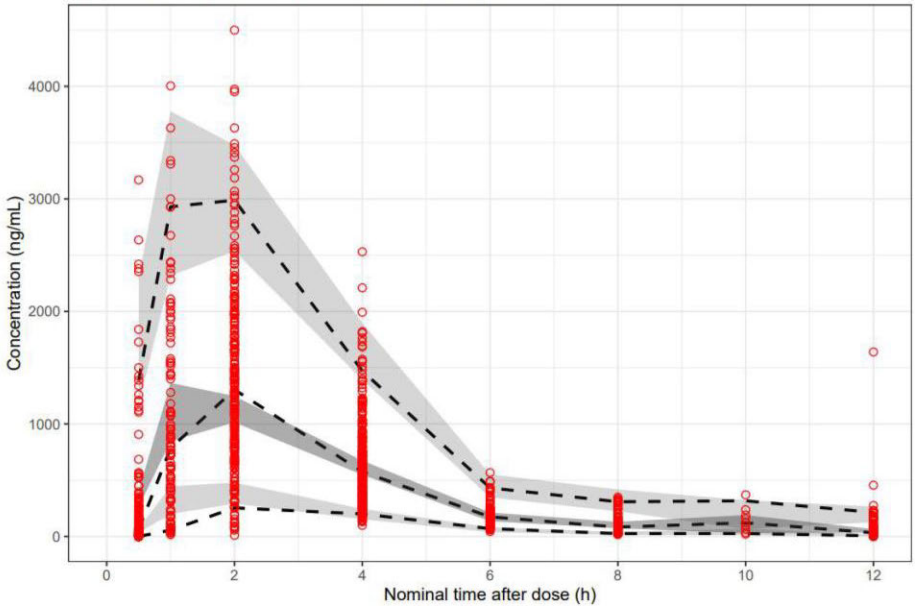
Source: Applicant's PopPK analysis report. Figure 7-14, page 50.

Figure 16 FDA - GOF Plots of Dabrafenib PK Stratification and Formulation Type (left figures-linear, right figures-log scale)



Source: Applicant's PopPK analysis report. Figure 7-12, page 48.

Figure 17 FDA - Observed and VPC-Simulated Dabrafenib Concentration Profiles



Source: Applicant's PopPK analysis report. Figure 7-15, page 51.

Reviewer's assessment on dabrafenib PopPK analysis

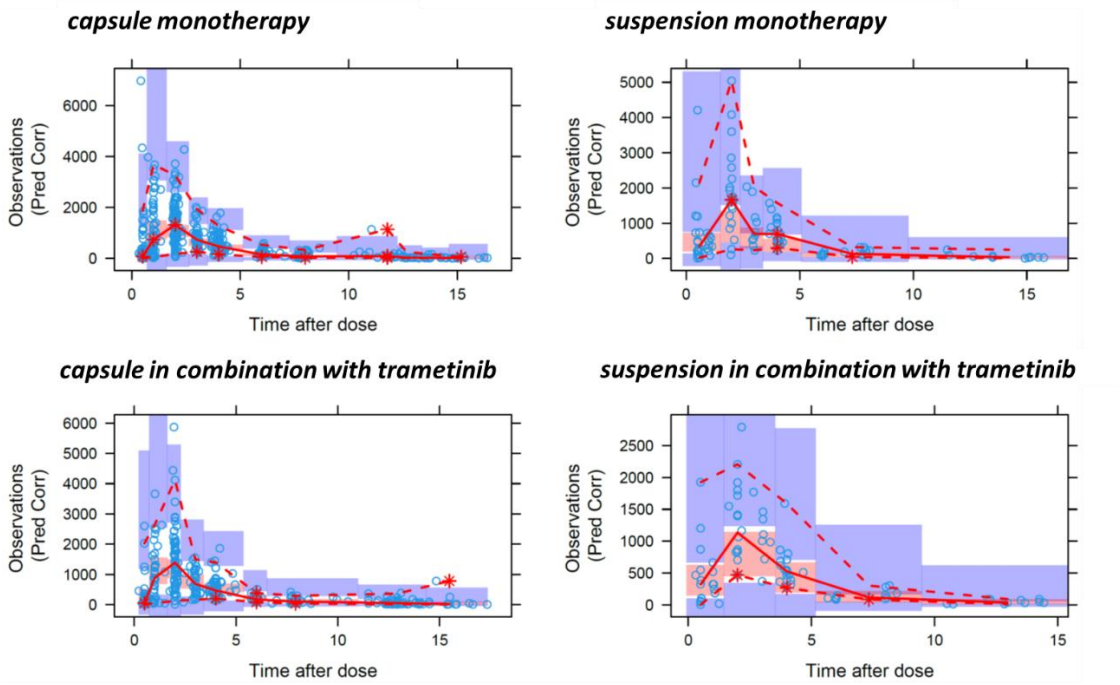
The Applicant's final PopPK model generally describes the PK of pediatric patients ages 6 to 17 years old taking dabrafenib capsule formulation. However, the model tends to underpredict dabrafenib concentration following administration of suspension. Fixing rBA of 0.8 by leveraging the adult rBA data does not appear to adequately capture formulation effect on PK in pediatric patients. With emerging data with the suspension formulation, the formulation effect in pediatric patients should be further characterized. With the current submission, the Applicant proposed the use of only capsule formulation in pediatric patients (ages 6 to 17 years old) and used this model to simulate dabrafenib exposures following capsule formulation. Therefore, the reviewer conducted sensitivity PopPK analysis and simulations to evaluate sensitivity of parameter estimates and to verify the Applicant's prediction of dabrafenib exposures to assess the pediatric dosing regimen.

The reviewer's assessments are summarized below:

- No notable difference in PopPK parameters between pediatric and adult patients was observed: the mean posteriors for PopPK parameters based on pediatric PK data are generally similar to the mean priors for adult PopPK parameters. The baseline apparent CL (CL/F) for the reference weight (80 kg) is 14.1 L/h in pediatric patients (vs. 16.7 L/h in adult popPK analysis).

- Based on the GOF plots, the model generally well describes the observed data with capsule formulation both as monotherapy and combination therapy. However, the model tends to underpredict with suspension formulation as both monotherapy and in combination with trametinib.
- The Applicant's provided VPC plots were generated based on all data. Since various dose levels were studied in the pediatric studies, prediction corrected VPC (pcVPC) is more appropriate diagnostic to generate visual predictive check. In the reviewer's pcVPC plot stratified by formulation and combination status (Figure 18), the simulation-based prediction generally captures the central tendency and variability of the observed dabrafenib concentrations with capsule formulation. As noted in GOF plots, there is slight underprediction with suspension formulation.

Figure 18 FDA - Prediction Corrected VPC for the Final PopPK Model for Dabrafenib by Formulation and Combination Status



Source: Reviewer's plots

- The weight effect on apparent CL is small with the estimated allometric exponent of 0.221, which suggests that a higher mg/kg dose would be needed in pediatric patients to achieve similar exposures as adult. The magnitudes of sex and formulations effect were fixed in the modeling based on the previous adult PopPK analysis and the result from the relative BA study (CDRB436G2101, F1 = 0.8 for suspension), respectively. Covariate-

IIV (ETAs) plots do not show an apparent bias ETAs for CL, Vc, Q, and Ka across BWT, age, sex, and combination status, except for the skewed distribution of ETA for CL with suspension.

- To examine sensitivity of the parameter estimates to the underprediction with suspension noted in the Applicant's model, the reviewer conducted a sensitivity analysis by estimating F1 for suspension (instead of fixing as 0.8). In this analysis, F1 was estimated to be 1.21 for suspension (vs. capsule formulation) with a decrease in OFV and IIV for CLbase, and an improvement in ETA for CL-formulation. Other parameter estimates remained similar to the Applicant's model with most change (10% increase in CLbase). The reviewer used this model to perform sensitivity simulations to project dabrafenib exposures at the proposed dose regimen for pediatric patients (See Section 16.4.1.3. PopPK simulations for pediatric dosing regimen).

	Applicant's final model OFV = 13189		Reviewer's sensitivity run OFV = 13182	
Parameters	Estimates	IIV (%CV)	Estimates	IIV (%CV)
CLbase, L/h	13.6	75.2%	14.9	68.8%
Vc, L	47.5	54.5%	48.4	53.9%
Vp, L	196.4 FIX	-	196.4 FIX	-
Q, L/h	5.31	97.4%	5.10	100.3%
Ka, 1/h	1.19	126.4%	1.17	125%
ALAG1, h	0.41	-	0.41	-
Emax of CLind	19.5	-	18.3	-
Alpha	1.02	-	1.02	-
T_{50}, h	38.1	-	40.5	-
WT on CL	0.22	-	0.19	-
WT on Q	1.28	-	1.12	-
WT on Vc	0.657	-	0.591	-
Sex on CL	0.899 FIX	-	0.899 FIX	-
Combo on CL	0.713	-	0.703	-
F1 for suspension	**0.8 FIX**	**-**	**1.21**	**-**
$\omega_{CL}\omega_{Vc}$	0.319		0.292	
Prop error	0.315	-	0.315	-
Additive error	1 FIX		1 FIX	
%CV for IIV was calculated by sqrt(exp(ω^2)-1).				

16.4.1.2. Trametinib PopPK analysis for Pediatric Patients

Applicant's PopPK analysis for Trametinib

Previous PopPK model based on adult data: The PopPK of trametinib was described using a two-compartment model with dual sequential 1st order absorption (Ka1, Ka2) and 1st order elimination (CL/F). Sex and weight were significant covariates on CL/F, and weight was also a significant covariate on Q/F. The reference weight used in the modeling was 79 kg. Use of dabrafenib, yes or no, was a covariate on the relative bioavailability (rBA) of trametinib, reflecting the effect of dabrafenib on the PK of trametinib.

Pediatric PopPK analysis: A Bayesian approach was used to estimate PK parameter for trametinib in pediatric patients ages 6 to 17 years old from X2101 and G2201 (only HGG cohort). For those parameters that were in the previous PopPK models, previous estimates (Table 105) were used as weakly informative priors (with ~50% coefficient of variance, CV, assumed). The relative bioavailability (rBA) of liquid formulation with respect to the solid formulation for trametinib was set to the value (rBA=1) estimated from the ratio of AUC from the available clinical study reports [MEK115892].

Table 105 FDA – Priors used in the Bayesian modeling for trametinib

Parameter	Notation	Prior	Variance to prior fixed effect	Degree of freedom to prior of random effect	Informativeness of prior and rationale
Apparent clearance	CL/F (L/h)	5.07	6.43	NA	Moderate (50% CV)
Apparent central volume	Vc/F (L)	184	8464	NA	Moderate (50% CV)
Apparent intercompartmental clearance	Q/F (L/h)	60	1	NA	Fixed
Apparent peripheral volume	Vp/F (L)	433	46872	NA	Moderate (50% CV)
Absorption rate constant 1	Ka1 (1/h)	0.134	0.0045	NA	Moderate (50% CV)
Absorption rate constant 2	Ka2 (1/h)	1.55	0.6	NA	Moderate (50% CV)
Time when Ka1 transitions to Ka2	MTime (h)	0.404	0.041	NA	Moderate (50% CV)
Effect of weight on CL/F	WTCL	0.194	0.0094	NA	Moderate (50% CV)
Effect of sex on CL/F	SEXCL	1.24	0.384	NA	Moderate (50% CV)
Effect of weight on VC/F	WTVC	1	1	NA	Weak (100% CV)
Effect of weight on VP/F	WTVP	1	1	NA	Weak (100% CV)
Effect of weight on Q/F	WTQ	3.30	0.72	NA	Moderate (50% CV)
Effect of combination with dabrafenib on relative bioavailability F1	F1COMBO	0.876	0.192	NA	Moderate (50% CV)
Effect of formulation on F1	FORMF1	1	0.01		Fixed
Effect of formulation on Ka2	FORMKa2	1	0.1		High (30% CV)
Variance parameter	M	0.1	0.001*	NA	Fixed
Variance of CL/F	ω^2_{CL}	0.0603	NA	4	Weak
Variance of Vc/F	ω^2_{Vc}	0.809	NA	4	Weak
Covariance of CL/F and Vc/F	$\omega_{CL}\omega_{Vc}$	0.124	NA	4	Weak
Variance of Q/F	ω^2_{Q}	1.48	NA	4	Fixed
Variance of Vp/F	ω^2_{Vp}	0.0225	NA	4	Weak
Variance of Ka1	ω^2_{Ka1}	0.941	NA	4	Fixed
Variance of Ka2	ω^2_{Ka2}	0.0225	NA	4	Fixed
Variance of MTime	ω^2_{MTIME}	0.0225	NA	4	Fixed

Source: Applicant's PopPK analysis report. Table 6-6, page 26.

Data: A total of 852 trametinib PK observations across 95 patients (81 patients in X2101 study, and 14 patients in G2201) were available for the model development (697 concentrations in X2101 study, and 155 concentrations in G2201 study). Mean (range) of body weight and age were 47.6 (17.7, 155.6) kg and 11.7 (6, 17) years old. A total of 49 patients (52%) received trametinib monotherapy, and 46 patients (48%) received trametinib in combination with dabrafenib. Concentrations below the limit of quantification were not used in modeling (0.09% of concentrations in X2101, and 3.22% of concentrations in G2201, across all age ranges).

Covariates: The following pre-specified covariates and covariate-parameter relations were evaluated or reevaluated:

- BWT on apparent central and peripheral volume (estimated, not previously in the adult model)
- BWT on total apparent clearance, and apparent intercompartmental clearance (re-estimated)
- combination with dabrafenib on rBA (re-estimated)
- sex on apparent clearance (re-estimated)
- rBA of liquid formulation with respect to the solid formulation was fixed to 1
- formulation on absorption rate constant Ka2 (estimated, not previously in the adult model)

Results: The parameters updated by the PopPK model for trametinib with the data from the three pediatric studies are listed in Table 106. Three MCMC chains were run with different sets of initial values for fixed effect parameters and the trace plots for the 3 chains show that the three chains were adequately mixed. In Gelman-Rubin test, the point estimates and corresponding upper confidence boundaries of PSRF were close to 1. Standard GOF plots stratified by combination and formulation type, GOF plots for all trametinib PK data, and VPC plots are presented in Figure 19, Figure 20, and Figure 21, respectively.

Table 106 FDA – Trametinib parameter posteriors and covariate effects updated by the PopPK model with pediatric data

Parameter Name	Mean	SD	Naive SE	Time-series SE	2.5%	25%	50%	75%	97.5%	Effective N	95% Confidence Interval
Q (L/h)	60	Fixed	NA	NA	NA	NA	NA	NA	NA	NA	NA
M (-)	0.1	Fixed	NA	NA	NA	NA	NA	NA	NA	NA	NA
FORMF1 (-)	1	Fixed	NA	NA	NA	NA	NA	NA	NA	NA	NA
CL (L/h)	5.02	0.43	0.002	0.014	4.23	4.72	5.005	5.296	5.912	948	(4.23 - 5.912)
VC (L)	164.186	32.262	0.152	1.013	107.841	141.668	161.691	183.912	234.608	1021	(107.841 - 234.608)
VP (L)	342.986	62.938	0.297	1.706	226.761	300.072	340.263	383.517	472.252	1366	(226.761 - 472.252)
KA1 (1/h)	0.022	0.006	0	0	0.014	0.018	0.022	0.025	0.035	834	(0.014 - 0.035)
KA2 (1/h)	2.055	0.402	0.002	0.01	1.347	1.771	2.027	2.309	2.932	1740	(1.347 - 2.932)
MTIME (h)	0.395	0.03	0	0.001	0.332	0.377	0.397	0.416	0.451	1785	(0.332 - 0.451)
WT_CL (-)	0.397	0.072	0	0.002	0.253	0.349	0.398	0.446	0.537	1220	(0.253 - 0.537)
WT_Q (-)	1.543	0.628	0.003	0.023	0.363	1.131	1.525	1.923	2.848	772	(0.363 - 2.848)
SEX_CL (-)	0.857	0.066	0	0.002	0.73	0.811	0.855	0.9	0.99	1037	(0.73 - 0.99)
COMBO_F1 (-)	0.696	0.047	0	0.002	0.609	0.664	0.695	0.727	0.791	872	(0.609 - 0.791)
FORM_KA2 (-)	1.349	0.246	0.001	0.004	0.896	1.176	1.341	1.509	1.849	4591	(0.896 - 1.849)
WT_VC (-)	0.679	0.243	0.001	0.008	0.237	0.516	0.671	0.829	1.201	931	(0.237 - 1.201)
WT_VP (-)	1.469	0.319	0.002	0.01	0.839	1.26	1.476	1.677	2.091	1025	(0.839 - 2.091)
ω^2_{CL}	0.064	0.018	0	0	0.035	0.051	0.062	0.075	0.106	2734	(0.035 - 0.106)
$\omega_{CL}\omega_{Vc}$	0.076	0.035	0	0.001	0.012	0.052	0.074	0.097	0.151	2568	(0.012 - 0.151)
ω^2_{Vc}	0.476	0.119	0.001	0.002	0.288	0.392	0.461	0.543	0.751	3782	(0.288 - 0.751)
ω^2_{Vp}	0.05	0.049	0	0.002	0.01	0.021	0.035	0.061	0.184	490	(0.01 - 0.184)
SIGMA.1.1.	0.055	0.004	0	0	0.048	0.052	0.055	0.057	0.062	7119	(0.048 - 0.062)
MCMCOBJ	-2025.761	83.279	0.393	3.018	-2180.412	-2084.626	-2027.788	-1970.063	-1857.844	773	(-2180.412 - -1857.844)
Model#	runA7_3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

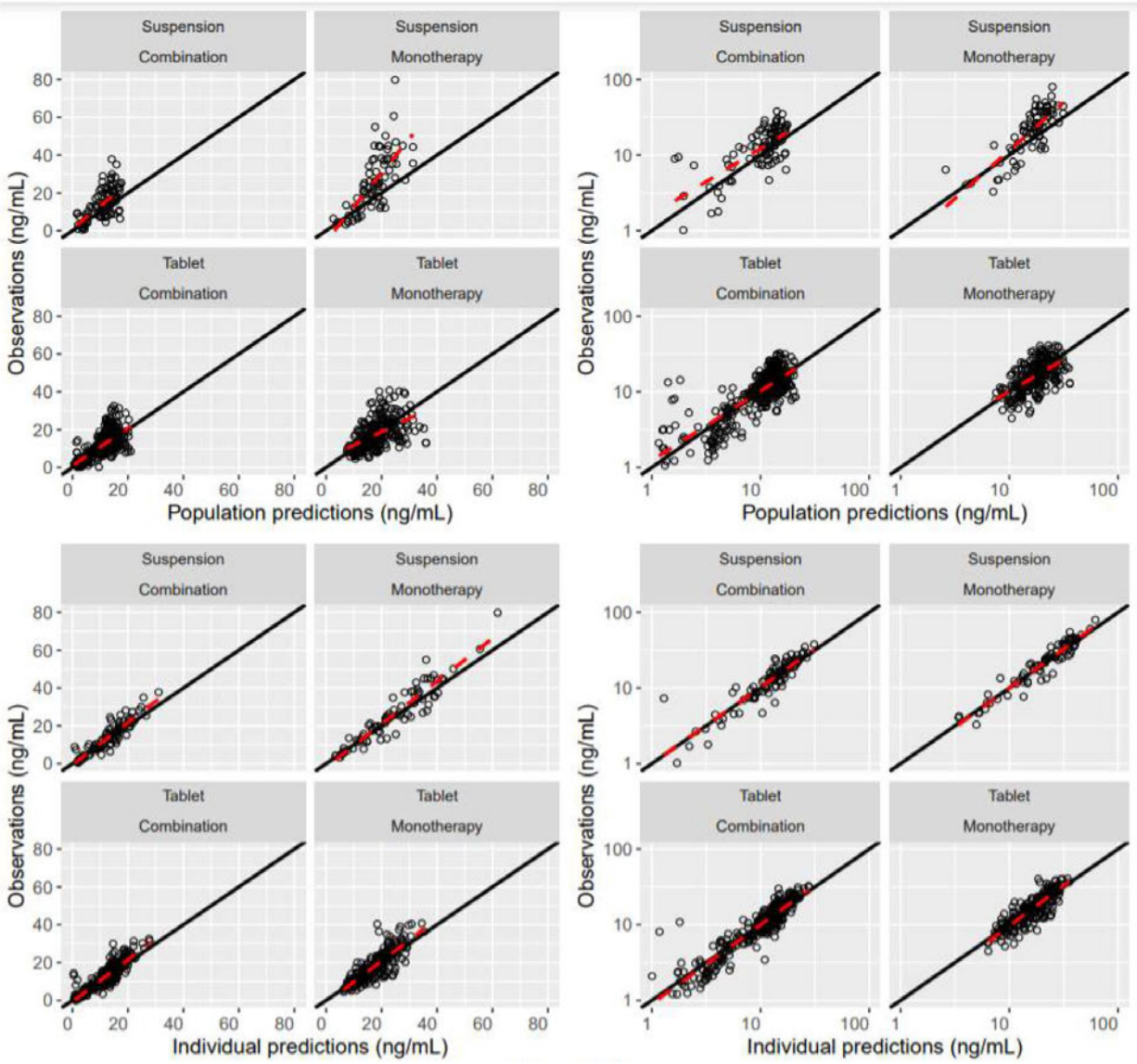
‡: statistics summarized (using the coda package) from pooled Bayesian posterior samples from 3 chains with 15000 samples per chain. SD, standard deviation; naïve SE, standard error without consideration of autocorrelation within a chain; time-series SE, standard error with consideration of autocorrelation; effective N, posterior sample size void of autocorrelation; 95% CI, 2.5th – 97.5th percentiles of the posterior samples.

#: parameter estimate statistically insignificant, i.e., 95% CI includes the null value;

All parameters in the form of covariate_PK parameter are parameters representing covariate effects. The dashes in parentheses indicate the related parameters are unitless. SIGMA.1.1.is the variance of the 1st component of the double exponential error model

Source: Applicant's PopPK analysis report. Table 7-5, page 52-53.

Figure 19 FDA - GOF Plots: Observed vs. PREP, IPRED of trametinib PK Stratified by Combination and Formulation Type

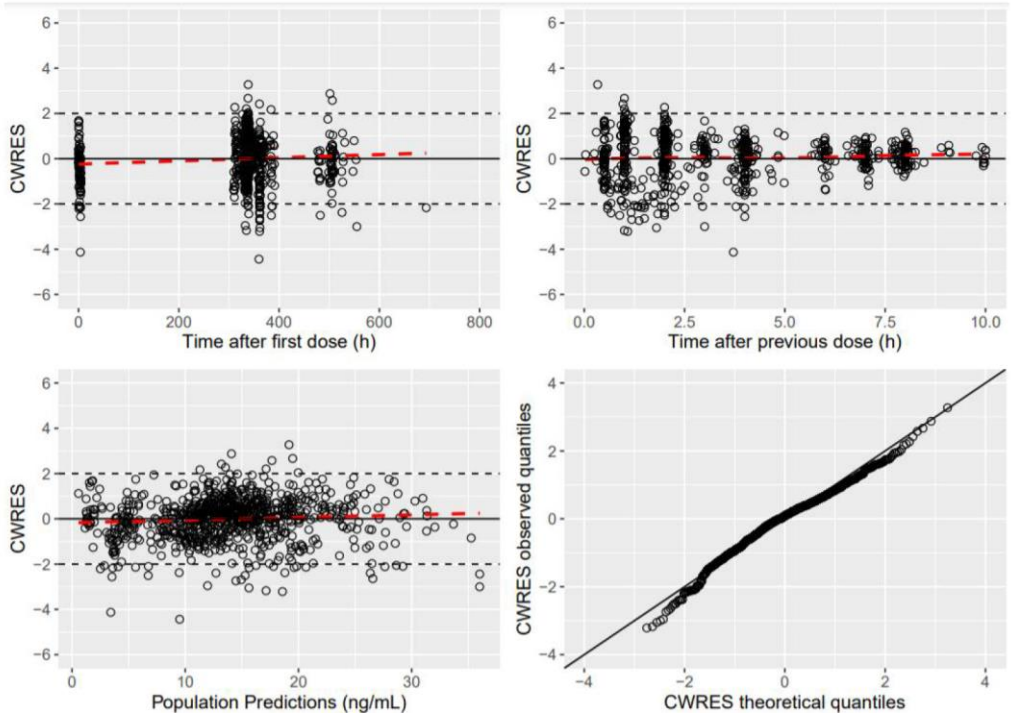


Source: Applicant's PopPK analysis report. Figure 7-19, page 60.

Reviewer's note: thought Applicant's figure noted "suspension", "powder for oral solution" of trametinib was used in the pediatric patients.

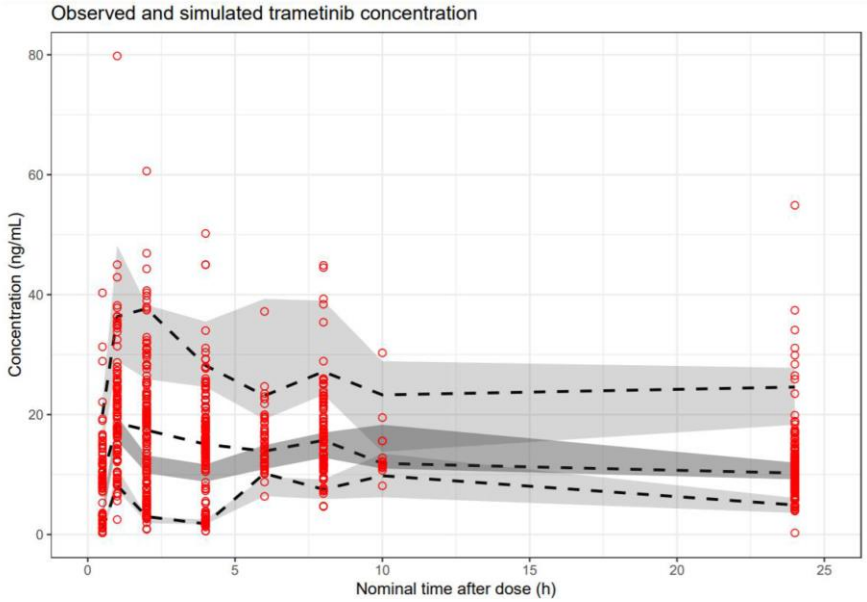
I

Figure 20 FDA - Residual Based Diagnostic of Trametinib PopPK Model



Source: Applicant's PopPK analysis report. Figure 7-21, page 62.

Figure 21 FDA - Observed and VPC_Simulated Dabrafenib Concentration Profiles



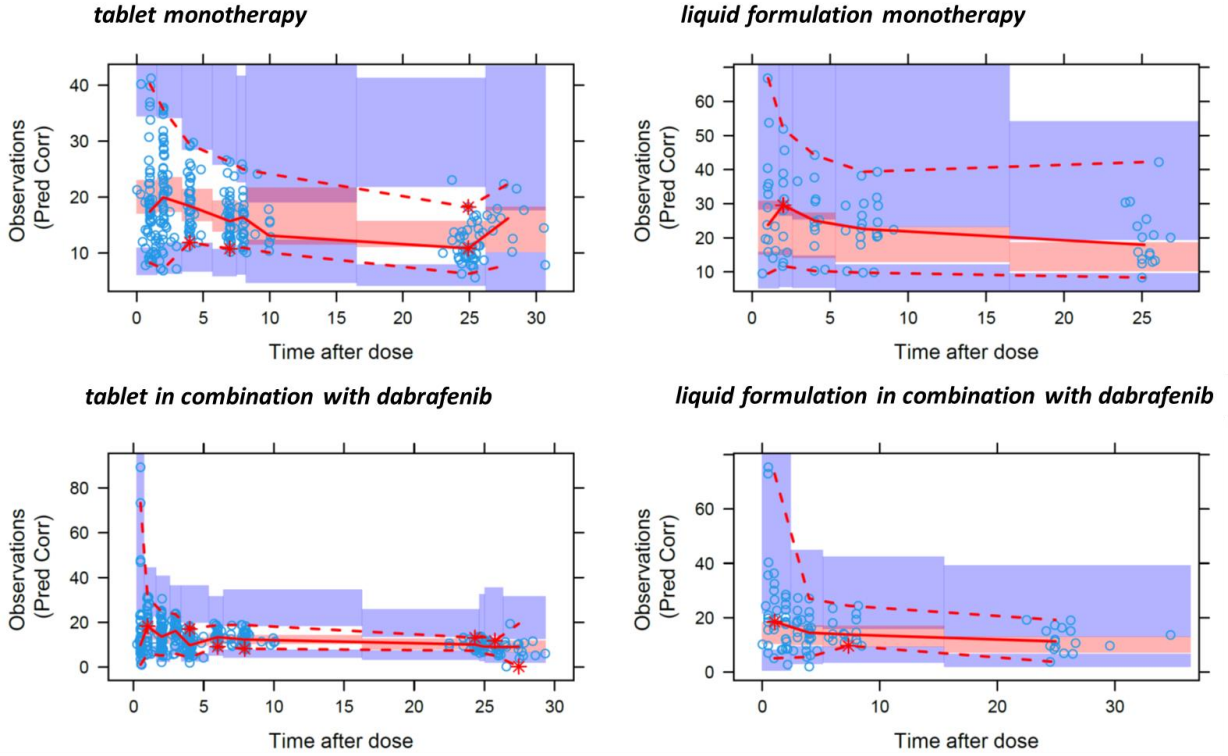
Source: Applicant's PopPK analysis report. Figure 7-22, page 63.

Reviewer's assessment on trametinib PopPK analysis

The Applicant's PopPK model is acceptable to describe the PK of pediatric patients ages 6 to 17 years old taking trametinib tablet formulation. However, the model tends to underpredict at higher trametinib concentrations with liquid formulation as monotherapy. With the current submission, the Applicant proposed the use of solid formulations (i.e., tablets) in pediatric patients (ages 6 to 17 years old). Therefore, the reviewer conducted sensitivity simulations to confirm the Applicant's prediction of trametinib exposures. For further use of this model for describing/simulating PK of trametinib liquid formulation in pediatric patients, formulation effect should be re-evaluated. Reviewer's assessment is summarized below:

- The mean parameter posteriors based on pediatric PK data are generally similar to the parameter priors from adult popPK analysis. Particularly, the apparent CL (CL/F) for the reference weight (79 kg) is 5.02 L/h (vs. 5.07L/h in adult popPK analysis).
- Based on the GOF plots, the model generally well describes the observed data, except for underprediction with liquid formulation administered as monotherapy.
- The Applicant provided VPC plots were generated based on all data. As various dose levels were studied in the pediatric studies, the reviewer generated prediction corrected VPC (pcVPC). In the pcVPC stratified by formulation and combination status (Figure 22), the model prediction generally captures the central tendency and variability of the observed trametinib concentrations except for monotherapy of liquid formulation.

Figure 22 FDA - Precited-corrected VPC plots Stratified by Formulation and Combination Status (Applicant's Trametinib PopPK Model)



Source: Reviewer's analysis.

- Covariate analysis:
  - Body weight-based dosing is reasonable. As the estimated allometric exponent of weight effect was 0.397, a higher mg/kg would be needed in pediatric patients to achieve similar trametinib exposures as in adults. A slight trend of age and ETA for CL was noted but the magnitude (slope) is shallow. Also, age is highly correlated with body weight and use of liquid formulation which are significant covariates and already included in the PopPK model.
  - The effect of combination with dabrafenib on F1 was lower (0.696) compared to that estimated for adult PopPK (0.876). No clear explanation can be made for the discrepancy as the current PopPK analysis includes multiple significant factors that are highly correlated (weight, age, formulation, combination, and dabrafenib dose).
  - Female pediatric patients tend to have 14% lower CL than male pediatric patients.

  - The rBA of liquid formulation with respect to the solid formulation was fixed to 1. Model diagnostics plots showed underprediction and the ETA-covariate plots showed a skewness with liquid formulation.
- The reviewer conducted a sensitivity analysis to assess sensitivity of parameter estimates to the misspecification of formulation effect by estimating F1 for suspension instead of fixing as 1. The results indicated that the parameter estimates from the Applicant's model was not sensitive; however, model fit was generally improved based on OFV, GOF plots, pcVPC, and ETA-formulations plots. The reviewer used this model to perform sensitivity simulations to project trametinib exposures to evaluate pediatric dose regimen for trametinib (See Section 3. PopPK simulations for pediatric dosing regimen).

	Applicant's final model OFV = -2021		Reviewer's sensitivity run OFV = -2043	
Parameters	Estimates	IIV (%CV)	Estimates	IIV (%CV)
CL, L/h	5.02	25.6%	5.05	23.6%
Vc, L	163	77.4%	166	75.2%
Vp, L	340	21.3%	357	19.8%
Q, L/h	60 FIX	184.2% FIX	60 FIX	184.2% FIX
Ka1, 1/h	0.0228	125% FIX	0.0231	125% FIX
Ka2, 1/h	2.06	15.1% FIX	2.08	15.1% FIX
MTIME, h	0.393	15.1% FIX	0.394	15.1% FIX
WT on CL	0.404	-	0.375	-
WT on Q	1.59	-	1.63	-
SEX on CL	0.848	-	0.857	-
COMBO on F1	0.695	-	0.696	-
M	0.1 FIX	-	0.1 FIX	-
F1 for suspension	**1 FIX**	**-**	**1.2**	-
Form on Ka2	1.35	-	1.35	-
WT on Vc	0.655	-	0.614	-
WT on Vp	1.48	-	1.43	-
Prop error	0.0551 FIX	-	0.0551 FIX	-
Additive error	143 FIX	-	143 FIX	-
%CV for IIV was calculated by sqrt(exp(ω^2)-1).				

Source: Reviewer's analysis.

16.4.1.3. PopPK simulations for pediatric dosing regimen

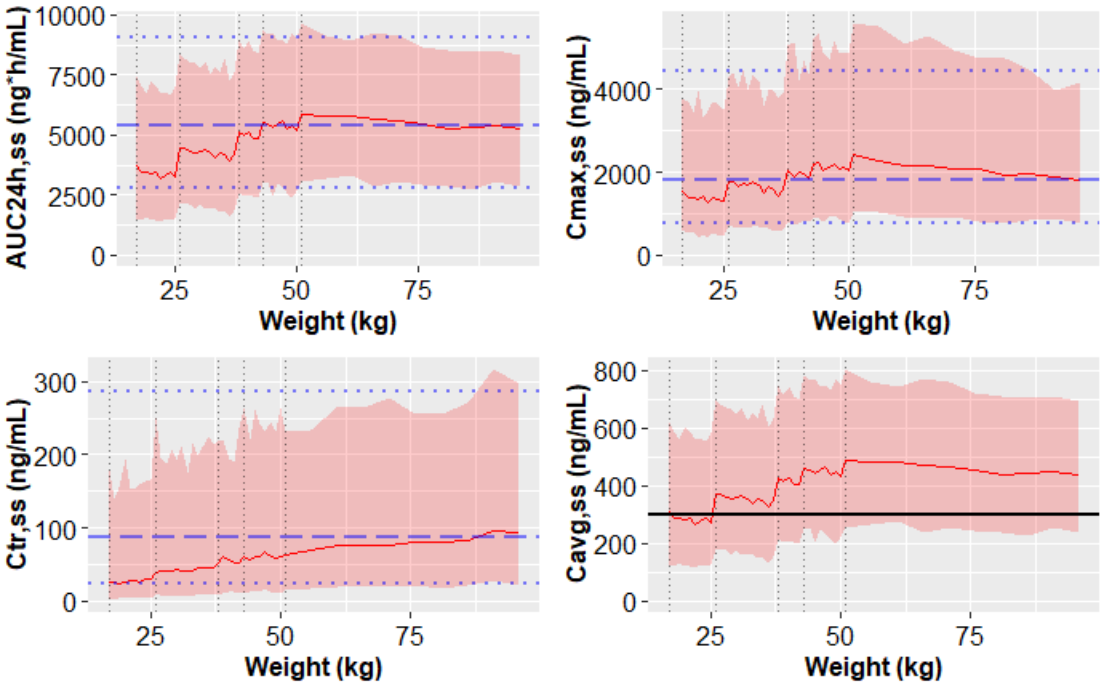
Applicant's proposed dosage for pediatric patients ages 6 to 17 years old

The Applicant performed PopPK simulations at different doses of trametinib tablets and dabrafenib capsules to support the proposed doses of dabrafenib and trametinib in combination in pediatric patients ages 6 to 17 years old. The selection of doses in pediatric patients was based on the doses that yield steady state exposures (C_{max}, C_{trough}, AUC_{tau} [AUC_{0-12h} for dabrafenib; AUC_{0-24h} for trametinib], and Cavg [AUC_{tau} divided by 12 h for dabrafenib; AUC_{tau} divided by 24 h for trametinib]) matching the therapeutic exposures in adult melanoma patients, targeting Cavg of 300 ng/mL for dabrafenib and 10 ng/mL of trametinib. Applicant's predicted exposures following the proposed dosage are presented in Section 6. For the purpose of this submission only solid formulations were simulated, as currently only tablet (trametinib) and capsule (dabrafenib) are available.

Reviewer's assessment on Applicant proposed dosage

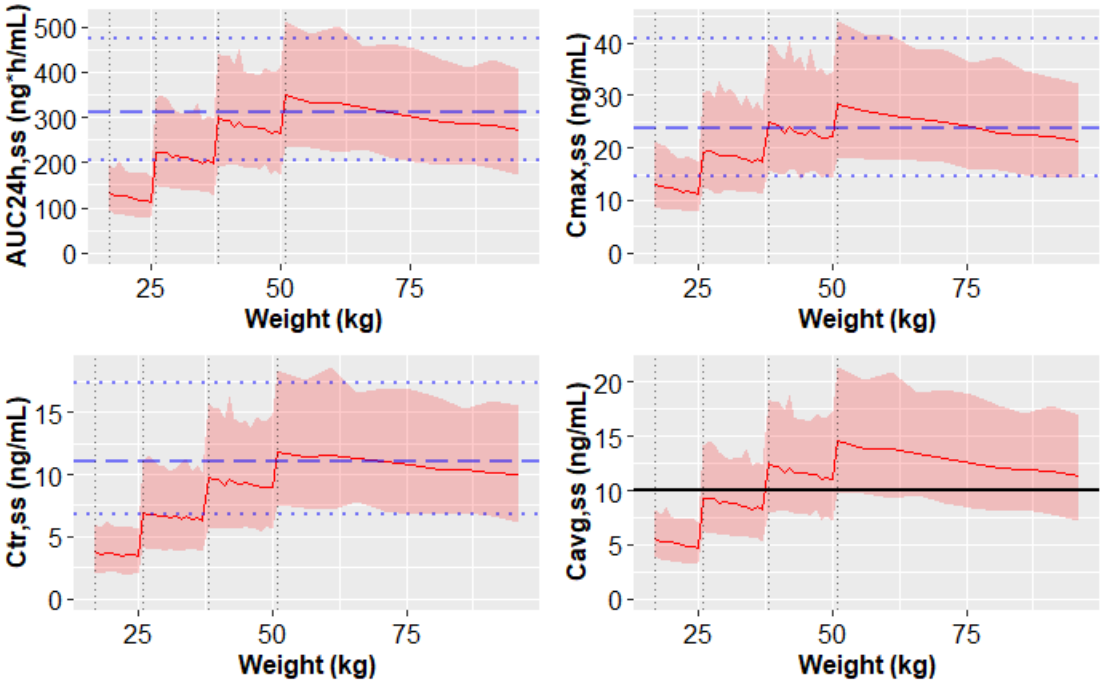
To verify the Applicant's projection of exposures following the proposed dosing regimen, the reviewer conducted sensitivity simulations using the reviewer's sensitivity PopPK models for each drug identified in the assessment of PopPK analysis. The simulations were performed with 300 virtual patients for each whole number of body weight ((b) (4) …50 kg) and for every 5 kg ((b) (4)…100 kg) with male to female ratio of 1:1. All simulations were conducted separately for each drug, with solid formulations only (capsules for dabrafenib, and tablets for trametinib), and in combination of the two drugs. The results are presented by body weight in Figure 23(dabrafenib) and Figure 24(trametinib).

Figure 23 FDA - Simulated Dabrafenib Exposures by Body Weight Following Applicant's Proposed Dosage



Source: Reviewer's analysis. Red solid lines represent geometric mean of simulated exposures (AUC, Cmax, Ctrough, Cavg) and red ribbons represent 5th – 95th percentiles of the simulated exposures. The horizontal blue lines represent 5th percentile, geometric mean, and 95th percentile of the reference adult exposures (AUC, Cmax, Ctrough). For the plot of Cavg, black horizontal dotted line represents the target Cavg (300 ng/mL). Residual unexplained variability (RUV) is only included in the plot of Cmax for adult reference and pediatric predicted exposures.

Figure 24 FDA - Simulated Trametinib Exposures by Body Weight Following Applicant's Proposed Dosage



Source: Reviewer's analysis. Red solid lines represent geometric mean of simulated exposures (AUC, Cmax, Ctrough, Cavg) and red ribbons represent 5th – 95th percentiles of the simulated exposures. The horizontal blue lines represent 5th percentile, geometric mean, and 95th percentile of the reference adult exposures (AUC, Cmax, Ctrough). For the plot of Cavg, black horizontal dotted line represents the target Cavg (300 ng/mL). RUV is only included in the plot of Cmax for adult reference and pediatric predicted exposures.

The reviewer's sensitivity simulations showed similar results as the Applicant's and summarized below:

Trametinib: Following the Applicant's proposed dosage for trametinib (in combination with dabrafenib), the predicted trametinib exposures in pediatric patients (red ribbons) are largely within the predicted adult exposure range (blue dotted lines) for body weight greater than 37 kg. However, the predicted exposures for the weight group (b) (4) are below the lower end of adult reference exposures. Particularly, the mean Cavg for the weight group (b) (4) . The predicted Cavg for weight group 26 to 37 kg is slight lower than the target, greater than 60% of patients are expected to have trametinib Cavg below the target efficacy threshold.

Concerning substantial lower trametinib exposures for weight group (b) (4) the current available PK and safety/efficacy data from Study X2101 are limited to support the proposed dosage for this weigh group and the lack of a lower strengths of solid formulations (tablet for trametinib) does not allow for fine dose adjustments in the lowest weight bracket (b) (4) Potential dose-increase to the next available dose (b) (4) is not supported as there are limited PK and safety experience above the trametinib dose of (b) (4) in pediatric patients.

Concerning potential lower trametinib exposures for weight group (26 to 37 kg), the Applicant provided preliminary PK results from Study G2201: Cavg was similar or above 10 ng/mL in all patients (n=3) in this body-weight group (26 to 37 kg) who received the 1 mg tablet. In 9 patients who received the oral solution formulation at doses of 0.75 to 1 mg, the rBA-corrected Cavg was above the efficacy target of 10 ng/mL in all 9 cases. Taken together with the trametinib PopPK analysis, the proposed trametinib dose for 26 to 37 kg is acceptable.

Dabrafenib: Following the Applicant's proposed dosage for dabrafenib (in combination with trametinib), the predicted dabrafenib exposures in pediatric patients (red ribbons) are largely within the predicted adult exposure range (blue dotted lines). There is a trend of lower exposures with lower body weight (red solid lines): the mean Ctrough and AUC with the lowest body weight (b) (4)

FDA recommended dosage for pediatric patients ages 6 to 17 years old

FDA recommends the following dosage for dabrafenib and trametinib for pediatric patients ages 6 to 17 years old, with two main modifications 1) removal of the dose recommendation for the lowest weight group, and 2) modification of dabrafenib dosage for (b) (4) from the Applicant's proposed dose (b) (4) The FDA recommended dose is presented below. The predicted exposures of the FDA recommended dose are presented in Figure 25 and Figure 26.

Table 107 Dabrafenib: Applicant's Proposed Dose and FDA Recommended Dose

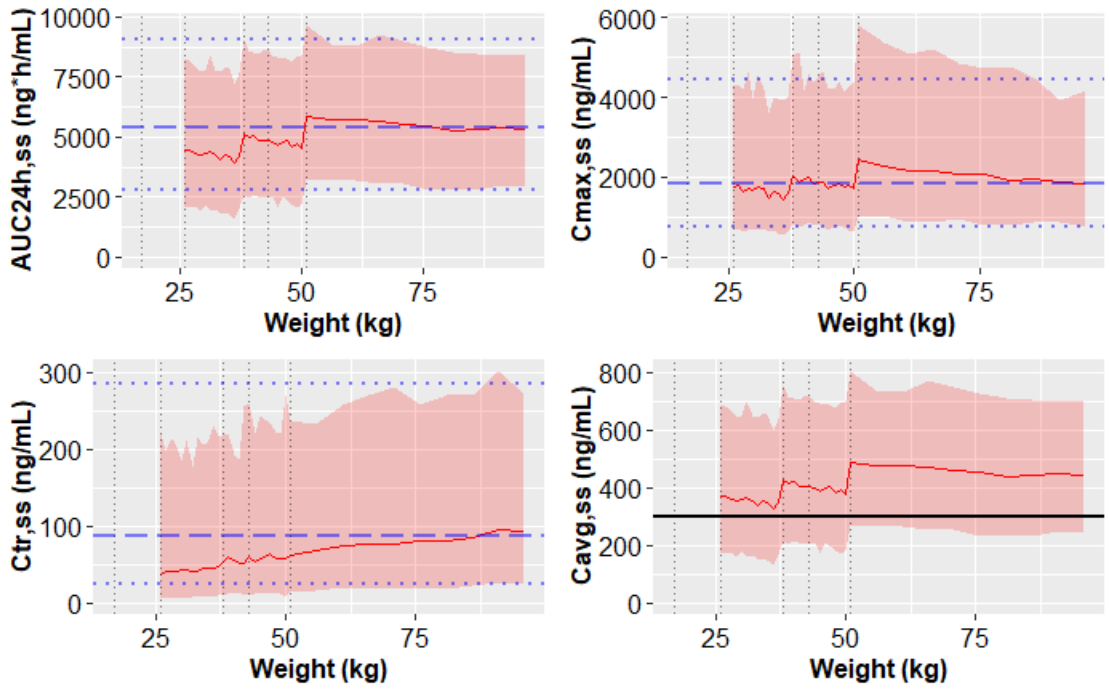
Body weight	**Applicant's proposed dose**	**FDA recommended dose**
(b) (4)		Not recommended
26-37 kg	75 mg BID	75 mg BID
(b) (4)		

[redacted] (b) (4)		
≥51 kg	150 mg BID	150 mg BID

Table 108 Trametinib: Applicant's Proposed Dose and FDA Recommended Dose

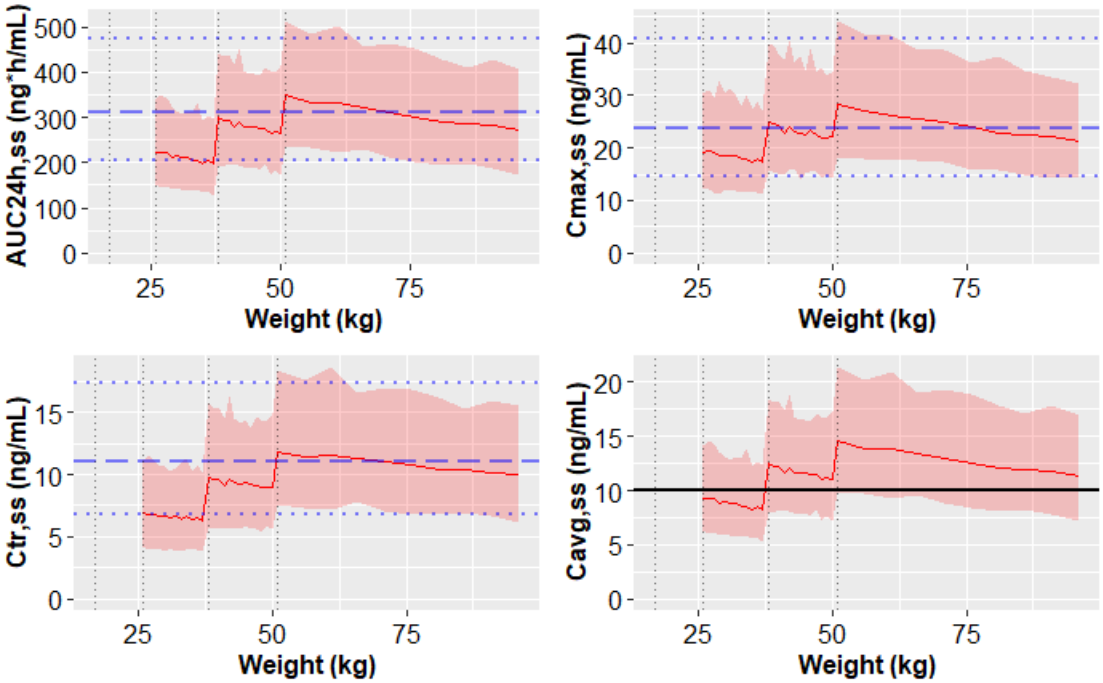
Body weight	Applicant's proposed dose	FDA recommended dose
[redacted] (b) (4)		Not recommended
26-37 kg	1 mg QD	1 mg QD
38-50 kg	1.5 mg QD	1.5 mg QD
≥51 kg	2 mg QD	2 mg QD

Figure 25 FDA - Simulated Dabrafenib Exposures by Body Weight Following FDA Recommended Dosage



Source: Reviewer's analysis. Red solid lines represent geometric mean of simulated exposures (AUC, Cmax, Ctrough, Cavg) and red ribbons represent 5th – 95th percentiles of the simulated exposures. The horizontal blue lines represent 5th percentile, geometric mean, and 95th percentile of the reference adult exposures (AUC, Cmax, Ctrough). For the plot of Cavg, black horizontal dotted line represents the target Cavg (300 ng/mL) for dabrafenib. RUV is only included in the plot of Cmax for adult reference and pediatric predicted exposures.

Figure 26 FDA - Simulated Trametinib Exposures by Body Weight Following FDA Recommended Dosage



Source: Reviewer's analysis. Red solid lines represent geometric mean of simulated exposures (AUC, Cmax, Ctrough, Cavg) and red ribbons represent 5th – 95th percentiles of the simulated exposures. The horizontal blue lines represent 5th percentile, geometric mean, and 95th percentile of the reference adult exposures (AUC, Cmax, Ctrough). For the plot of Cavg, black horizontal dotted line represents the target Cavg (10 ng/mL) for trametinib. RUV is only included in the plot of Cmax for adult reference and pediatric predicted exposures

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Clinical Pharmacology Team Leader	Hong Zhao	Office of Clinical Pharmacology	Sections: 6 and 18	**Select one:** X Authored X Approved
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