



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

09 November 2023
EMA/542043/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Spexotras

International non-proprietary name: Trametinib

Procedure No. EMEA/H/C/005886/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



Table of contents

1. Background information on the procedure	7
1.1. Submission of the dossier.....	7
1.2. Legal basis, dossier content.....	7
1.3. Information on paediatric requirements.....	7
1.4. Information relating to orphan market exclusivity.....	8
1.4.1. Similarity.....	8
1.5. Steps taken for the assessment of the product.....	8
2. Scientific discussion	9
2.1. Problem statement	9
2.1.1. Disease or condition.....	9
2.1.2. Epidemiology	9
2.1.3. Biologic features.....	10
2.1.4. Clinical presentation and prognosis	10
2.1.5. Management.....	11
2.2. About the product	12
2.3. Type of application and aspects on development	13
2.4. Quality aspects	14
2.4.1. Introduction.....	14
2.4.2. Active Substance	14
2.4.3. Finished Medicinal Product.....	17
2.4.4. Discussion on chemical, pharmaceutical and biological aspects.....	19
2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects	20
2.4.6. Recommendation(s) for future quality development	20
2.5. Non-clinical aspects	20
2.5.1. Introduction.....	20
2.5.2. Pharmacology	21
2.5.3. Pharmacokinetics.....	22
2.5.4. Toxicology	23
2.5.5. Ecotoxicity/environmental risk assessment	25
2.5.6. Discussion on non-clinical aspects.....	26
2.5.7. Conclusion on the non-clinical aspects.....	28
2.6. Clinical aspects	28
2.6.1. Introduction.....	28
2.6.2. Clinical pharmacology	33
2.6.3. Discussion on clinical pharmacology.....	47
2.6.4. Conclusions on clinical pharmacology	51
2.6.5. Clinical efficacy	51
2.6.6. Discussion on clinical efficacy.....	86
2.6.7. Conclusions on the clinical efficacy.....	92
2.6.8. Clinical safety.....	92
2.6.9. Discussion on clinical safety	119
2.6.10. Conclusions on the clinical safety	123
2.7. Risk Management Plan (version 19.2)	124

2.7.1. Safety concerns.....	124
2.7.2. Pharmacovigilance plan	124
2.7.3. Risk minimisation measures	125
2.7.4. Conclusion	127
2.8. Pharmacovigilance.....	127
2.8.1. Pharmacovigilance system	127
2.8.2. Periodic Safety Update Reports submission requirements	127
2.9. Product information	127
2.9.1. User consultation	127
3. Benefit-Risk Balance.....	128
3.1. Therapeutic Context	128
3.1.1. Disease or condition.....	128
3.1.2. Available therapies and unmet medical need	128
3.1.3. Main clinical studies	129
3.2. Favourable effects	130
3.3. Uncertainties and limitations about favourable effects	130
3.4. Unfavourable effects.....	131
3.5. Uncertainties and limitations about unfavourable effects	132
3.6. Effects Table.....	132
3.7. Benefit-risk assessment and discussion	135
3.7.1. Importance of favourable and unfavourable effects.....	135
3.7.2. Balance of benefits and risks.....	136
3.7.3. Additional considerations on the benefit-risk balance	136
3.8. Conclusions	137
4. Recommendations	137

List of abbreviations

BOR	best overall response
BRAF	B-Raf proto-oncogene, serine/threonine kinase
CBR	clinical benefit rate
CCNU	lomustine
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
CPP	critical process parameter
C+V	carboplatin plus vincristine
CR	complete response
CRC	colorectal cancer
cuSCC	cutaneous squamous cell carcinoma
DAD	diode array detection
DMSO	dimethyl sulfoxide
DOE	design of experiments
DOR	duration of response
D+T	dabrafenib plus trametinib
DT	dispersible tablet
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ERBB3	receptor tyrosine-protein kinase erbB-3
ERK	extracellular signal-regulated kinase
FAS	full analysis set
FPFV	first patient first visit
GC	gas chromatography
GC-MS	gas chromatography mass spectrometry
GMP	good manufacturing practice
HGG	high grade glioma
HPLC	high performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IGFR1	insulin-like growth factor receptor 1
IPR	individual patient requests

IR	infrared
KF	Karl Fischer titration
KRAS	Kirsten rat sarcoma virus
LCH	Langerhans cell histiocytosis
LDPE	low density polyethylene
LGG	low grade glioma
LPLV	last patient last visit
LS	least squares
MAP	managed access programme
MAPK	mitogen-activated protein kinase
MEK	mitogen-activated extracellular signal-regulated kinase
mOS	median overall survival
mPFS	median progression-free survival
MS	mass spectrometry
NE	not estimable
NMR	nuclear magnetic resonance
NR	not reached
NRAS	neuroblastoma rat sarcoma virus
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PDGFR β	platelet-derived growth factor receptor β
p-ERK	phosphorylated extracellular signal-regulated kinase
PFS	progression free survival
Ph. Eur.	European Pharmacopoeia
pHGG	paediatric high-grade glioma
pLGG	paediatric low-grade glioma
PK	pharmacokinetics
PR	partial response
QbD	quality by design
RANO	response assessment in neuro-oncology
RAPNO	response assessment in pediatric neuro-oncology
RAS	rat sarcoma virus

RP2D	recommended phase II dose
SCE	summary of clinical efficacy
SmPC	summary of product characteristics
TPCV	6-thioguanine, procarbazine, CCNU, vincristine
TPDCV	6-thioguanine, procarbazine, dibromodulcitol, CCNU, vincristine
TTR	time to response
UV	ultraviolet
WT	wild type
XR(P)D	X-ray (powder) diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 9 September 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Spexotras, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 March 2021.

Spexotras, was designated as an orphan medicinal product EU/3/20/2374 on 9 December 2020 in the following condition: Treatment of glioma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Spexotras as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: <https://www.ema.europa.eu/en/medicines/human/EPAR/spexotras>.

The applicant applied for the following indication:

Low-grade glioma (LGG)

Spexotras in combination with dabrafenib dispersible tablets is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy.

High-grade glioma (HGG)

Spexotras in combination with dabrafenib dispersible tablets is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0423/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001147-PIP02-20 (P/0423/2020) was completed.

The PDCO issued an opinion on compliance for the PIP P/0423/2020.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Janet Koenig

The application was received by the EMA on	9 September 2022
The procedure started on	29 September 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 December 2022
The CHMP Co-Rapporteur's Assessment was circulated to all CHMP and PRAC members on	30 December 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 January 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 January 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 March 2023
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
— A GCP inspection at 3 (2 investigator sites (in Sweden and Germany) and the sponsor site (in Switzerland) between 12-16 December 2022. The outcome of the inspection carried out was issued on	24 April 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	2 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 May 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 May 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 July 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint	30 August 2023

Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	
The CHMP agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	14 September 2023
The applicant submitted the responses to the second CHMP List of Outstanding Issues on	10 October 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the second List of Outstanding Issues to all CHMP and PRAC members on	25 October 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Spexotras on	9 November 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant has applied for the following two indications:

Low-grade glioma (LGG)

Spexotras in combination with dabrafenib dispersible tablets is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy.

High-grade glioma (HGG)

Spexotras in combination with dabrafenib dispersible tablets is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment.

2.1.2. Epidemiology

Paediatric gliomas constitute approximately 46% of primary brain and other CNS tumours in children and adolescents aged 0-19 years (Ostrom et al 2020).

LGGs are rare paediatric tumour types with an incidence of 1.71 cases per 100,000 (Ostrom et al 2020).

HGGs are even more rare tumours in the paediatric population, with an incidence of 1.11 cases per 100,000 (Ostrom et al 2020). Approximately 350-400 new cases of paediatric HGG are diagnosed in Europe yearly (EMA 2011).

2.1.3. Biologic features

Gliomas are a diverse group of primary CNS tumours of glial origin. These tumours are divided into LGG (WHO grade I and II) and HGG (WHO grade III and IV).

The WHO classification categorises gliomas from grade I through grade IV based upon increased level of histopathologic features such as cytological atypia, mitotic activity, microvascular proliferation, and necrosis.

2.1.3.1. LGG

LGG represents a diverse group of histologically different tumour types that are historically distinguished from HGG by their lower mitotic rates (Louis 2016, Lassaletta 2017). This is a heterogeneous group of tumours with different locations, histologic subtypes, ages at presentation, and clinical behaviour.

Pilocytic astrocytoma is the most common histologic subtype of LGG. According to the applicant, evolving molecular characterization reveals that most LGGs will have only a small number of mutations, and these mutations often converge on the activation of the RAS/MAPK pathway (Lassaletta 2017).

BRAF V600E mutations have been identified in 17% of paediatric LGGs (Lassaletta et al 2017, Ryall et al 2020).

2.1.3.2. HGG

HGG include a variety of heterogeneous lesions with differing histologies, the most common being anaplastic astrocytoma (WHO Grade III) and glioblastoma multiforme (WHO grade IV).

BRAF V600E mutations have been identified in 6% of paediatric and young adult HGGs (Mackay et al 2017).

2.1.4. Clinical presentation and prognosis

2.1.4.1. LGG

Patients with LGG typically have a more prolonged natural history. From the time of diagnosis, 10-year OS for molecularly unselected paediatric patients with LGG, is 85–96% (Ostrom et al 2015).

In paediatric LGG patients harbouring the BRAF V600E mutation, retrospective data suggests that chemotherapy results in unfavourable PFS and OS outcomes (Lassaletta et al 2017, Ryall et al 2020).

Further, patients with LGG who have progressed to secondary HGG are more likely to have had BRAF V600 mutation in their LGG at initial diagnosis (Mistry 2015).

2.1.4.2. HGG

Long-term outcomes for patients with paediatric HGGs are poor despite aggressive multimodality therapy with neurosurgery, radiotherapy, and chemotherapy. From the time of diagnosis, the median duration of survival for HGG is approximately 9-15 months in children (Mackay et al 2017), and 5-year survival ranges from 10 to 35% (Broniscer 2004; Finlay 2005; Broniscer 2006; Cohen 2011; Wolff 2010).

Independent of other known prognostic factors such as age, tumour location and histology, the extent of surgical resection is one of the strongest predictors of survival in children with HGG (Finlay 1995; Jones 2012).

For paediatric HGG, the BRAF V600E mutation is more frequently found in favourable prognosis subgroups of this disease, and is not found in some of the worst prognostic subgroups, such as those arising from the brainstem (Mackay et al 2017). Thus, the BRAF V600E mutation in newly diagnosed paediatric patients with HGG is associated with an improved OS versus those patients with tumours that are wildtype at BRAF V600.

2.1.5. Management

2.1.5.1. LGG

Treatment goals for patients with LGG are generally to prolong overall and progression free survival while minimizing morbidity of treatment. Surgical removal, when possible, is often the treatment of choice. The extent of resection is predictive of progression free interval. Most patients will eventually experience progression of their disease and require post-surgical therapy.

Because of the potential risk for long term neurocognitive effects of radiotherapy in paediatric LGG patients, the post-surgical therapy often includes chemotherapy with carboplatin and vincristine, which has been employed in the systemic treatment of paediatric patients with LGG for decades and served as the standard of care treatment in several large studies (Ater 2012, Gnekow 2017).

There are multiple treatment schedules for administering carboplatin with vincristine in first systemic therapy of paediatric LGG, the most widely utilised are the COGA9952 protocol (Ater 2012) and the SIOP-LGG-2004 protocol (Gnekow 2017). There have been no randomised comparisons of these regimens, but they seem comparable in overall outcomes.

For molecularly unselected paediatric patients with LGG who could not be cured by surgical resection and were enrolled into studies of chemotherapy such as carboplatin with vincristine regimens, the overall response rate (ORR) at 6 months was 29% (Gnekow et al 2017). In a similar study, the ORR was 35% in unselected paediatric patients with LGG requiring systemic therapy with carboplatin and vincristine (Ater et al 2012).

Paediatric patients with LGG harbouring a BRAF V600 mutation seems to have a poorer prognosis than those without this mutation, and require improved treatment options. Reports from Lassaletta et al 2017 and Nobre et al 2020 suggest a lower ORR of 10% for these patients when treated with chemotherapy.

2.1.5.2. HGG

Current therapies for children with HGGs are limited. The present standard of care for newly diagnosed children with HGG is gross total surgical resection, followed by focal irradiation to the tumour bed plus additional chemotherapy (MacDonald 2011). Among younger patients (<3 years of age), radiotherapy is generally not used due to its substantial neurocognitive toxicity. These patients are often treated with radiation sparing approaches such as chemotherapy alone (Broniscer 2004).

Temozolomide is most often used in the recurrent disease setting. However, in 5 trials evaluating temozolomide monotherapy or temozolomide-based combinations, the response rate in recurrent or refractory, paediatric HGG ranged from 0-12% (Lashford 2002; Nicholson 2007; Ruggiero 2006; Warren 2012; Hummel 2013).

A variety of targeted agents have also been evaluated in this patient population and response rates have been noted to be less than 10%. So far no targeted agents have been approved for patients with paediatric HGG.

Currently, temozolomide is the only authorised anticancer substance in EU for paediatric HGG (for use in relapsed or progressive disease), although mostly based on adult efficacy data. The applicant states that the treatment of children with HGG reflects a significant unmet need, with almost no improvement in survival outcomes in recent years.

2.2. About the product

Trametinib is an orally available reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. MEK proteins are components of the extracellular signal-related kinase (ERK) pathway. In human cancers, this pathway is often activated by mutated forms of BRAF which activates MEK. Trametinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity.

The recommended once-daily dose of Spexotras is determined by body weight (Table 1).

Table 1. Dosing regimen by body weight

Body weight*	Recommended dose	
	Volume of oral solution (ml) once daily	corresponding to mg trametinib
8 kg	6 ml	0.30 mg
9 to 10 kg	7 ml	0.35 mg
11 kg	8 ml	0.40 mg
12 to 13 kg	9 ml	0.45 mg
14 to 17 kg	11 ml	0.55 mg
18 to 21 kg	14 ml	0.70 mg
22 to 25 kg	17 ml	0.85 mg
26 to 29 kg	18 ml	0.90 mg
30 to 33 kg	20 ml	1 mg
34 to 37 kg	23 ml	1.15 mg
38 to 41 kg	25 ml	1.25 mg
42 to 45 kg	28 ml	1.40 mg
46 to 50 kg	32 ml	1.60 mg
≥51 kg	40 ml	2 mg
*Round body weight to the nearest kg, if necessary. The recommended dose for patients with a body weight less than 8 kg has not been established. Please refer to the dabrafenib dispersible tablets SmPC, “Posology” and “Method of administration”, for dosing instructions for treatment with dabrafenib when used in combination with Spexotras.		

In the sought indication for treatment of LGG and HGG in patients aged 1 year and older harbouring a BRAF V600E mutation trametinib is administered in combination with dabrafenib. Dabrafenib is an orally available, inhibitor of V600-mutant BRAF kinase. The combination of dabrafenib with trametinib results in the inhibition of two sequential kinases in the mitogen-activated protein kinase pathway (MAPK), resulting in enhanced MAPK pathway inhibition. Although mechanisms of resistance to BRAF inhibitor monotherapy may be diverse, modulation of the MAPK pathway by co-inhibiting downstream MEK1/2 along with the BRAF inhibition has been shown to be achievable with a beneficial tolerability profile in various cancers.

The combination of dabrafenib and trametinib is currently approved for the treatment of adults with several BRAFV600 mutant tumour types.

In this application, the applicant seeks approval for the age-appropriate pharmaceutical forms of dabrafenib and trametinib, that can be dosed and administered in patients 1 year of age. The solid formulations of dabrafenib (50 and 75 mg capsules) and trametinib (0.5 and 2 mg tablets) approved for treatment of solid tumours in adult patients are suitable for non-body weight adjusted (flat) dosing in adults, while the proposed liquid dosage forms (dabrafenib 10 mg dispersible tablets and trametinib 0.05 mg/mL oral solution after reconstitution) allow for accurate body weight-adjusted dosing in paediatric patients.

2.3. Type of application and aspects on development

The development programme

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

The paediatric development programme of dabrafenib and trametinib was initiated in 2012.

- Initial clinical pharmacology studies determined the relative bioavailability of dabrafenib dispersible tablet compared to capsules in adult healthy subjects (Study CDRB436G2101) and of trametinib powder for oral solution compared to film-coated tablets (Study MEK115892) in adult patients with solid tumours.
- The recommended phase 2 doses (RP2D) and preliminary safety and efficacy information was obtained in two Phase I/IIa paediatric studies: study CDRB436A2102 ("Study A2102") which investigated dabrafenib monotherapy, and study CTMT212X2101 ("Study X2101") which investigated trametinib monotherapy and D+T combination therapy.
- The primary claims for treatment of paediatric glioma with D+T are based on the pivotal phase II Study CDRB436G2201 ("Study G2201"), which investigates D+T combination therapy in paediatric patients ≥ 1 year of age with BRAF V600 mutation positive LGG and r/r HGG.

Scientific advice

On 18 December 2014, GlaxoSmithKline R&D Ltd requested scientific advice for their product dabrafenib (EMA/CHMP/SAWP/177117/2015). At that time, GSK sought advice from CHMP, SAWP, related to the initiation of a phase II trial of monotherapy dabrafenib in paediatric patients with BRAF V600E-mutant HGGs, and, regarding the overall development plan to seek an indication in paediatric patients with recurrent or refractory BRAF V600E-mutant HGG.

The CHMP agreed that BRAF inhibition in paediatric HGG deserves further investigation. The company was advised to consider an alternative trial design, utilising combination with trametinib as comparator, given that the addition of a MEK inhibitor to dabrafenib may be of benefit by increasing the duration of response. The CHMP also stressed the idea of moving combination therapy to earlier treatment lines. Few data were available regarding the proposed dose schedule, and CHMP recommended further analysis of phase I data and discussions including the anticipated levels to be obtained in the CNS, before start of a phase II trial.

The proposed sample size (at that time consisting of 20 HGG patients planned for monotherapy dabrafenib) was considered very limited. The CHMP commented on the limitations and uncertainties

associated with the planned single-arm study design, although truly outstanding ORR results combined with a meaningful response duration may be considered of value in a paediatric HGG population with a real need of effective treatments and with a short life expectancy.

Regarding the proposed safety database, at that time comprised of 85 paediatric patients, the CHMP commented that it is unlikely that 85 paediatric patients are enough to characterise the safety profile of the target HGG population. However, given the high unmet medical need in this area and considering the experience in adults, if outstanding results are observed in children and no major concerns are identified in the phase II study, such safety database could be considered sufficient, but, post-approval measures are likely to be required.

On 15 June 2022, a pre-submission meeting with the Rapporteur- and Co-Rapporteur teams was held, related to the applicant's (Novartis) intention to submit an application for dabrafenib dispersible tablets and trametinib powder for oral solution, for the treatment of paediatric patients with BRAF V600E mutation-positive glioma (LGG and HGG).

The MPA pointed out the need to address the 12 week radiotherapy washout period in the HGG cohort, to minimise the influence of potentially late responders, pseudo progression, and the carry-over of adverse reactions. Regarding the proposed duration of treatment in SmPC section 4.2 with the wording "as long as clinical benefit is observed or until the development of unacceptable toxicity", MPA commented that the proposal of potential treatment beyond progression requires a justification in the submitted dossier. Further, the MPA stated that in line with current practice, the presentation of efficacy data for the single arm HGG cohort should be limited to ORR and duration of response, and should not include PFS or OS results.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a powder for oral solution containing 0.05 mg/ml of the active substance trametinib following reconstitution. The active substance is present as the solvate, trametinib dimethyl sulfoxide.

The other ingredients are: sulfobutylbetadex sodium, sucralose (E955), citric acid monohydrate (E330), disodium phosphate (E339), potassium sorbate (E202), methyl parahydroxybenzoate (E218), strawberry flavour.

The product is available in an amber glass bottle with a child-resistant screw cap closure as described in section 6.5 of the SmPC. The medicinal product is co-packaged with a 20 ml oral dosing syringe graduated with 0.5 ml increments. A pre-attached press-in bottle adapter is also present to enable use with the dosing syringe.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of trametinib dimethyl sulfoxide is N-(3-{3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)yl}phenyl)acetamide with (methylsulfinyl)methane corresponding to the molecular formula $C_{26}H_{23}FIN_5O_4.C_2H_6OS$. It has a relative molecular mass of 693.53 g/mol and the following structure:

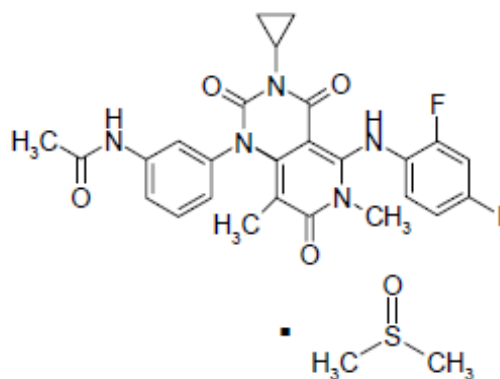


Figure 1. Active substance structure

The active substance, trametinib dimethyl sulfoxide, has been approved in a previous centralised marketing authorisation procedure for the finished product Mekinist, EMEA/H/C/2643, from the same applicant. No changes to the active substance are made as compared to that used for the Mekinist film-coated tablet formulation. The chemical structure of trametinib dimethyl sulfoxide was elucidated by a combination of ^1H NMR and ^{13}C NMR, MS and IR. The solid state properties of the active substance were measured by XRPD.

Trametinib dimethyl sulfoxide is a 1:1 stoichiometric DMSO solvate, where DMSO is fully incorporated into the crystal lattice, the active substance is a white to almost white solid powder. The active substance has very low aqueous solubility across the physiological pH range. The active substance is slightly soluble in the solvent DMSO. Trametinib dimethyl sulfoxide is classified as a BCS class II compound based on its low solubility and high permeability. Trametinib dimethyl sulfoxide does not exhibit stereoisomerism. A micronised active substance was selected for reasons of homogeneity and content uniformity in the finished product.

Polymorphism has been observed for trametinib, however only one form (form I) is observed with the incorporation of DMSO into the crystal lattice. Trametinib dimethyl sulfoxide form 1 can desolvate to trametinib (non-solvated parent) when exposed to neat solvents other than DMSO, aqueous DMSO systems with high water contents, or at elevated temperature and humidity. The proposed process and associated controls consistently produce the DMSO solvated form I, this form is stable and is maintained following micronisation. A regular test for polymorphism is included in the active substance specification.

2.4.2.2. Manufacture, characterisation and process controls

The active substance is synthesised in seven main steps using well defined starting materials with acceptable specifications. The same synthetic route is to be applied at two proposed manufacturing sites.

The proposed starting materials are suitably justified in line with the principles of ICH Q11. The origin and fate of potential impurities, including potential genotoxic impurities has been justified. Three materials were designated as potential genotoxins. The control strategy in place assures these are suitably purged or transformed prior to the final active substance. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The manufacturing process has been developed using elements of QbD such as risk assessment, and design of experiment (DOE) studies. Critical process parameters and proven acceptable ranges have been clearly highlighted in line with the development data. Relevant process parameters, for example the mixing time, temperatures, etc. are provided in relation to the CPPs. The CPPs ensure relevant impurity purge, control the formation of impurities, and in the last stage the CPPs also ensure correct crystallisation and particle size of the active substance.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. The proposed synthetic route is the same as that used to prepare the clinical and stability batches.

The active substance is packaged in LDPE bags which comply with EC 10/2011 as amended.

2.4.2.3. Specification

The active substance specification includes tests for: appearance, identity (IR), assay (HPLC), solid state form (XPRD), dimethyl sulfoxide content (HPLC), related substances (HPLC), residual solvents (GC), water content (KF), residue on ignition (Ph. Eur.) and particle size (laser light diffraction).

No impurities are present at higher than the qualification threshold according to ICH Q3A. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from batches of the active substance are provided encompassing the proposed manufacturing sites. The results are within the specifications, comparable between the sites, and consistent from batch to batch.

2.4.2.4. Stability

Stability data from batches of active substance from the initial manufacturer stored in the intended commercial package for up to 60 months under long term conditions (30°C / 65% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. 48 months of long-term data for batches from the same site are also presented. Stability data from batches for up to 3 months under the same conditions from the second manufacturer were provided, and overall the results from the initial manufacturer are considered representative for the purposes of stability. Regarding ongoing stability studies any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The following parameters were tested: appearance, identity (IR), assay (HPLC), solid state (XPRD) impurities (HPLC), water content (KF). The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications and no significant changes or trends were observed at the long term or accelerated storage conditions.

Photostability testing following the ICH guideline Q1B was performed, no significant change was observed upon exposure to light.

Results on stress conditions were provided in the solid state and in a solution phase. The active substance was chemically stable in the solid state under all stress testing conditions, in the solution

phase decreases in assay and corresponding increases in impurities were seen upon exposure to the stress testing conditions.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the applicant's proposed retest period along with the chosen storage conditions.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Spexotras is a powder for oral solution containing 0.05 mg/ml of the active substance trametinib following reconstitution. The powder is white or almost white in colour and each bottle contains trametinib dimethyl sulfoxide equivalent to 4.7 mg of trametinib.

A trametinib containing formulation is marketed as Mekinist 0.5 mg & 2 mg film-coated tablets by the same applicant for the treatment of adult patients. To expand the use to the paediatric population and those with difficulty swallowing, an appropriate liquid formulation has been developed in the form of the powder for oral solution.

The active substance development was based on the manufacturing process already used for the above mentioned tablet formulation. The same micronised form of the active substance is used as in the approved tablet formulation and there are no differences in the manufacture of this between the formulations. The polymorphic form of the active substance is suitably stable, and a regular control for soluble content is also indicated in the finished product specification.

The excipient sulfobutylbetadex sodium was considered a novel excipient as this was the first oral use of this excipient (previously it had been included in parenteral formulations). The applicant had initially not provided the requisite information related to the use of a novel excipient and a major objection was raised. To resolve this, the applicant provided the detailed information required in the dossier and this information was considered acceptable. An appropriate flavouring agent and preservative system were also identified as important aspects for the dosage form in terms of quality and patient acceptability. The choice and selection of the preservative system used was considered appropriate, and was supported by preservative efficacy testing. Other than the flavouring agent, all excipients used are described in the Ph. Eur. and comply with the relevant standards. The formulation contains excipients of known effect; sulfobutylbetadex sodium, sodium, and methyl parahydroxybenzoate. These excipients are appropriately declared in the product information. The choice of the excipients was suitably justified for the intended age group and the list of excipients is included in section 6.1 of the SmPC.

The proposed formulation was developed alongside the clinical trial programme, and following the introduction of the powder for oral solution formulation only minor changes were made with no impact on bioavailability, the amounts of sucralose and strawberry flavour were reduced to improve organoleptic properties.

During development batches were manufactured at various scales and at different manufacturing sites, and the information provided during development suggests the process is sufficiently robust.

The primary packaging is an amber glass bottle of 180 ml with a child-resistant screw cap closure. The materials comply with Ph. Eur. and relevant regulatory requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the

product. For the oral dosing syringes suitable information has been provided on medical device requirements and the devices are CE marked.

2.4.3.2. *Manufacture of the product and process controls*

The manufacturing process consists of several steps. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies on production scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. *Product specification*

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form; appearance, identification (HPLC-UV, HPLC-DAD), identification of preservatives (HPLC), assay (HPLC), assay of preservatives (HPLC), soluble content (HPLC), degradation products (HPLC), water content (KF), reconstitution time (in-house), content uniformity (HPLC), microbiological quality (Ph. Eur.).

Appropriate limits have been defined for the relevant specification tests. The limit for unspecified impurities complies with the requirements of ICH Q3B, and limits for preservatives at release and shelf life have been set to ensure appropriate microbiological quality.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product.

The information originally provided concerning analytical methods and their validation was initially accepted. However late in the procedure the applicant outlined that one of the impurities present in the product was in fact a degradation product of the active substance. The applicant's method for the detection and quantification of degradation products was not at this time considered capable of accurately separating this impurity from a chromatographic peak present for the flavouring agent based on the data provided. The potential levels of this impurity and any impact on safety were therefore unknown and a major objection was raised. To resolve this issue the applicant presented further data and also implemented a further system suitability test to be used to enable routine detection and quantification of this impurity. This information was sufficient to resolve the major objection, and the data demonstrates that the levels present of this impurity are below the relevant qualification threshold and not of a safety concern. The applicant also committed to the submission of a closing sequence in order to reflect in the dossier the final information provided in response to the CHMP concerns. A recommendation for further quality development (REC 1) was raised with a view to enabling further improvement in the detection and quantification of this impurity. The applicant

outlined that they had begun work on an improved method using diode array detection (DAD) to allow improved separation and quantification of this impurity. The applicant was recommended to continue to develop, validate, and implement this DAD method.

Batch analysis results were provided at the proposed commercial batch size confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from batches of finished product stored for up to 36 months under long term conditions (5°C / 60% RH) and for up to six months under accelerated conditions (25°C / 60% RH & 30°C / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for soluble content (HPLC), assay (HPLC), degradation products (HPLC), assay of preservatives (HPLC), appearance, water content (KF), reconstitution time (in-house), and microbiological quality (Ph. Eur.). Additional testing not described in the specifications was also performed for water activity (Ph. Eur.), pH (Ph. Eur.), and preservative efficacy (Ph. Eur.). At the long-term storage conditions no significant changes were observed and the product remained within specification. After six months of accelerated testing at 25°C / 60% RH changes were observed, including changes to appearance and potassium sorbate content however the product remained within specification. At six months exposure to accelerated testing at 30°C / 75% RH significant changes were observed including decreases in assay, soluble content, potassium sorbate content and increases in degradation products which led to out of specification results. The analytical procedures used were considered stability indicating following the resolution of the major objection related to the method for degradation product testing.

In addition, product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Upon exposure the results for a single unknown impurity reached the specification limit, and while the limit was not exceeded the proposed instruction to protect from light was considered appropriate.

The product is intended for reconstruction prior to use, and in-use stability studies using the reconstituted oral solution were performed. Stability batches were subjected to in-use stability testing at various ages of the batches, including batches towards the end of the proposed shelf life. In-use testing was conducted at 5°C, 25°C / 60% RH, and 30°C / 75% RH which were the same conditions as applied to the powder. The results from the in-use testing show that the proposed in-use shelf life of 35 days following reconstitution is appropriate with an instruction not to store above 25°C or freeze the oral solution.

Based on available stability data, the proposed shelf-life of 36 months for the powder prior to reconstitution and store in a refrigerator (2°C – 8°C) protected from light and moisture as stated in the SmPC (section 6.3) are acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. During the procedure two quality major objections were raised.

A major objection related to the information required for the novel excipient sulfobutylbetadex sodium was raised by CHMP, as this is the first oral use of this excipient. This was resolved by the provision of the detailed information in the dossier required for the inclusion of novel excipients within a formulation.

At a late stage another quality major objection was raised, as the applicant indicated with their response package that one of the impurities needed to be considered as a relevant degradation product of the active substance. The analytical method in place in the finished product was not at that time considered suitable for the separation and quantification of this impurity based on the validation data that had been provided. The presence and levels of this impurity in the finished product could therefore not be satisfactorily determined and confirmed as safe and appropriate. To resolve this the applicant provided further information and analysis of the method and implemented a further system suitability test to ensure the impurity could be routinely detected and quantified.

At the time of the CHMP opinion, there was an unresolved quality issue which had no impact on the Benefit/Risk ratio of the product, this pertains to further improvements in the analysis of degradation products in the finished product and the implementation of the proposed DAD method. This point is agreed as a recommendation for future quality development (see recommendation 1).

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is expected to validate and apply the proposed DAD method for improved separation and quantification of the relevant degradation impurity noted in the finished product. This method should be submitted for use by the end of February 2024 via the most relevant variation.

2.5. Non-clinical aspects

2.5.1. Introduction

The applicant has included the non-clinical study reports previously submitted for the approved non-orphan parent brand Mekinist (trametinib). All prior non-clinical data for trametinib has been reviewed in procedures related to Mekinist and no re-assessment of the non-clinical data has been performed although previous evaluation of juvenile toxicity was specially considered in light of the novel paediatric glioma indication. All non-clinical studies were conducted in mice, rats, monkeys, rabbits and dogs. All pivotal safety studies were carried out in compliance with GLP regulations.

A short summary of previously submitted data, based on EPAR of Tafenlar is presented below.

An updated environmental risk assessment (ERA) has been submitted.

2.5.2. Pharmacology

Pharmacology studies with trametinib as a single agent and in combination with dabrafenib were submitted and reviewed in relation to the non-orphan parent compound Mekinist (trametinib, tablets). The following information under this paragraph are extracted from the published EPAR for Mekinist (trametinib, tablets) (see also Mekinist published EPAR).

2.5.2.1. Primary pharmacodynamic studies

A series of *in vitro* and *in vivo* investigations have been conducted in order to characterise the primary pharmacology of trametinib. It was shown that trametinib is a selective inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. It inhibits MEK1 and 2 phosphorylation as well as the phosphorylation of ERK1 and 2 thereby inducing INK4B (p15) protein (an endogenous cyclin dependent kinase [CDK] inhibitor). Following a screening of kinases, it was shown that trametinib preferentially inhibits BRAFV600E-mediated MEK1 activation ($IC_{50} = 0.7$ nM) over phospho-MEK1 activity ($IC_{50} = 13$ nM) and MEK2 activation ($IC_{50} = 0.9$ nM) over phospho-MEK2 activity ($IC_{50} = 11$ nM). Eighty (80) % of BRAF and 72% of RAS mutant cell lines were sensitive to trametinib. Trametinib caused G0/G1 arrest in HT-29 and Colo205 cells by inhibiting ERK phosphorylation, resulting in quantitative and qualitative changes in cell cycle proteins downstream and subsequently induced apoptosis. Trametinib inhibits growth of BRAF V600 mutant melanoma cell lines, lung cancer and glioma cells and demonstrates anti-tumour effects in BRAF V600 mutant melanoma animal models.

BRAF V600-activating mutations have been identified in paediatric tumours, including gliomas, where dabrafenib, trametinib and their combination have proven beneficial in adults with tumours harbouring BRAF V600-activating mutations.

2.5.2.2. Secondary pharmacodynamic studies

Trametinib, as the parent compound or the DMSO solvate, was evaluated in a total of 50 kinase assays covering 44 unique kinase enzymes. Trametinib was inactive ($IC_{50} > 10$ μ M) against all but the B-RafV600E MEK1 cascade assay (BRAMA). This assay monitors the ATPase activity of phosphorylated-MEK1 that results from the phosphorylation of MEK by BRAFV600E. The IC_{50} of 63 nM for trametinib was due to inhibition of MEK activation rather than the direct inhibition of BRAFV600E. Trametinib was also evaluated against 171 different kinase assays using an external kinase screening panel which found no significant (>50%) inhibition was observed when screened at a single concentration of 10 μ M. In a separate study, trametinib was examined for effects in 7 enzyme assays (phospholipase A2, cyclooxygenase isoform 1 [COX1], constitutive NO synthase [NOS], phosphodiesterase 4, protein kinase C, acetylcholinesterase, monoamine oxidase A). Trametinib at a fixed concentration of 10 μ M showed no significant inhibitory effect on these enzymes.

2.5.2.3. Safety pharmacology programme

At the relevant low dose of 3 mg/kg, tolerated by rats and dogs, with the exception of diarrhoea and inhibition of body weight gain, no significant effects on general behaviour, physiologic function or acute neurotoxicity were observed. However, administration of trametinib to rats at the high dose of 100 mg/kg (non GLP) resulted in decreased body weight gain, sporadic incidence of reduced spontaneous locomotion, prone position, blepharoptosis, diarrhoea, piloerection and mydriasis, described in order of

onset. Subsequent studies showed that this dose leads to morbidity and mortality. Following increasing oral doses of trametinib it was shown that it had no effect on the respiratory system of rats up to a dose of 0.125 mg/kg in which case it produced a mild, transient decrease in body temperature (up to 0.8°C) at 1 hour post dose. In a preliminary, *in vitro* screening assay, trametinib was found to inhibit hERG channel tail current in a concentration-dependent manner. In an *in vitro* rabbit preparation it was shown that trametinib produced significant decreases in isometric contractile force and the Tp-e interval at high concentrations. In a GLP study done on dogs with increasing oral doses, trametinib had no effect on ECG parameters, blood pressure or heart rate.

2.5.3. Pharmacokinetics

In previous applications the PK, distribution, metabolism and elimination of trametinib have been investigated in a series of oral or intravenous *in vivo* studies in the mouse, rat, dog, monkey and human, and in *in vitro* studies, using non-radiolabelled and ¹⁴C-labelled drug. Trametinib was absorbed slowly after oral dosing in the rat (T_{max} 4-8 h), whereas peak plasma concentrations were reached 1-2 h post-dose in mouse and monkey and 3 h in dog. After iv administration, trametinib showed a moderate to low plasma clearance in all species examined. The half-life values were long, 3.7 h for mouse, 6.1 h for rat, 6.7 h for monkey and 14.5 h for dog. In these studies trametinib distributed to liver, kidney, renal cortex, Harderian gland, pancreas, salivary glands and adrenal cortex. Trametinib-related radioactivity was also distributed into the brain, although to a limited extent (brain-blood ratio: 0.1-0.6). Seven days after the single dose, drug-related radioactivity was still observed in spleen, kidney, liver and preputial gland, suggesting potential accumulation of trametinib-related material in these organs when administered daily. No selective association of trametinib-related radioactivity with melanin-containing tissues was observed. Studies on placental transfer of trametinib were not performed. The *in vitro* plasma protein binding of trametinib at high (0.5-5 µg/mL) and clinically relevant concentrations (0.001-0.05 µg/mL) was high in all species: 95% in mouse and 96% in rat, 97% in dog, 98% in monkey and 97% in human and no concentration dependency was observed.

Three metabolites of trametinib were identified in *in vitro* studies: M5, M6 and M7. These metabolites were all products of deacetylation, which is the predominant pathway in trametinib elimination. CYP3A4 oxidation is considered a minor pathway of metabolism. The major *in vitro* metabolites of trametinib observed in humans were also detected in the non-clinical species. The major circulating component in rats and dogs was unchanged trametinib, accounting for 64-94% and 58-79% of total plasma radioactivity, respectively. A similar pattern was observed in humans. In both rats and dogs, the two Phase I metabolites M5 and M7 were detected in plasma at levels of <6% and 9% of drug-related material, respectively, while M6 (N-glucuronidation of M5) was detected in rat bile and accounted for <12% of the dose.

The predominant route of elimination of drug-related radioactivity was via faeces in rats and dogs (59-98%). Most of the radioactivity was recovered in excreta within 3 days in rats and dogs. However, small amounts of radioactivity continued to be eliminated until 7 days, indicating protracted elimination consistent with the long half-lives.

Pharmacokinetic drug interactions

In vitro data showed that trametinib is an inhibitor of both human OATP1B1 and OATP1B3 P-gp BCRP. In addition, it was shown that trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP3A4. Trametinib was found to be an *in vitro* inhibitor of CYP2C8, CYP2C9 and CYP2C19 and an inducer of CYP3A4.

2.5.4. Toxicology

For the initial MAA concerning the non-orphan parent brand Mekinist (trametinib, tablets) the toxicity of trametinib was tested in rats and dogs by oral gavage. In addition, safety pharmacology studies were carried out in rats (oral administration), in rabbit (oral administration), and in dogs (oral and iv administration over 10 minutes). An oral combination toxicity study in dogs in which trametinib and dabrafenib were given in combination for 4 weeks was also performed.

A standard battery of genotoxicity studies was conducted and reproduction and embryofetal toxicity studies were performed in rats and rabbits. Phototoxicity was assessed in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay. Carcinogenicity studies with trametinib have not been conducted.

A new safety evaluation for the cyclodextrin excipient sulfobutylbetadex sodium was included.

For clarity, a short summary, based on previous Mekinist EPARs is given in the sections below. A discussion on the uncertainties concerning the cyclodextrin excipient sulfobutylbetadex sodium and the safety of Spexotras/Finlee combination therapy in young children has been included.

2.5.4.1. Repeat dose toxicity

Trametinib was well tolerated by rats at oral doses up to 0.125 mg/kg/day for 3 weeks and 0.031 mg/kg/day for 13 weeks. Trametinib was well tolerated by dogs at oral doses up to 0.025 mg/kg/day for 3 weeks and no adverse effects were seen at 0.023 mg/kg/day for 13 weeks.

In repeat-dose studies the effects seen after trametinib exposure are found mainly in the skin, gastrointestinal tract, haematological system, bone and liver. Most of the findings are reversible after drug-free recovery. In rats, hepatocellular necrosis and transaminase elevations were seen after 8 weeks at ≥ 0.062 mg/kg/day (approximately 0.8 times human clinical exposure based on AUC). In mice, lower heart rate, heart weight and left ventricular function were observed without cardiac histopathology after 3 weeks at ≥ 0.25 mg/kg/day trametinib (approximately 3 times human clinical exposure based on AUC) for up to 3 weeks. The preclinical findings indicate a low likelihood of myocardial necrosis caused directly by trametinib. The vascular and myocardial calcification seen in mice is believed to be a consequence of altered calcium phosphorus homeostasis.

In rats, hypertrophy of the physis and increased bone turnover were observed, mineralisation of multiple organs was associated with increased serum phosphorus and was closely associated with necrosis in heart, liver, kidney and haemorrhage in the lung at exposures comparable to the human clinical exposure. Increases in cystic follicles and decreases in corpora lutea were observed in female rats at exposures below the human clinical exposure based on AUC. Additionally, in juvenile rats given trametinib, decreased ovarian weights, slight delays in hallmarks of female sexual maturation (vaginal opening and increased incidence of prominent terminal end buds within the mammary gland) and slight hypertrophy of the surface epithelium of the uterus were observed. All of these effects were reversible following an off-treatment period and attributable to pharmacology. However, in rat and dog toxicity studies up to 13 weeks in duration, there were no treatment effects observed in male reproductive tissues.

In rats and dogs given trametinib at or below clinical exposures, bone marrow necrosis, lymphoid atrophy in thymus and GALT and lymphoid necrosis in lymph nodes, spleen and thymus were observed, which have the potential to impair immune function.

In a study in dogs in which trametinib and dabrafenib were given in combination for 4 weeks, signs of gastro-intestinal toxicity and decreased lymphoid cellularity of the thymus were observed at lower

exposures than in dogs given trametinib alone. Otherwise, similar toxicities were observed as in comparable monotherapy studies.

2.5.4.2. Genotoxicity

Trametinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells and micronuclei in the bone marrow of rats.

2.5.4.3. Carcinogenicity

Carcinogenicity studies with trametinib have not been conducted. The lack of dedicated carcinogenicity studies is acceptable in accordance with the ICH S9 guideline.

2.5.4.4. Reproductive and developmental toxicity

In animals, no fertility studies have been performed, but toxic effects were seen on female reproductive organs. Trametinib may impair fertility in humans.

Trametinib resulted in maternal and foetal toxicity and in addition trametinib has teratogenic properties (increased incidence of ossification defects).

In rat, dose-responsive decrease in mean maternal body weight gain was seen. Decreased foetal weights and increased post-implantation loss were seen at exposures below or slightly above the clinical exposures based on AUC.

In rabbits a dose-dependent decrease in maternal mean body weight gain occurred at all doses during the post dosing phase of the study. Increased abortion rates occurred and there were significant dose-dependent reductions in mean foetal body weights at all doses.

With trametinib in repeat-dose studies, increases in cystic follicles and decreases in corpora lutea were observed in female rats at exposures below the human clinical exposure based on AUC. Additionally, in juvenile rats given trametinib, decreased ovarian weights, slight delays in hallmarks of female sexual maturation (vaginal opening and increased incidence of prominent terminal end buds within the mammary gland) and slight hypertrophy of the surface epithelium of the uterus were observed. All of these effects were reversible following an off-treatment period and attributable to pharmacology. However, in rat and dog toxicity studies up to 13 weeks in duration, there were no treatment effects observed in male reproductive tissues.

A dose-dependent increase in the incidence of skeletal defects was observed primarily related to incomplete ossification of the extremities, skull, vertebrae and sternebrae. An increased incidence of less than the expected number of ossified metacarpals, incompletely ossified parietals or incompletely ossified hyoid also occurred. In addition, increases in less than the expected number of ossified phalanges, slightly enlarged anterior fonticuli, incompletely ossified interparietal, nasal bone variations in shape, incompletely ossified caudal vertebrae, and incompletely ossified sternebrae, and the malformations curved scapula and markedly enlarged anterior fonticulus occurred. The increased incidence of incomplete ossification and skeletal malformations were seen at sub-clinical exposures based on AUC.

2.5.4.5. Toxicokinetic data

The toxicokinetics show that trametinib exposure in animals is very low in comparison to human (0.08-1.32xhuman based on C_{max} and 0.09-1.24xhuman based on AUC). There was no clear effect of co-administration of trametinib or dabrafenib on the exposure to each agent in dogs.

2.5.4.6. Local tolerance

Local tolerance studies with trametinib were carried out. These studies included *in vitro* ocular and skin irritancy studies. In *in-vitro* studies Trametinib was considered to be a non-irritant. In mouse administration of trametinib resulted in a stimulation index (H3-thymidine incorporation into draining lymph nodes) of >3 in the absence of systemic toxicity or local irritation and therefore was considered to be a sensitiser.

2.5.4.7. Other toxicity studies

Antigenicity and Immunotoxicity studies

Regarding the immunotoxicity of trametinib, in the repeated dose toxicity studies done on rats with a daily oral dosing for up to 13 weeks, it was shown that the principal immune-related adverse effect was bone marrow degeneration/necrosis and lymphoid necrosis in lymph nodes, spleen and thymus. In addition, adverse skin and gastric changes were associated with inflammation, characterised by increased cellularity (lymphocytes and plasma cells) in lymph nodes and decreased circulating mean lymphocyte counts (up to 63%). In these rats there was an increase in circulating leukocyte counts (neutrophils and monocytes), bone marrow myeloid hyperplasia, and increased extramedullary haematopoiesis in the spleen. All adverse findings had reversed or partially reversed at the end of the recovery period. The same gastrointestinal and haematopoietic perturbations were seen in studies on dogs under the same experimental conditions as for rats. Furthermore, in the dog 4-week combination study in which dogs were treated with trametinib and dabrafenib, decreased lymphoid cellularity of the thymus was observed at a lower dose than in the 3-week dog study in which only trametinib was given.

Combination with dabrafenib

In a study in dogs in which trametinib and dabrafenib were given in combination for 4 weeks, signs of gastrointestinal toxicity and decreased lymphoid cellularity of the thymus were observed at lower exposures than in dogs given trametinib alone. Otherwise, similar toxicities were observed as in comparable monotherapy studies.

Phototoxicity studies

Trametinib was phototoxic in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay at significantly higher concentrations than clinical exposures (IC₅₀ at 2.92 µg/ml, ≥130 times the clinical exposure based on C_{max}), indicating that there is low risk for phototoxicity to patients taking trametinib

2.5.5. Ecotoxicity/environmental risk assessment

The data submitted in this MAA is the same which were assessed during the initial MAA and type II variation (Procedure No. EMEA/H/C/WS1274). The applicant has refined the F_{pen} based on orphan designation EMA: EU/3/20/2374 for all glial tumours combined being 2.63 per 10,000 persons (RTI-HS, 2020). Trametinib remains below the trigger level of a Phase II assessment with an overall PEC of

0.00026 µg/L. In spite of the fact that no Phase II risk assessment is required for trametinib, chronic toxicity studies in *Daphnia magna*, fish and algae have been conducted with trametinib.

With addition of the proposed indication, trametinib is not expected to pose a risk to the environment.

Table 2. Summary of main study results

Substance (INN/Invented Name): Trametinib dimethyl sulfoxide						
CAS-number (if available): 871700-17-3						
PBT screening			Result		Conclusion	
Bioaccumulation potential- log K_{ow}		OECD107	4.04		Not Potential PBT	
Phase I						
Calculation		Value	Unit		Conclusion	
PEC _{surfacewater} , refined (e.g. prevalence,)		0.00026	µg/L		> 0.01 threshold No	
Other concerns (e.g. chemical class)					N	
Phase IIa Effect studies						
Study type		Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test 72h/ <i>Pseudokirchnereriella subcapita</i>		OECD 201	NOEC	0,04	mg/L	
<i>Daphnia</i> sp. ReproductionTest 21d, semi static, <i>Daphnia magna</i>		OECD 211	NOEC	0,013	mg/L	reproduction
Fish, Early Life Stage Toxicity Test 28d, flow through/ <i>Pimephales promelas</i>		OECD 210	NOEC	0,004	mg g/L	0.003mg/L (mean measured

2.5.6. Discussion on non-clinical aspects

The non-clinical studies submitted for the marketing authorisation application for trametinib were considered adequate and acceptable for the assessment of non-clinical aspects for the product trametinib. The lack of dedicated carcinogenicity studies for trametinib is acceptable in accordance with the ICH S9 guideline. Relevant information has been included as necessary in the SmPC. Considering the targeted paediatric population, the discussion of the non-clinical assessment focus on juvenile toxicity. Previously submitted data in the context of the Mekinist MA (EMA/H/C/002643) are considered acceptable.

Assessment of paediatric data on non-clinical aspects

Juvenile toxicity study

In the oral juvenile toxicity study in rats some findings were similar to findings seen in adult animals but in general, trametinib adverse effects occurred at greater incidence and severity and at lower exposures than in adult rats. Adverse events observed in both juvenile and adult animals included growth and bone effects, eye (corneal mineralisation/dystrophy), skin, liver, heart and female reproductive system effects (delay in a physical landmark of sexual maturity and mammary gland development, lower corpora lutea and lower ovarian weights, all reversible).

There were toxicological findings in juvenile animals that had not been seen in adult animals such as decreased ovarian weights, light delays in hallmarks of female sexual maturation (vaginal opening and increased incidence of prominent terminal end buds within the mammary gland) and slight hypertrophy of the surface epithelium of the uterus. These findings were all reversible and are adequately described in section 5.3 of the SmPC.

Uncertainties identified regarding the use of cyclodextrin in Spexotras formulation.

The sulfobutylbetadex sodium excipient has been used in several IV drug formulations, but it has not been previously used in approved oral formulations. The sulfobutylbetadex sodium excipient is not present in the non-orphan parent compound Mekinist® and has therefore not been tested in the previous non-clinical toxicity studies. All previous toxicology studies were indeed performed with a different formulation as the one intended for the paediatric indication, meaning without the cyclodextrin sulfobutylbetadex sodium. This adds to the uncertainty when it comes to interpretation of the juvenile toxicology and its relevance to foresee toxicity in small children.

Although the applicant has included a comprehensive safety evaluation of sulfobutylbetadex sodium there is still an uncertainty with regards to the safety of the cyclodextrin excipient sulfobutylbetadex sodium (also referred to as Betadex sulfobutyl ether sodium, sulfobutylether-7-beta-cyclodextrin or SBE- β -CD) alone and in combination with Finlee (dabrafenib) in young children.

Cyclodextrins (CDs) are excipients which can influence the properties of the active substance and other medicines. In preclinical studies in animals that were administered CDs intravenously, there were observations of renal toxicity and ototoxicity (hearing loss). Safety aspects of CDs have been considered during the development and safety assessment of the medicinal product. There are limited safety data on the effects of CDs in children <2 years of age.

The trametinib oral solution contains 100 mg/ml of sulfobutylbetadex sodium which may have the potential to affect the solubility and bioavailability of other oral medicinal products. Caution should be taken when the trametinib oral solution is administered with oral medicinal products that have low bioavailability and a narrow therapeutic index (e.g. imipramine, desipramine)

In patients receiving Spexotras, the daily dose of sulfobutylbetadex sodium ranges, based on weight, from 75-79 mg/kg/day thereby exceeding (with about 4 times) the 20 mg/kg/day dose level considered to be without harmful effects in *Questions and answers on cyclodextrins used as excipients in medicinal products for human use (EMA/CHMP/495747/2013)*.

According to *Cyclodextrins used as excipients (EMA/CHMP/333892/2013)* and *Questions and answers on cyclodextrins used as excipients in medicinal products for human use (EMA/CHMP/495747/2013)*, harmful effects of cyclodextrins are not to be expected at doses below 20 mg/kg/day, a dose which will be exceeded 4 times with Spexotras treatment. Moreover, it states that for doses $\geq$ 20 mg/kg/day cyclodextrins (all routes of administration), there is insufficient safety data in children below two years of age and therefore, a case by case judgement should be made regarding the risk/benefit for the patient. In this regard, paediatric glioma is considered a serious condition with limited treatment options.

Considering the known reversible kidney changes (vacuolation of the kidney tubular cells without loss of kidney function) seen in animals and the potential risk of cyclodextrin-induced hearing loss (ototoxicity), the applicant has sufficiently discussed and summarised the non-clinical data regarding the cyclodextrin-related kidney and hearing loss effects. Based on the non-clinical data and the estimated lower bioavailability of sulfobutylbetadex sodium when dosed orally, the risk of sulfobutylbetadex sodium-induced kidney and ototoxicity are considered low.

Trametinib is already used in existing marketed products and no significant increase in environmental exposure is anticipated. Therefore Trametinib is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

No new non-clinical data has been submitted in the context of this application and previous data provided in the context of the authorised trametinib product Mekinist are considered sufficient to characterise the non-clinical profile of Spexotras.

From a non-clinical perspective, the MAA is approvable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The application was also selected for a routine inspection of two investigator sites (in Sweden and Germany) and the sponsor site in Switzerland. The investigator site inspections revealed some major findings, but no finding was graded as critical.

The routine GCP inspection performed at the sponsor site resulted in a total of eight findings, of which two were deemed as critical findings.

During the inspections two main areas of concern were identified, which may have affected the reliability of the data reported in the clinical study report which was submitted as part of the MAA. These are data management and the handling of the PK samples.

Data management

Entries in the eCRFs that originated prior to the interim data base lock were still changeable in the live eCRF at the time of inspections, and indeed had changed after interim analysis and after the clinical study report was submitted for marketing authorisation application. Thus, the data reported in the submitted clinical study report does not represent a fully cleaned dataset. Due to inadequate cleaning measures at the time of the data snapshot, which is evident from the cleaning measures and data changes that took place after the snapshot, the robustness of these data for scientific analysis is compromised. Therefore, the validity of the data used for the analysis and originally submitted in the MAA could not be ensured and the applicant was requested to submit a cleaned safety dataset together with an analysis and discussion on the potential impact of the cleaned safety dataset on the currently established safety profile and, ultimately, the benefit/risk balance. This has been provided by the applicant as requested and overall the changes are considered to be minor, without impact on the safety conclusion or benefit/risk balance.

Handling of PK samples:

There was no documented evidence available at the investigator's site that the PK samples were handled and processed as required according to the lab manual. An effect on the reliability of the PK data could not be excluded.

This finding was observed during the inspection of site 3304. The sponsor admitted that the sites were not asked to document the details of the handling and processing of the PK samples, and that this was not part of the monitoring. Thus, due to the lack of source data neither the sponsor representatives

(monitors) nor the inspectors were able to verify the proper handling of the PK samples and adherence to the provisions made by the sponsor.

Although the PI of site 3304 stated in his response to the inspection report that the site handled the PK samples according to the instructions of the QM manual of the site, this response is considered not to reflect the actual facts, as it is stated in the monitoring report of the visit dated 10-11 Apr 2019 at site 3304, "*Finding #39: Centrifugation of some PK samples delayed and not performed within one hour after collection. According to discussion with personnel at the site it is not possible as laboratory is located within another building.*"

According to the sponsor's response to the inspection report (IR), Trametinib is not stable in whole blood at room temperature ("*Trametinib (GSK code GSK1120212) was not stable (Report 2012N140703_00; 8262883 Trametinib Whole Blood RT): at the first time point tested (2 hours), 61,2% of trametinib was still present in the sample, which was lower than the 85% acceptance criterion*"). Stability under wet ice conditions can be confirmed for 4 hours.

Given the limited stability of Trametinib in whole blood at RT, the lack of source documentation and traceability of the handling and processing of the PK samples is considered to impact the validity of the reported PK data for Trametinib. Overall, the data indicate a concentration, temperature and time-dependence in the loss of trametinib. A flaw of the data is the available concentration, with no data available between 12 and 50 ng/mL, when the most relevant concentration range is between 10-20 ng/mL, which also corresponds to the concentration range where saturation seems to happen.

The data confirms that the loss of trametinib in whole blood when stored on ice is negligible irrespective of concentration. This would apply to the deviation noted at site 3304, where the deviation only pertains the time to centrifugation and not the storing on ice.

In the case where samples are not stored on ice (site 2004), a loss of trametinib of 30% would be expected, based on the data at 12 ng/mL from study DMPK R1600155e. The concentration from samples from site 2004 should thus not be relied on. Trametinib PK data from two patients are available from site 2004. The overall bias due to data from site 2004 is nevertheless small a, considering that PK data is available for 39/41 HGG patients (and 69/73 LGG patients) in study G2201. This data likely contributes to the general variability in PK.

As study G2201 provides the reference therapeutic exposure and supports the posology, the integrity of the PK data was discussed, however as stability of dabrafenib and its metabolites has been demonstrated, there is no consequence of a delayed centrifugation, and the data may be used without restriction. Overall, the applicant has also provided sufficient evidence that it can be reasonably expected that the samples were generally treated adequately, and the impact of the deviations identified are agreed to be minor. Thus, data from study G2201 (and X2101) can be used in the popPK analyses and support the simplified posology.

- **Tabular overview of clinical studies**

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage
CDRB436G2101 Start: 7-Jul-2017 End: 28-May-2018 Countries: United States	A randomised, open-label, three-period cross-over study to investigate the relative bioavailability of two new oral suspension formulations of dabrafenib (10 x 10 mg	Total: 26 Age: 20-75 (47.9) years Groups: 6 A/B/C: 5 B/C/A: 4	Form(s): Dabrafenib 10mg dispersible tablets and 50 mg HPMC capsules Duration: (Day -1 to end of study) for an individual subject was approximately 197 days or 6.5 months

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage
Study Status: complete Report date: 07-Mar-2019	dispersible tablets reconstituted in water) in comparison to dabrafenib HPMC capsules (2 x 50 mg) following a single oral dose of 100 mg in healthy adult volunteers	C/A/B: 4 A/C/B: 4 B/A/C: 4 C/B/A: 5	Doses: Treatment A: single oral dose of dabrafenib 100 mg given as 10 x 10 mg dispersible tablets (Variant A) in the form of in-situ reconstituted oral suspension formulation Treatment B: single oral dose of dabrafenib 100 mg given as 10 x 10 mg dispersible tablets (Variant B) in the form of in-situ reconstituted oral suspension formulation Treatment C: single oral dose of dabrafenib 100 mg given as 2 x 50 mg HPMC capsules
MEK115892 Start: 30-Jul-2012 End: 12-Nov-2012 Countries: United States Study Status: complete Report date: 20-Sep-2013	An Open-Label, Two-Period, Randomised, Crossover Study to Assess the Relative Bioavailability of GSK1120212 Tablet Formulation and the GSK1120212 Paediatric Oral Solution Formulation Following Single-Dose Administration to Adult Subjects with Solid Tumours	Total: 16 Age: 32-85 (61.8) years	Form(s): Trametinib (GSK1120212): 2mg film-coated tablet and 0.05 mg/mL powder for oral solution Duration: 14 days
CTMT212X2102 Start: 20-Oct-2016 End: 29-Aug-2019 Countries: Belgium, Netherlands, Spain, United Kingdom, United States Study Status: Complete Report date: 18-May-2020	A Phase I, open-label study to determine the effect of repeat dosing of trametinib on the pharmacokinetics of a combined oral contraceptive (norethindrone plus ethinyl estradiol) in female patients with solid tumours	Total: 19 Age: 34-59 (47.3) years Groups: 1 Treatment group: 19	Form(s): Trametinib 0.5 mg (if dose reduction required) and 2 mg tablet Combination oral contraceptive (1 mg norethindrone/ 0.035 mg ethinyl estradiol) tablet Duration: PK phase was 21 days (5 days for Period 1, 16 days in Period 2). Patients could continue receiving treatment after PK phase. Doses: Oral Contraceptive (1 mg norethindrone / 0.035 mg ethinyl estradiol) po qd days 1 through 21 Trametinib 2 mg po qd days 6 through 21
BRF113771 Start: 27-Jul-2011 End: 15-Nov-2012 Countries: United Kingdom, United States Study Status: complete Report date: 20-May-2013	A Four-Part, Open-Label Study to Evaluate the Effects of Repeat Dose GSK2118436 on the Single Dose Pharmacokinetics of Warfarin, the Effects of Repeat Dose Oral Ketoconazole and Oral Gemfibrozil on the Repeat Dose Pharmacokinetics of	Total: 60 Age: in years Part A: 32 – 81 (58.8) Part B: 34 – 79 (58.6) Part C: 21 – 88 (54.4) Part D: 25 – 83 (52.0) Groups: Part A (warfarin): 14 Part B (ketoconazole): 16	Form(s): Dabrafenib 50 and 75 mg capsules Warfarin 5 mg tablets Ketoconazole 200 mg tablets Gemfibrozil 600 mg tablets Duration: Part A: 29 days Part B: 22 days Part C: 22 days Part D: 18 days

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage
	GSK2118436, and the Repeat Dose Pharmacokinetics of GSK2118436 in Subjects with BRAF Mutant Solid Tumours	Part C (gemfibrozil): 17 Part D (repeat dose dabrafenib): 13	Doses: all po Part A: warfarin 15 mg on days 1 and 22; dabrafenib 150 mg bid day 8 through day 29 Part B: dabrafenib 75 mg in AM on day 1 then bid on days 2 through 21 and a morning dose on day 22; ketoconazole 400 mg od on days 19 thorough 22 Part C: dabrafenib 75 mg in AM on day 1 then bid on days 2 through 21 and a morning dose on day 22; gemfibrozil 600 mg bid on days 19 thorough 21 and a morning dose on day 22 Part D: dabrafenib 150 mg AM dose on day 1, then 150 mg BID on days 2 through 18
CDRB436A2103 Start: 20-Dec-2013 End: 31-Mar-2016 Countries: Australia United Kingdom United States Study Status: Complete Report date: 1-Dec-2016	An open-label study to evaluate the effects of a potent CYP3A4 inducer and the effects of a pH elevating agent on the repeat dose pharmacokinetics of dabrafenib (GSK2118436) in subjects with BRAF V600 mutation positive tumours	Total: 23; 17 evaluable for PK Age: 33-78 (57.7) years Groups: 1 Treatment group: 23	Form(s): dabrafenib 75 mg capsule, rifampin 300 mg capsule, and rabeprazole 20 mg tablet Duration: Planned duration of treatment was 29 days Doses: Dabrafenib: 150 mg po BID for 29 days (Study Days 1 to 29). Rabeprazole: 40 mg po QD for 4 days (Study Days 16 to 19) Rifampin: 600 mg po QD for 10 days (Study Days 20 to 29)
CDRB436A2104 Start: 03-Mar-2015 End: 01-Aug-2016 Countries: Spain Study Status: Complete Report date: 16-May-2017	An open-label phase 1 study to evaluate the effects of dabrafenib (GSK2118436) on the single dose pharmacokinetics of an OATP1B1/1B3 substrate and of a CYP3A4 substrate in subjects with BRAF V600 mutation positive tumours	Total: 16 Age: 29-64 (49.1) years Groups: 1 Treatment group: 16	Form(s): dabrafenib 75 mg capsule, rosuvastatin 10 mg tablet, midazolam 3 mg oral syrup Duration: planned duration of treatment was 23 days Doses: Dabrafenib: 150 mg po BID on study days 8 to 22 with a morning dose on day 23 Rosuvastatin: 10 mg single doses on study days 1, 8 and 22 Midazolam: 3 mg single doses on study days 1, 8 and 22
MEK113709 Start: 02-May-2011 End: 30-Sep-2011 Countries: United States Study Status: complete Report date: 25-Apr-2012	An Open-Label, Two-Period, Randomised, Crossover Study to Evaluate the Effect of Food on the Single Dose Pharmacokinetics of the MEK Inhibitor, GSK1120212, in Subjects with Solid Tumours	Total: 24 Age: 38 - 76 (61.0) years Groups: Treatment AB: 10 Treatment BA: 14	Form(s): GSK1120212 2 mg tablet Duration: 2 single doses followed by 7 days of serial blood sampling after each dose Doses: Treatment A: single dose of GSK1120212 2 mg po fasted

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage
			Treatment B: single dose of GSK1120212 2mg po with a high-fat/high-calorie meal
CDRB436A2102 Start: 23-May-2013 End: 04-Dec-2020 Countries: Australia, Canada, Denmark, France, Germany, Spain, United Kingdom, United States Study Status: complete Report date: 20-Apr-2021	Phase I/IIa, 2-part, Multicentre, Single-Arm, Open-Label Study to Determine the Safety, Tolerability, and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Patients with Advanced BRAF V600- Mutation Positive Solid Tumours	Total: 27 Age: 1.2 - 17.0 (8.76) years Groups: 4 3 mg/kg: 3 3.75 mg/kg: 10 4.5 mg/kg: 8 5.25 mg/kg: 6	Form(s): Dabrafenib: 10, 25, 50 and 75 mg capsules and 150mg powder and 10mg tablets for oral suspension Duration: at least 6 months (without disease progression or withdrawal from the study for any reason) Doses: Doses PO. Weight-based per available regulatory guidance. Part 1 dose escalation; part 2 tumour specific expansion per protocol
CTMT212X2101 Start: 07-Jan-2015 End: 29-Dec-2020 Countries: Australia Canada France United Kingdom United States Study Status: complete Report date: 06-May-2021	An Open-Label, Dose Escalation, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the MEK Inhibitor Trametinib in Children and Adolescents Subjects with Cancer or Plexiform Neurofibromas and Trametinib in Combination with Dabrafenib in Children and Adolescents with Cancers Harboring V600 mutation	Total: - Part A: 50 - Part B: 41 - Part C: 18 - Part D: 30 Age (years): - Part A: 0.4-17 (7.2) - Part B: 1.0-17 (7.4) - Part C: 1.4-17 (8.3) - Part D: 2-16 (8.8) Groups: Part A: TMT mg/kg/day 0.0125: 3 0.025: 19 0.032: 12 0.04: 16 Part B: - Neuroblastoma: 11 - Low grade glioma fusion: 10 - Neurofibromatosis Type-1 associated plexiform neurofibromas: 10 - BRAF V600 mutant solid tumour: 10 Part C: 0.025 TMT mg/kg/day + 50% DRB recommended phase 2 dose: 3 0.025 TMT mg/kg/day + 100% DRB recommended phase 2 dose: 9 0.032 TMT mg/kg/day + 100% DRB recommended phase 2 dose: 6 Part D: - Low grade glioma: 20	Form(s): trametinib 0.125, 0.5, and 2 mg tablets and powder for oral solution. dabrafenib 50 and 75 mg capsules, powder for oral suspension and 10 mg tablets for suspension. Duration: at least 6 months (without disease progression or withdrawal from the study for any reason) Doses: Dose escalation per protocol. Doses po. Trametinib The total daily trametinib dose was not to exceed the adult dose (2 mg) in any subject. Dabrafenib capsules (50 mg and 75 mg) were administered twice daily.

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage
		• Langerhans Cell Histiocytosis: 10	
CDRB436G2201 Start: 28-Dec-2017 Data cut-off date: 23-Aug-2021 Countries: Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Israel, Italy, Japan, Netherlands, Russian Federation, Spain, Sweden, Switzerland, United Kingdom, United States Study Status: ongoing Report date: 25-Jul-2022	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)	Total: LGG: 110 HGG: 41 Age (years): LGG: 1-17 (9.1) HGG: 2-17 (12.12) Groups: 2 LGG Cohort: 2 dabrafenib and trametinib: 73 cisplatin and vincristine: 37 HGG Cohort: 1 dabrafenib and trametinib: 41	Form(s): dabrafenib 50 and 75 mg capsules and 10 mg dispersible tablet trametinib 0.5 and 2 mg film-coated tablets and 5 mg powder for oral solution carboplatin and vincristine: as locally available Duration: until any of the following - disease progression per RANO criteria or loss of clinical benefit determined by the investigator, unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or parent/legal guardian, lost to follow-up, death, or study termination by the sponsor Doses: dabrafenib (divided into 2 po doses per day): 5.25 mg/kg/day < 12 years old; 4.5 mg/kg/day ≥ 12 years old Trametinib (po qd): 0.032 mg/kg/day < 6 years old 0.025 mg/kg/day ≥ 6 years old carboplatin: 175 mg/m ² IV weekly infusion vincristine: 1.5 mg/m ² IV weekly infusion

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

In this pair of submissions (Spexotras = trametinib and Finlee = dabrafenib), Novartis seeks approval for the age-appropriate pharmaceutical forms for dabrafenib and trametinib that can be conveniently dosed and administered in patients 1 year of age. The proposed liquid dosage forms (dabrafenib 10 mg dispersible tablets and trametinib 0.05 mg/mL oral solution after reconstitution) allow for body weight-adjusted dosing in paediatric patients, including any indicated dose reduction steps; they are referred to as "liquid formulations".

The paediatric development programme is supported by 5 clinical studies and population PK modelling. Two relative bioavailability studies were performed in adults:

- dabrafenib DT compared to capsules (Study CDRB436G2101 "G2101", healthy subjects)
- trametinib PfOS compared to FCT (Study MEK115892, adults with solid tumours)

Several formulations were used in the paediatric development programme for each substance, as detailed in Table 3 and in Table 4 and Table 5 by age group in the paediatric studies for dabrafenib, and trametinib, respectively.

Table 3. Overview of drug product formulations used in the liquid formulation development programme

Formulation	G2101	MEK115892	A2102	X2101	G2201
Dabrafenib					
HPMC capsule, marketed strengths (50 and 75 mg)	Y (50 mg)		Y	Y	Y
HPMC capsule, additional strengths (10 and 25 mg)			Y		
Powder for oral suspension (150 mg)			Y	Y	
Dispersible tablet, Variant A (10 mg)	Y				
Dispersible tablet, Variant B (10 mg), FMI	Y		Y	Y	Y
Trametinib					
FCT, marketed strengths (0.5 and 2 mg)		Y (2 mg)		Y	Y
FCT, additional strength (0.125 mg)				Y	
PfOS, CSF (4.7 mg)		Y		Y	
PfOS, FMI (4.7 mg)					Y

CSF: clinical service form; FMI: final market image

Table 4. Summary of dabrafenib data by formulation type, study, and age range – popPK dataset

Age Group	Formulation	Arm	Study	Number of subjects
<1-5 years	Capsule	Monotherapy	A2102	3
	Capsule	Combination	G2201	2
	Capsule	Combination	X2101	1
	Powder in stick-packs	Monotherapy	A2102	19
	Powder in stick-packs	Combination	X2101	13
	DT for oral suspension	Combination	G2201	22
	DT for oral suspension	Combination	X2101	1
6-11 years	Capsule	Monotherapy	A2102	18
	Capsule	Combination	G2201	18
	Capsule	Combination	X2101	8
	Powder in stick-packs	Monotherapy	A2102	10
	Powder in stick-packs	Combination	X2101	7
	DT for oral suspension	Combination	G2201	16
12-17 years	Capsule	Monotherapy	A2102	34
	Capsule	Combination	G2201	49
	Capsule	Combination	X2101	16
	Powder in stick-packs	Monotherapy	A2102	1
	Powder in stick-packs	Combination	X2101	1
	DT for oral suspension	Combination	G2201	4

Table 5. Summary of trametinib data by formulation type, study, and age range – popPK dataset

Age Group	Formulation	Arm	Study	Number of subjects
<1-5 years	Liquid	Monotherapy	X2101	32
		Combination	G2201	24
		Combination	X2101	14
	Solid	Monotherapy	X2101	5
		Combination	X2101	1
6-11 years	Liquid	Monotherapy	X2101	10
		Combination	G2201	21
		Combination	X2101	6
	Solid	Monotherapy	X2101	18
		Combination	G2201	13
		Combination	X2101	9
12-17 years	Liquid	Monotherapy	X2101	1
		Combination	G2201	7
		Combination	X2101	1
	Solid	Monotherapy	X2101	20
		Combination	G2201	46
		Combination	X2101	16

Methods

Validated LC-MS/MS methods were used for trametinib, dabrafenib, and dabrafenib metabolites hydroxy-, desmethyl-, and carboxy-dabrafenib.

Trametinib association with blood cells is time and concentration dependant. At a concentration of 12 ng/mL trametinib in whole blood at room temperature, a concentration decrease was observed: 0.5h: -19.4%; 1h: -30.4%; 1.5h: -37.5%; 2h: -41.3%; 4h: -54.3%; 6h: -49.1%. At a concentration of 190 ng/mL trametinib in whole blood at room temperature, the concentration decrease was 0.5h: -0.2%; 1h: -1.0%; 1.5h: 0.6%, 2h: 1.1%; 4h: --0.6%; 6h: -1.9%.

There was no significant loss of trametinib when whole blood was stored on ice for 4h.

Radio-HPLC of radiolabelled trametinib in whole blood at 37°C for 4 hours did not reveal any other peak than trametinib. Trametinib distribution between blood and plasma (Cb/Cp) was also concentration-dependant: 3.38 (1 ng/mL), 3.2 (10 ng/mL) and 1.1 (50 ng/mL).

According to the clinical study manual, trametinib PK samples should be immediately stored on ice and centrifuged within 1h of sampling.

Population pharmacokinetic analysis

A population pharmacokinetic analysis was performed where the objectives were to characterise population PK of the liquid formulations of dabrafenib and trametinib in 1-17 year old patients and to support dose recommendation of liquid formulations of dabrafenib and trametinib in combination in paediatric 1-17 year old patients. The pharmacokinetic data used in the population analysis included concentration measurements collected from two clinical studies in paediatric patients (CTMT212X2101 [MEK116540] and CDRB436G2201) including a total of 1927 PK observations from 244 patients. Both liquid and solid formulations of dabrafenib and trametinib were used for model development. Observations below the lower limit of quantification (0.09% of concentrations in X2101 and 1.77% of

concentrations in G2201) and PK samples flagged by the pharmacokinetic scientist as outliers were excluded from the modelling.

Modelling was performed using the Markov Chain Monte Carlo (MCMC) Bayesian method to develop a final model. A PopPK model for the solid formulation of trametinib was already established with rich PK data in adult patients with BRAF V600 mutation positive unresectable or metastatic melanoma, which was used as a source of prior information when developing the paediatric model. The final paediatric model was a two-compartment model with dual sequential 1st order absorption (absorption rate constants 1 and 2, referred to as Ka1 and Ka2) and 1st order elimination (apparent clearance [CL/F]).

During the covariate model development, covariates were evaluated using criteria for statistical significance (95% confidence interval overlapping with the null value) and clinical significance. The final model included weight on CL, central volume of distribution (VC), inter-compartmental clearance (Q) and peripheral volume of distribution (VP). In addition, formulation was included on rate of absorption (Ka2) and relative bioavailability (Frel also referred to as F1) as well as sex on CL. The parameters of the final model are shown in Table 6. The final model evaluation included prediction-corrected visual predictive checks (pcVPCs) shown in Figure 2 (stratified on formulation) and Figure 3 (stratified on weight).

Table 6. Final model parameters

Parameter Name	Mean	95% Confidence Interval
Q (L/h)	60	NA
M (-)	0.1	NA
CL (L/h)	5.212	(4.661 - 5.788)
VC (L)	118.285	(81.746 - 158.281)
VP (L)	371.939	(294.231 - 455.501)
KA1 (1/h)	0.026	(0.018 - 0.037)
KA2 (1/h)	1.432	(0.993 - 1.96)
MTIME (h)	0.372	(0.316 - 0.425)
WT_CL (-)	0.472	(0.393 - 0.548)
WT_Q (-)	0.586	(0.366 - 0.807)
SEX_CL (-)	0.862	(0.798 - 0.929)
Combo_F1 (-)	0.721	(0.666 - 0.778)
Form1_F1(-)	1.234	(1.135 - 1.338)
WT_VC (-)	0.966	(0.704 - 1.248)
WT_VP (-)	0.995	(0.809 - 1.17)
Form1_KA2 (-)	2.232	(1.67 - 2.837)
ω^2_{CL}	0.038	(0.023 - 0.056)
$\omega_{CL}\omega_{VC}$	0.095	(0.054 - 0.144)
ω^2_{VC}	0.522	(0.347 - 0.772)
ω^2_Q	0.54	(0.306 - 0.875)
ω^2_{VP}	0.059	(0.011 - 0.145)
ω^2_{KA1}	0.618	(0.33 - 1.084)
ω^2_{KA2}	0.04	(0.009 - 0.137)
ω^2_{MTIME}	0.146	(0.063 - 0.28)
SIGMA.1.1.	0.049	(0.044 - 0.053)
MCMCOBJ	-5007.743	(-5478.655 - -4520.511)

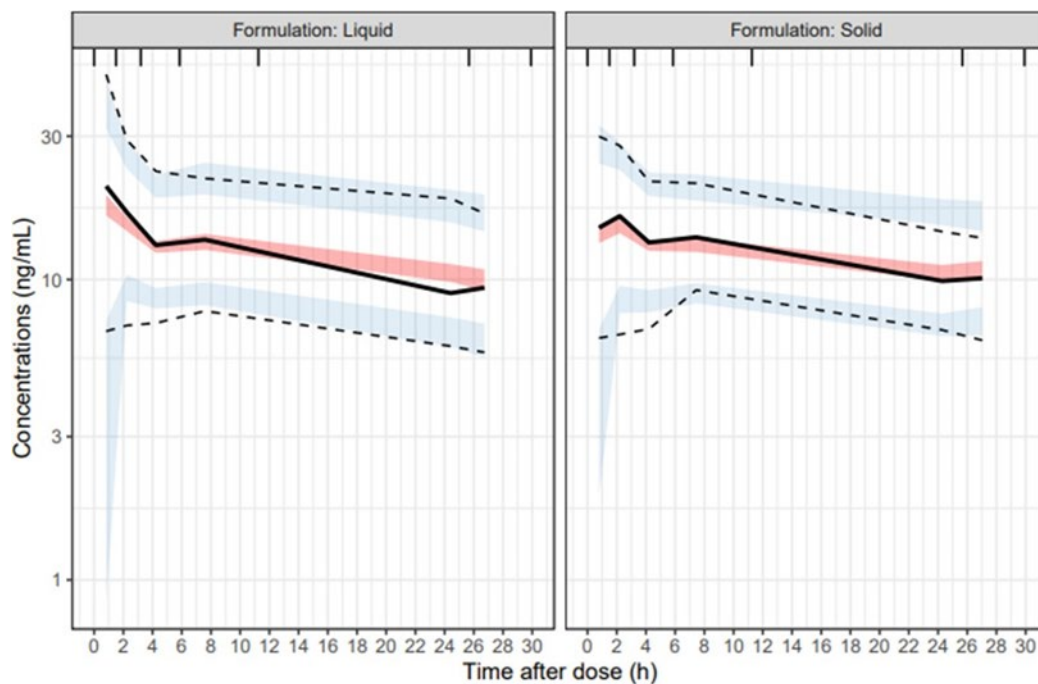


Figure 2. Prediction-corrected VPC for trametinib final PopPK model stratified by formulation

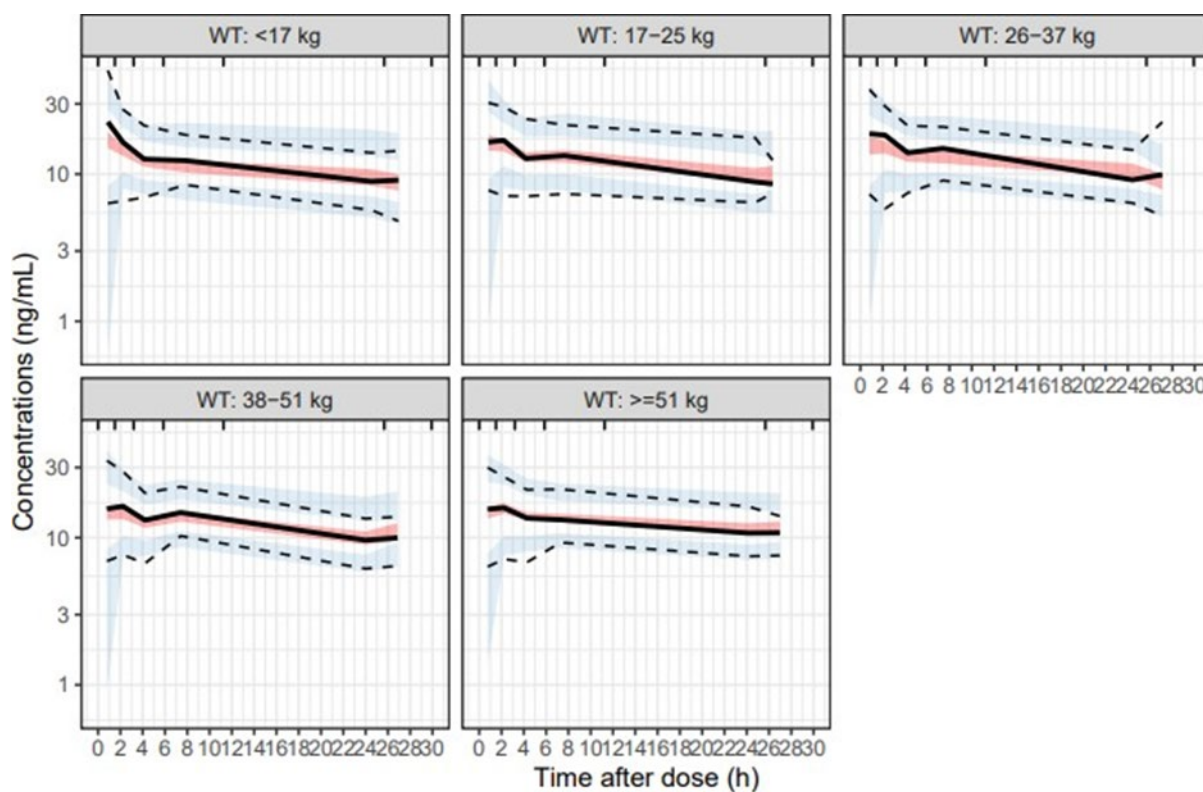


Figure 3. Prediction-corrected VPC for trametinib final PopPK model stratified by weight

The final model was used to perform simulations of several exposure metrics at steady state to support a simplified posology, shown in Figure 4. In general, the simplified trametinib posology was developed

with the goals of achieving an efficacy target of trametinib steady state average concentration (Cavg) ≥ 10 ng/mL, with the constraint of the upper recommended dose-range of 0.04 mg/kg/day.

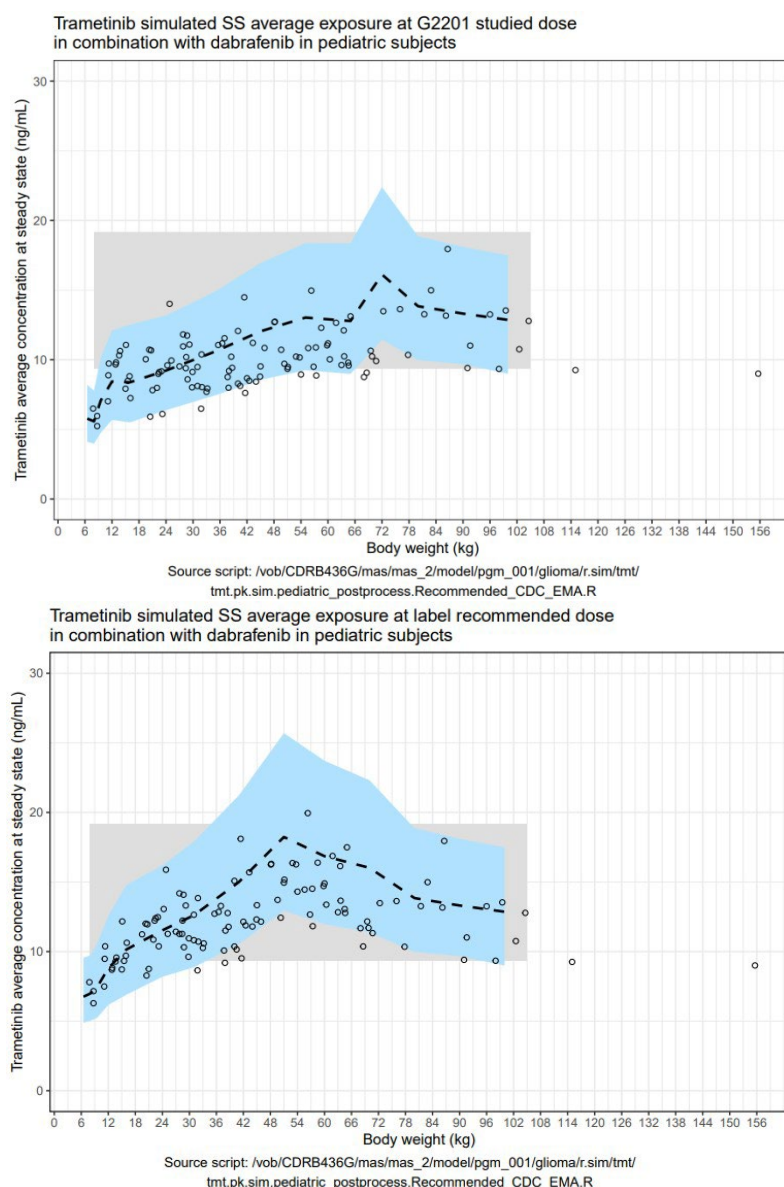


Figure 4. Trametinib simulated steady-state exposure at trametinib dosing using the liquid formulation according to the study G2201 protocol (top panel, included for reference) and for the recommended dosing (lower panel) in combination with dabrafenib in paediatric patients. The black dashed line is the median simulated paediatric Cavg and the blue shaded area represent 90% prediction interval of the simulated paediatric patients. The horizontal grey band represents the 5th to 95th percentiles of the observed Cavg in patients from G2201 study (calculated using non-compartmental analysis). Black circles represent the simulated individual predicted Cavg at respective doses for patients in G2201 (using the actual EBEs and covariates from patients in study G2201).

Absorption

Trametinib has low solubility and *in vitro* data indicate that trametinib has high permeability. Trametinib is a substrate of human P-gp *in vitro* but not a substrate of BCRP.

The absolute bioavailability previously established for the marketed tablet formulation of trametinib (Mekinist) was 72.3%

In study MEK115892, for a single-dose administration in the fasted state in adults, it was shown that trametinib exposures were similar when 2 mg was given as an oral solution and the tablet formulation (AUCinf Ratio 1.12, 90% CI 1.00-1.24). Cmax of the solution was 71% higher compared to the Cmax of the tablet formulation. The median Tmax was 1.0 h for the oral solution compared to 1.8 h for the tablet formulation. In the pivotal paediatric study, steady-state geometric mean (%CV) Cmax and AUCtau were 22.7 ng/ml (41.1%) and 339 ng*hr/ml (22.2%) in the LGG cohort and 21.3 ng/ml (36.3%) and 307 ng*hr/ml (22.8%) in the HGG cohort.

Based on the popPK the Cmax at steady state (Cmax,ss) values were compared between the solid and liquid formulations across all subjects in study G2201. The geometric mean dose-normalised Cmax,ss were 880 and 791 ng/mL/(mg/kg) for the solid and liquid formulations, respectively. The geometric mean (non-dose-normalised) Cmax,ss were 21.03 and 23.97 ng/mL for the solid and liquid formulations, respectively.

Food effect

The impact of food on the pharmacokinetics of the reconstituted oral solution has not been investigated. Administration of a single dose of trametinib (tablet formulation) with a high-fat, high-calorie meal resulted in a 70% and 10% decrease in Cmax and AUC, respectively, compared to fasted conditions. In all trials, trametinib was recommended to be administered once daily under fasting conditions, either one hour before or two hours after a meal.

Distribution

The *in vitro* plasma protein binding of trametinib was investigated by equilibrium dialysis in human plasma at concentrations of 1 and up to 50 ng/mL. The mean *in vitro* plasma protein binding of trametinib in human plasma was determined to be 97.4% and not concentration dependent.

In another *in vitro* plasma protein binding study of [¹⁴C]GSK1120212 (trametinib) and its metabolite GSK1790627 (M5) in human, the plasma protein binding of M5 was high, 98.8%, and approximately equivalent to that of trametinib of 98.6% at a concentration range of 1 ng/mL to 50 ng/mL.

Trametinib volume of distribution was estimated in the absolute bioavailability study in adults, with an IV microdose of 5 µg [¹⁴C]-trametinib administered together with a single oral 2 mg dose. The geometric mean Vd was 1060 L (arithmetic mean 1200 L), after IV dosing.

Elimination

The plasma clearance following intravenous dosing in the absolute bioavailability study was 3.2 L/h.

Trametinib terminal t1/2 is 127 hours (5.3 days) based on single dosing under fasted condition.

A mass balance study was performed where subjects with solid tumour malignancies received a single oral dose of [¹⁴C]-trametinib as an oral suspension (2 mg, 79 µCi) in fasted state. All plasma, blood, urine and faeces were collected at various times or intervals through 240 hours post-dose. The mass-balance study was terminated early and results are only available from two individuals and the collection was performed for 10 days although the recovery was still low. Mean total recovery in the mass-balance study was only 37-48%, with 35-39 % of the dose in faeces and 2-9% in urine over 10 days. Faecal excretion appears the major route of elimination after [¹⁴C]-trametinib oral dose, with

81.3 and 94.3% of the excreted dose in 10 days (39.2 and 35% of the administered dose) in the two patients, respectively, excreted in the faeces, with parent, M5, and M7 identified. Urine is the minor excretory pathway (18.6 and 5.6% of the excreted dose, 9.0 and 2.1% of the administered dose excreted in 10 days) with urinary drug related material consisting of parent, M5, M7, and M9. Following single and repeated doses of trametinib, trametinib as parent is the main circulating component in plasma.

Metabolism

The metabolism of trametinib in humans was investigated in a number of studies and the following metabolic scheme is suggested for trametinib:

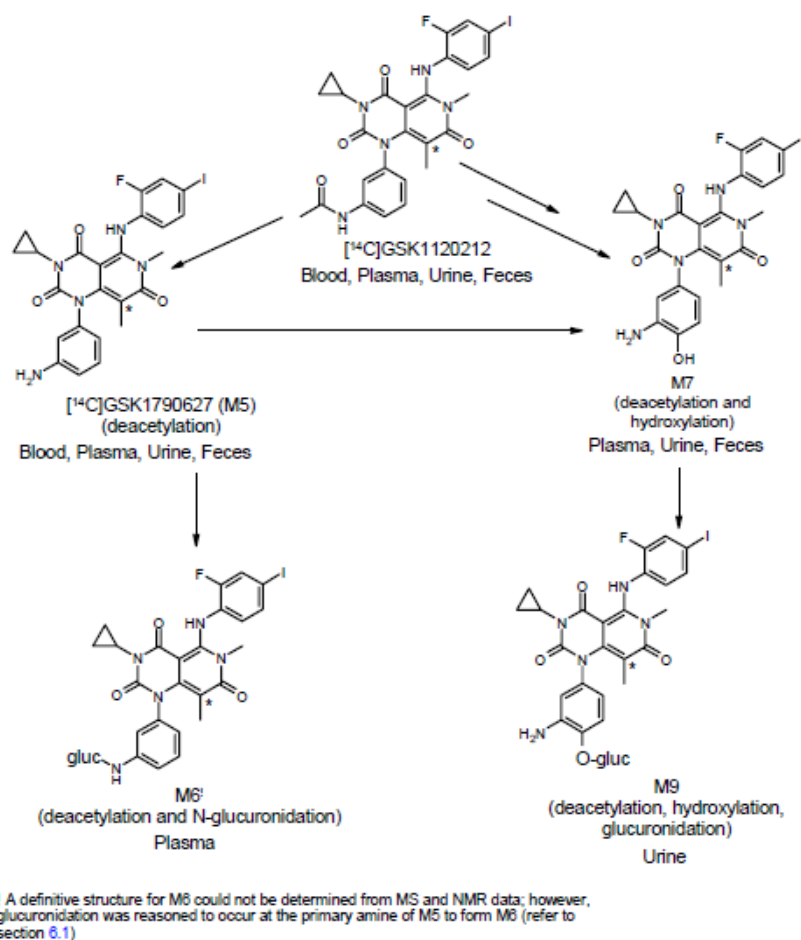


Figure 5. Proposed metabolic scheme for trametinib (GSK1120212) in male humans.

Trametinib is metabolised via deacetylation alone or in combination with mono-oxygenation. The deacetylated metabolite was further metabolised by glucuronidation. CYP3A4 oxidation is considered a minor pathway of metabolism. Trametinib is a substrate of human carboxylesterases 1b, 1c and 2 (hCES1b, hCES1c, and hCES2), which were involved in the formation of metabolite M5.

Dose proportionality and time dependencies

The increase in exposure (C_{max} and AUC) was dose-proportional between 0.125 mg and 4 mg following repeated dosing of tablet formulation in adults. Trametinib accumulates with repeat daily dosing. A mean accumulation ratio of 6.0 was observed for the tablet formulation at 2 mg once daily dose. Steady state was achieved by Day 15.

Target population

For all studies in the target population, several formulations were used for each substance, as detailed in Table 3 and in Table 4 and Table 5. Data was pooled for the different formulations in the NCA analysis, while the distinction is made between formulations in the popPK analysis, where all target population data is included as well.

Study X2101 was a 4-part, Phase I/IIa, multicentre, open-label clinical study in paediatric patients (n=139, between 4.8 months and < 18 years of age inclusive) evaluating the safety, PK, PD and clinical activity of trametinib in children and adolescents with cancer or plexiform neurofibromas and D + T combination therapy in children and adolescents with cancers harbouring BRAF V600 mutation. Patients from 1 month of age could be included, except in part C and D where patients from 12 months of age were to be included.

The primary objective of the study was to determine a safe and tolerable trametinib dose in paediatric patients that would achieve a similar exposure as the recommended adult dose. PK characterization and pop PK was a secondary objective. This study had 4 parts:

- Part A: trametinib monotherapy dose escalation (n=50, PK for n=47). Trametinib dose levels of 0.0125, 0.025, and 0.04 mg/kg/day were initially evaluated. The second dose level (0.025 mg/kg/day) of trametinib was equivalent to the recommended dose in adults (2 mg daily based on 80 kg adult). Based on preliminary PK, Part A extension was amended to explore the intermediate trametinib dose level of 0.032 mg/kg/day in patients under 6 years of age.
- Part B: trametinib monotherapy dose expansion (n=41, PK for n=39). Based on Part A, a dose of 0.032 mg/kg was evaluated for patients < 6 years old and a dose of 0.025 mg/kg for patients ≥ 6 years old.
- Part C: D + T dose escalation (n=18, PK for n=18). Trametinib RP2D 0.025 mg/kg/day was administered, before extending to subjects < 6 years. The RP2D of dabrafenib was based on Study A2102: 5.25 mg/kg/day in patients < 12 years old and 4.5 mg/kg/day in patients ≥ 12 years old. The tested combination were thus: Trametinib 0.025 mg/kg/day + 50% Dabrafenib RP2D, Trametinib 0.025 mg/kg/day + 100% Dabrafenib RP2D, Trametinib 0.032 mg/kg/day + 100% Dabrafenib RP2D.
- Part D: clinical activity of D + T, dose expansion (n=30, PK for n= 29). Based on Part C, a dose of 0.032 mg/kg trametinib + 100% of the dabrafenib RP2D was evaluated in patients < 6 years old and a dose of 0.025 mg/kg trametinib + 100% of the dabrafenib RP2D was evaluated in patients ≥ 6 years old. The dabrafenib RP2D was defined based on [Study A2102] as 5.25 mg/kg/day in patients < 12 years old and 4.5 mg/kg/day in patients ≥ 12 years old.

Trametinib was administered orally, once daily under fasted conditions (at least 1 hour before or 2 hours after a meal). Dabrafenib was administered orally, twice daily under fasted conditions.

Trametinib steady state C_{avg} (Table 6) achieved the efficacy target (~10 ng/mL) on Cycle 1 Day 15 at the trametinib dose level of 0.025 mg/kg/day and above. The RP2Ds for trametinib monotherapy were determined based on DLTs and similar exposure as in adults and were 0.032 mg/kg/day for patients < 6 years old, and 0.025 mg/kg/day for patients ≥ 6 years old and were not to exceed the adult dose (2 mg). 100% RP2D (but not 50%) of dabrafenib was confirmed to reach the relevant target.

Table 7. Geomean (CV%) PK parameters (day 15) of trametinib and dabrafenib

Dose	Cavg (ng/mL)	AUCtau (hr*ng/mL)	Cmax (ng/mL)
Part A (trametinib dose escalation)			
Trametinib 0.0125 mg/kg/day n = 3	5.76 (24.8)	138 (24.8)	9.61 (32.9)
Trametinib 0.025 mg/kg/day n = 19	13.9 (27.1)	334 (27.1)	21.1 (33.3)
Trametinib 0.032 mg/kg/day n = 9	15.2 (16.9)	364 (16.9)	26.1 (16.8)
Trametinib 0.04 mg/kg/day n = 15	21.3 (20.7)	511 (20.7)	32.6 (28.9)
Part B (trametinib monotherapy expansion)			
Trametinib 0.025 mg/kg/day n = 38	14.3 (35.8)	343 (35.8)	24.2 (35.6)
Part C (D + T dose escalation); (trametinib PK parameters)			
Trametinib 0.025 mg/kg/day + 50% Dabrafenib RP2D n = 1	12.1 (NE)	290	26.0
Trametinib 0.025 mg/kg/day + 100% Dabrafenib RP2D n = 1	13.8 (NE)	331	24.5
Trametinib 0.032 mg/kg/day + 100% Dabrafenib RP2D n = 6	9.83 (28.4)	236 (28.4)	23.7 (36.3)
Part C (D + T dose escalation); (dabrafenib PK parameters)			
Trametinib 0.025 mg/kg/day + 50% Dabrafenib RP2D n = 3	239 (116.6)	2870 (116.6)	630 (235.2)
Trametinib 0.025 mg/kg/day + 100% Dabrafenib RP2D n = 7	347 (24.6)	4160 (24.6)	1560 (35.3)
Trametinib 0.032 mg/kg/day + 100% Dabrafenib RP2D n = 6	337 (47.9)	4040 (47.9)	1440 (43.3)
Part D (D + T expansion) (trametinib PK parameters)			
Trametinib 0.032 mg/kg/day + 100% Dabrafenib RP2D n = 5	9.50 (33.1)	228 (33.1)	25.9 (35.8)
Trametinib 0.025 mg/kg/day + 100% Dabrafenib RP2D n = 21	11.9 (28.4)	286 (28.4)	20.0 (38.1)
Part D (D + T expansion) (dabrafenib PK parameters)			
Trametinib 0.032 mg/kg/day + 100% Dabrafenib RP2D n = 6	346 (30.2)	4150 (30.2)	1840 (35.2)
Trametinib 0.025 mg/kg/day + 100% Dabrafenib RP2D n = 21	332 (47.3)	3990 (47.3)	1290 (68.7)

NE: Not estimable, due to not enough patients.

The phase II study G2201 was conducted to evaluate the effect of D + T combination therapy in children and adolescent patients 1 year of age and older with BRAF V600 mutation-positive LGG or relapsed or refractory HGG. PK characterisation was a secondary objective. The doses used for dabrafenib were based on study A2102 Part 2, 5.25 mg/kg/day (≤ 12 years old) and 4.5 mg/kg/day (> 12 years old) divided into 2 equal doses, capped at 150 mg twice daily. The doses used for trametinib were based on study X2101 Part B (0.032 mg/kg/day in < 6 years old and 0.025 mg/kg/day in ≥ 6 years old), capped at 2 mg per day. Both dabrafenib and trametinib were given under fasted conditions.

This study used dabrafenib capsules, trametinib tablets and both to be marketed liquid dosage forms dabrafenib 10 mg DT for oral suspension and trametinib PfOS. Patients were permitted to switch the formulations during the trial, and their PK parameters were pooled in the NCA analysis, but not in the popPK. The use of liquid formulations prevailed in paediatric patients up to 5 years, while the majority of older children took capsules (see tables above). PK parameters on day 15 (week 3 day 1) for dabrafenib and trametinib in the LGG and HGG cohort are presented in Table 8 and Table 9.

Table 8. LGG cohort: PK parameters on day 15: (a) dabrafenib; (b) trametinib**(a) dabrafenib**

Dose group	Statistics	AUClast (h × ng/mL)	Tlast (h)	AUCtau (h × ng/mL)	Cmax (ng/mL)	Tmax (h)	T1/2 (h)	Ctrough (ng/mL)	Cavg (ng/mL)	CL/F (mL/h)
Week 3 Day 1 (N=69)	n	54	54	47	54	54	18	54	47	47
	Mean (SD)	5610 (2970)	12.7 (1.52)	5530 (2670)	1730 (1210)	1.69 (1.09)	3.28 (1.25)	71.3 (74.2)	461 (222)	22100 (11400)
	CV%	52.9	12.0	48.2	69.7	64.3	38.2	104.2	48.2	51.7
	Geo-mean	4870	12.6	4910	1330	1.47	3.09	46.0	409	19200
	Geo-CV%	60.3	12.2	54.0	93.5	52.9	36.4	125.1	54.0	60.7
	Median	5050	12.4	4980	1460	1.35	3.11	49.1	415	21800
	Min-max	1230-15000	8.50-15.8	1190-12900	208-4870	0.50-6.00	1.34-7.15	2.96-387	99.3-1070	4670-54200

n = number of patients with corresponding evaluable PK parameters. Few patients discontinued prior to W3D1 or did not have sufficient data for calculation of PK parameters. Assumed steady state Ctrough is similar to steady state pre-dose concentration. Cavg = (AUCtau / Tau).
Source: Table 14.2-4.2L

(b) trametinib

Dose group	Statistics	AUClast (h × ng/mL)	Tlast (h)	AUCtau (h × ng/mL)	Cmax (ng/mL)	Tmax (h)	T1/2 (h)	Ctrough (ng/mL)	Cavg (ng/mL)	CL/F (mL/h)
Week 3 Day 1 (N=69)	n	55	55	44	55	55	14	55	44	44
	Mean (SD)	345 (107)	23.8 (3.23)	347 (73.1)	24.4 (8.93)	1.71 (1.20)	27.1 (7.63)	10.2 (3.00)	14.5 (3.05)	4430 (6800)
	CV%	30.9	13.6	21.1	36.6	69.9	28.2	29.3	21.1	153
	Geo-mean	328	23.6	339	22.7	1.53	25.7	9.82	14.1	3290
	Geo-CV%	33.4	17.0	22.2	41.1	54.6	37.9	30.1	22.2	69.0
	Median	337	24.0	348	24.0	1.30	27.6	9.97	14.5	3300
	Min-max	147-589	11.5-27.8	209-480	8.27-49.0	0.00-6.00	8.67-40.2	3.91-18.8	8.69-20.0	1180-47300

n = number of patients with corresponding evaluable PK parameters. Few patients discontinued prior to W3D1 or did not have sufficient data for calculation of PK parameters. Assumed steady state Ctrough is similar to steady state pre-dose concentration. Cavg = (AUCtau / Tau).
Source: Table 14.2-4.1L

Table 9. HGG cohort: PK parameters on day 15: (a) dabrafenib; (b) trametinib**(a) dabrafenib**

Dose group	Statistics	AUClast (h × ng/mL)	Tlast (h)	AUCtau (h × ng/mL)	Cmax (ng/mL)	Tmax (h)	T1/2 (h)	Ctrough (ng/mL)	Cavg (ng/mL)	CL/F (mL/h)
Week 3 Day 1 (N=39)	n	34	34	34	34	34	33	34	34	34
	Mean (SD)	4760 (2430)	12.5 (1.17)	4740 (2440)	1780 (979)	1.64 (0.750)	2.63 (0.927)	62.4 (61.7)	395 (203)	29700 (19300)
	CV%	51.0	9.4	51.5	55.1	45.6	35.2	98.8	51.5	64.9
	Geo-mean	4330	12.4	4300	1520	1.47	2.48	38.0	359	24100
	Geo-CV%	44.7	9.2	44.7	65.9	54.2	36.6	162.0	44.7	77.6
	Median	4210	12.0	4210	1740	2.00	2.27	39.8	351	26400
	Min-max	2080-15000	10.4-14.8	2040-15200	346-4630	0.50-4.00	0.94-4.95	1.27-246	170-1270	5270-96200

n = number of patients with corresponding evaluable PK parameters. Few patients discontinued prior to W3D1 or did not have sufficient data for calculation of PK parameters. Assumed steady state Ctrough is similar to steady state pre-dose concentration. Cavg = (AUCtau / Tau).
Source: Table 14.2-4.2H

(b) trametinib

Dose group	Statistics	AUClast (h × ng/mL)	Tlast (h)	AUCtau (h × ng/mL)	Cmax (ng/mL)	Tmax (h)	T1/2 (h)	Ctrough (ng/mL)	Cavg (ng/mL)	CL/F (mL/h)
Week 3 Day 1 (N=39)	n	36	36	33	36	36	24	36	33	33
	Mean (SD)	305 (93.9)	23.7 (4.21)	315 (74.8)	22.6 (7.46)	1.90 (1.27)	29.9 (11.9)	9.71 (3.09)	13.1 (3.11)	4080 (1880)
	CV%	30.8	17.8	23.8	33.0	67.1	39.7	31.8	23.8	46.0
	Geo-mean	282	22.6	307	21.3	1.67	26.7	8.73	12.8	3640
	Geo-CV%	53.7	43.6	22.8	36.3	58.1	62.6	72.7	22.8	53.9
	Median	296	24.0	289	20.8	1.95	30.1	9.46	12.0	3660
	Min-max	23.0-484	2.10-26.9	214-475	7.56-38.9	0.00-6.00	3.26-54.6	0.272-15.7	8.92-19.8	939-8870

n = number of patients with corresponding evaluable PK parameters. Few patients discontinued prior to W3D1 or did not have sufficient data for calculation of PK parameters. Assumed steady state Ctrough is similar to steady state pre-dose concentration. Cavg = (AUCtau / Tau).
Source: Table 14.2-4.1H

The Cavg values were comparable to the efficacy target plasma average concentrations of greater than 200 to 300 ng/mL for dabrafenib and of ≥ 10 ng/mL for trametinib that have been established in adult patients based on previous clinical exposure-response analyses in the approved indications. Similar dabrafenib and trametinib exposures were observed between patients with LGG and HGG.

Special populations

This medicinal product is intended to be used only in the paediatric population, therefore no data in elderly is available in the claimed indication, and children are the target population. Children with

hepatic or renal impairment were excluded from the paediatric studies. PK in special population was evaluated based on the adult popPK analysis, unless noted otherwise.

No dedicated renal impairment study was performed for trametinib. The pharmacokinetics of trametinib were characterised in adult patients enrolled in clinical trials with trametinib who had mild and moderate renal impairment using a population pharmacokinetic analysis. The popPK data regarding renal impairment suggest no effect of mild or moderate renal impairment. No data with trametinib in patients with defined severe renal impairment are available, in the SmPC it is recommended that trametinib in these patients is used with caution.

Population pharmacokinetic analyses and data from a clinical pharmacology study in adult patients with normal hepatic function or with mild, moderate or severe bilirubin and/or AST elevations (based on National Cancer Institute [NCI] classification) indicate that hepatic function does not significantly affect trametinib oral clearance.

Pharmacokinetic interaction studies

Results from a clinical study showed that trametinib increased the exposure to norethindrone when administered concomitantly (AUC increased ~20% and C_{max} ~ 3%). Trametinib did not affect the exposure to ethinyl estradiol when administered concomitantly (AUC increased ~5% and C_{max} decreased with ~8%). Based on these results, no loss of efficacy of hormonal contraceptives is expected when co administered with trametinib monotherapy.

Pharmacokinetics using human biomaterials

Trametinib as a substrate

Trametinib is mainly metabolised via deacetylation alone or with hydroxylation. Further metabolism occurs by glucuronidation. CYP3A4 oxidation is a minor pathway of metabolism. Trametinib is a substrate of human carboxylesterases 1b, 1c and 2 (hCES1b, hCES1c, and hCES2), which were involved in the formation of metabolite M5. Drug-drug interactions via these hydrolytic enzymes cannot be ruled out.

In vitro data demonstrate that trametinib is a substrate of human P-gp and it cannot be excluded that strong inhibition of hepatic P-gp may result in increased levels of trametinib.

Trametinib is not a substrate of CYP enzymes or of the transporters BCRP, OATP1B1, OATP1B3, OATP2B1, OCT1, MRP2, and MATE1. Trametinib is an *in vitro* substrate of BSEP, however trametinib exposure is unlikely to be affected by inhibition of BSEP.

Trametinib as a perpetrator

Based on *in vitro* studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP3A4. Trametinib was found to be an *in vitro* inhibitor of CYP2C8, CYP2C9 and CYP2C19, an inducer of CYP3A4 and an inhibitor of the transporters OAT1, OAT3, OCT2, MATE1, OATP1B1, OATP1B3, P-gp and BCRP. However, based on the low dose and low clinical systemic exposure relative to the *in vitro* potency of inhibition or induction values, trametinib is not considered to be an *in vivo* inhibitor or inducer of these enzymes or transporters, although transient inhibition of BCRP substrates in the gut may occur.

Excipient sulfobutylbetadex sodium

The liquid formulation of trametinib contains sulfobutylbetadex sodium as a solubilizing agent and therefore has theoretical potential for interactions with other drugs.

Exposure relevant for safety evaluation

Based on day 15 data from study G2201 pooled across doses, ages and formulations, geometric mean (CV%) steady state exposure of trametinib AUC_{tau} was 307 (22.8%) and 339 (22.2%) hr*ng/ml in the HGG and LGG cohorts, respectively, with C_{max} of 21.3 (36.3%) and 22.7 (41.1%) ng/mL.

2.6.2.2. Pharmacodynamics

Mechanism of action

Trametinib is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. MEK proteins are components of the extracellular signal-related kinase (ERK) pathway. In human cancers, this pathway is often activated by mutated forms of BRAF which activates MEK. Trametinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity.

Dabrafenib is an inhibitor of RAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway.

Thus, trametinib and dabrafenib inhibit two kinases in this pathway, MEK and RAF, and therefore the combination provides concomitant inhibition of the pathway. The combination of trametinib with dabrafenib has shown anti-tumour activity in BRAF V600 mutation-positive cancer cell lines *in vitro* and delays the emergence of resistance *in vivo* in BRAF V600 mutation-positive xenografts.

Primary and Secondary pharmacology

Primary pharmacology

No efficacy PD biomarker assessments or exposure-response analyses were performed for the present submission. The exposure-response relationships in the paediatric population with BRAF V600E mutation-positive glioma are hypothesised by the applicant to be similar to that of the previously established exposure-response relationships in adult patients with a variety of BRAF V600- mutation positive solid tumours.

In paediatric patients aged 1 year and older, a trametinib dose of 2 mg once daily in patients weighing ≥ 51 kg; a trametinib dose of 0.032 mg/kg in patients weighing 26 to 50 kg; and a trametinib dose of 0.038 mg/kg in patients weighing < 26 kg, is expected to achieve comparable plasma exposure to that previously reported to be effective in adult patients with BRAF V600 mutation-positive solid tumours.

Secondary Pharmacology

Trametinib, as the parent compound or the DMSO solvate, was evaluated in a total of 50 kinase assays covering 44 unique kinase enzymes. Trametinib was inactive (IC₅₀ > 10 μ M) against all but the B-RafV600E MEK1 cascade assay (BRAMA). This assay monitors the ATPase activity of phosphorylated-MEK1 that results from the phosphorylation of MEK by BRAFV600E. The IC₅₀ of 63 nM for trametinib was due to inhibition of MEK activation rather than the direct inhibition of BRAFV600E. Trametinib was also evaluated against 171 different kinase assays using an external kinase screening panel (Institutes for Pharmaceutical Discovery, Branford, CT) which found no significant ($> 50\%$) inhibition when screened at a single concentration of 10 μ M. In a separate study, trametinib was examined for effects in 7 enzyme assays (phospholipase A2, cyclooxygenase isoform 1 [COX1], constitutive NO synthase [NOS], phosphodiesterase 4, protein kinase C, acetylcholinesterase, monoamine oxidase A). Trametinib at a fixed concentration of 10 μ M showed no significant inhibitory effect on these enzymes.

The provided data are indicative of relative selectivity for the BRAF/MEK target.

2.6.3. Discussion on clinical pharmacology

Methods

During the routine GCP inspection of investigator sites of study G2201 (see also section 2.6.1 above), it was observed that no documentation was available on the handling and preparation of PK samples (e.g. time from blood sampling to centrifugation, centrifugation times and conditions, time to cooling) as the sponsor did not request the sites to document these points. Trametinib was stable on ice, but not stable after 2h in blood at room temperature (61.2 % remaining, DMPK-2012N140703_00). As study G2201 provides the reference therapeutic exposure for both formulations and supports the posology, the integrity of the PK data must be warranted. The applicant provided reassurance regarding the training of the staff at study sites, including the awareness of the need to place the samples on wet ice, with the exception of site 2004, where the manual was not followed regarding storage on ice. In the absence of additional deviation logs, it is assumed that samples were generally placed on ice, even if centrifugation may have been delayed. Handling of samples is similar for study X2101, where samples had to be centrifuged within a maximum of 30 min (1h in G2201), according to the manual. New stability data was provided, confirming the apparent instability of trametinib in whole blood at room temperature. Overall, the data indicate a concentration, temperature and time-dependence in the loss of trametinib. A flaw of the data is the available concentration, with no data available between 12 and 50 ng/mL, when the most relevant concentration range is between 10-20 ng/mL, which also corresponds to the concentration range where saturation seems to happen.

The data confirms that the loss of trametinib in whole blood when stored on ice is negligible irrespective of concentration. This would apply to the deviation noted at site 3304, where the deviation only pertains the time to centrifugation and not the storing on ice. In the case where samples are not stored on ice (site 2004), a loss of trametinib of 30% would be expected, based on the data at 12 ng/mL from study DMPK R1600155e. The concentration from samples from site 2004 should thus not be relied on. Trametinib PK data from two patients are available from site 2004. The overall bias due to data from site 2004 is nevertheless small, considering that PK data is available for 39/41 HGG patients (and 69/73 LGG patients) in study G2201. This data likely contributes to the general variability in PK.

Overall, the applicant has provided sufficient evidence that it can be reasonably expected that the samples were generally treated adequately, and the impact of the deviations identified on site 3304 and 2004 are agreed to be minor. Thus, data from study G2201 (and X2101) can be used in the popPK analyses and support the simplified posology for trametinib.

Absorption

The *in vitro* studies were adequately performed. Trametinib is an *in vitro* substrate of the efflux transporter P-gp and the proposed text in section 4.5 regarding that "caution is advised when co-administering trametinib with medicinal products that are strong inhibitors of P-gp" is considered acceptable.

The trametinib relative bioavailability study MEK115892 had an inadequate wash-out period of 7 days and the plasma concentrations collected in Period 2 were corrected based on the residual concentration from Period 1 and the corrected values were used for subsequent analysis of relative bioavailability. The study design is considered acceptable based on the long half-life (127 h) and study population (subjects with solid tumours). An early phase variant of the liquid oral dosage form was used in bioavailability study MEK115892 with lower amounts of sucralose and strawberry flavour compared to the late phase formulation used in the pivotal phase 3 study (G2201). The other excipients were similar.

The difference in composition between the early and late phase formulations is acceptable and the relative bioavailability study MEK115892 is considered representative for both formulations. The impact of the higher C_{max} with the liquid formulation at single dose was questioned and discussed not significantly higher at steady state. The increased C_{max} following trametinib liquid formulation compared to solid formulation is not considered clinically relevant, and AUC was similar.

No food interaction study was performed for the trametinib oral solution and the recommendation in the SmPC is that Spexotras and Finlee should be taken without food, at least one hour prior to or two hours after a meal. The fasting recommendation for Spexotras and Finlee is based on the posology criteria used in Phase II studies and the results from the food interaction study with the solid formulation for both dabrafenib and trametinib (tablet/capsule) (fasting vs high-fat, high-calorie meal) which was modest with a high-fat meal (10% and 30% decrease in single-dose AUC for trametinib and dabrafenib, respectively). The current fasting recommendation is not an optimal recommendation in small children. Practically, the recommendation results in 3 hours of fasting twice daily which is difficult to attain in small children and will be an extra stress factor for parents to these children with glioma.

According to EMA drug interaction guideline the possibility of an altered food effect should be considered and additional food interaction studies may be needed if the formulation is modified during the clinical development or if a new pharmaceutical form is developed.

The formulations of the tablet/capsule of Mekinist and Tafinlar are different compared to the applied liquid formulations (Spexotras and Finlee) and the conclusion that the food effect of the liquid formulations are expected to be similar to the immediate release solid formulations are not fully agreed. A study is needed to investigate the food effect for Spexotras and Finlee to explore whether less restrictive food recommendations (e.g. shorter fasting period, allowance of light or moderate meal) may be possible to facilitate compliance. A study investigating the effect of a low-fat low-calorie meal is planned with both dabrafenib and trametinib liquid formulations, as a post-authorisation measure (REC). Until the food effect study is available, the SmPC text in section 4.2 is agreed.

Some children of one year of age and older could still be breastfed or fed with baby formula. The applicant proposed to handle the food recommendation as in study G2201, i.e. that breastfeeding or baby formula would be allowed on demand. The corresponding SmPC text in section 4.2 is agreed.

Target population

As detailed in Table 3, Table 4 and table 5, diverse formulations were used during the paediatric development programme. Even though the respective final formulations were included in the pivotal study G2201, it seems that only a minority of patients received those in the group 6 years and older. This is regarded as a major flaw in the study planning and conduct, at least from the current point of view as these studies shall now build the basis for a MAA for the liquid formulation only. Since it is only the new liquid formulations that are applied for, the role of PK in this application is to ensure that all patients reach a safe and efficacious exposure as defined from study G2201 with the to be marketed formulation and proposed weight-based posology. The NCA pharmacokinetic results should be interpreted with caution due to the small number of subjects across the treatment groups and disease cohorts, and to the pooling of different formulations, despite them not being bioequivalent. The popPK analysis is more suitable, as it also takes the actual dose into account where dose adjustments were made or incomplete doses were taken. A comparison of the main PK parameters calculated by NCA based on formulations for 6-11 year old subjects showed comparable dose-normalised PK parameters between liquid formulation and solid formulation.

Population pharmacokinetic analysis

Pharmacokinetics of trametinib were evaluated in the target population consisting of paediatric glioma patients, including analysis using a population pharmacokinetic approach.

The objectives of the population pharmacokinetic (PopPK) analysis are considered relevant. The PopPK analysis has high impact for supporting the simplified dosing regimen. The PopPK analysis is also useful for describing differences between formulations. The pharmacokinetic data used for the PopPK analysis included concentration measurements collected from two clinical studies and appears overall reasonable. A reasonable number of patients are present in the different age groups and the body weight distribution covers a relevant range. However, most of the studied children from 6 years of age were administered the solid trametinib formulation. The trametinib liquid formulation which is the subject of the current procedure was therefore not studied extensively. C_{max} was clearly higher for the liquid than the solid trametinib formulation (+71%) following a single dose, however, at steady state, the relative difference between formulations is not as pronounced due to the long terminal half-life of trametinib. Steady-state PK results are considered more reflective of the clinical setting, compared to a single dose setting for trametinib. Although it is surprising that the dose-normalised $C_{max,ss}$ was higher for the solid than the liquid formulation, it could be agreed that these comparisons indicate that at steady-state, the difference in C_{max} between the solid and liquid formulation is less pronounced than following a single dose. Furthermore, the $C_{max,ss}$ was only slightly higher for the liquid formulation which is reassuring from a safety perspective. Some cautious interpretation may be required since the comparison may have been biased/confounded by weight; Heavier children were more likely to receive the solid formulation, compared to lighter children. As weight is known to be an influential covariate for trametinib (according to the PopPK analysis), it would have been more appropriate to somehow account for this when comparing the $C_{max,ss}$ between formulations. However, overall the current comparison of $C_{max,ss}$ indicates that the higher C_{max} of the liquid formulation will not translate to a clinically relevant elevated risk of safety.

A Bayesian approach was used for estimating model parameters. Overall relevant covariates were explored and an overall reasonable covariate model development was applied. Weight was implemented using estimated allometric exponents in the PopPK model. The applicant explored standard fixed allometric exponents (0.75 for clearances and 1 for volumes) also including allometric scaling of inter-compartmental clearance. Based on various goodness-of-fit plots and changes in the OFV, it is deemed acceptable to rely on estimated coefficients according to the final model.

The target exposure range derived based on the observed exposure in study G2201 (C_{avg} of 9.39-19.18 ng/mL) could be considered relevant in children with glioma and was defined using non-compartmental analysis, which is found adequate.

The applicant presented parameter estimates and various goodness-of-fit plots for the final model which is considered overall relevant. The parameter estimates were overall reasonable and with reasonable precision. An important diagnostic plot within the current procedure is pcVPCs (using actual time after dose as the independent variable) which were provided stratified by different weight-/age-groups, formulation and occasion/steady state. The final model did not show any relevant trends according to η vs covariate plots.

In the final PopPK model, the inter-compartmental clearance which is fixed to the adult value. When the inter-compartmental clearance was estimated based on the paediatric data, the estimates were similar, and it is considered acceptable to keep the inter-compartmental clearance fixed to the adult value. The current PopPK model assumes a two-compartment disposition model which is considered acceptable.

In addition to the target exposure range (see above), the predicted exposure following the dosing procedure for the liquid and solid formulation in the study G2201 protocol (also referred to as the observed posology) acts as another important reference for assessing the simplified posology. To allow efficient comparison across posologies, the applicant compared exposures following observed posology with the currently recommended simplified posology (Figure 4). The simulations indicate that the recommended posology achieves adequate exposure and is considered acceptable. The simulated exposure, represented by the 90% prediction interval, falls within the target exposure range to a reasonable extent. Below 30 kg, the lower end of the 90% prediction interval of the simulations is below the target exposure range, and below ~15kg, the median of the simulations (black dashed line) is below the target exposure range. This could imply that this subgroup may have suboptimal efficacy and, in theory, the dose in patients with body weight below ~15kg could be increased to achieve higher exposure. However, this is not considered a relevant approach in this case, since a dose of 0.04 mg/kg/day should not be exceeded based on findings from a dose ranging study in paediatric patients (Study X2101). In Study X2101, 0.0125, 0.025, 0.032 and 0.04 mg/kg/day dose levels were explored and due to signs of dose limiting toxicity for the 0.04 mg/kg/day arm, the applicant introduced a maximum dose of 0.04 mg/kg/day in paediatric patients. In line with the overall assessment it is considered that the maximum dose of 0.04 mg/kg/day is acceptable. Most likely, this maximum dose of 0.04 mg/kg/day would need to be exceeded in order to achieve higher exposure in patients below ~15 kg. Therefore, the recommended posology is considered acceptable, despite the somewhat low exposure in patients with weight below ~15 kg. Furthermore, it could be noted that the simulated exposure appears to be even lower for the G2201 protocol-defined posology (upper panel Figure 4) compared to the proposed posology (lower panel Figure 4). Between ~36-78kg, the upper end of the 90% prediction interval of the simulations is still within the target exposure range for the proposed posology, however, the median of the simulations (black dashed line) is still within the target exposure range. In summary, the proposed posology is considered acceptable.

Special populations

Based on the limited importance of renal excretion for trametinib clearance, the lack of a study in renally impaired patients is considered acceptable. Due to the limited number of data on hepatic impairment, it is agreed to state that caution should be applied when administering trametinib to patients with moderate and severe hepatic impairment. The SmPC statements for renally impaired patients in sections 4.2 and 5.2 are considered acceptable and adequate as well as the information regarding hepatic impairment. Regarding the remaining special populations and factors, body weight is the most influential predictor of PK which has been identified in the PopPK analysis. There are insufficient data to evaluate the potential effect of race on trametinib pharmacokinetics as clinical experience is limited to Caucasians. Based on population pharmacokinetic analyses in both adult and paediatric patients, gender was found to influence trametinib oral clearance. Although female patients are predicted to have higher exposure than male patients, these differences are unlikely to be clinically relevant and no dose adjustment is warranted.

Pharmacokinetic interaction studies

The interaction potential for trametinib as substrate and perpetrator of enzymes and transporters are adequately evaluated and relevant interaction are reflected in the SmPC. Discussion was required on the extrapolation of the interaction data from adults to the paediatric target age group, in particular with regards to carboxylesterase, that trametinib is a substrate of. The applicant further justified the extrapolation of the interaction data from adults to the paediatric target age group. Potential effect of an age dependent development of human carboxylesterases was discussed and denied, and it is

agreed that it is unlikely that the magnitude of drug interactions with respect to CES inhibition would differ between adult and paediatric patients.

The trametinib oral solution contains 100 mg/ml of sulfobutylbetadex sodium which may have the potential to affect the solubility and bioavailability of other oral medicinal products. Caution should be taken when the trametinib oral solution is administered with oral medicinal products that have low bioavailability and a narrow therapeutic index (e.g. imipramine, desipramine). The proposed warning is acceptable.

The interaction risk between sulfobutylbetadex sodium and dabrafenib is considered negligible, as the bioavailability of dabrafenib is relatively high.

Pharmacodynamics

No efficacy PD biomarker assessments or exposure-response analyses were performed for the present submission. Moreover, the extent of CNS penetration of the drug has not been measured. Exposure-response information in children with glioma would have given a better understanding of the exposure-response in children and how it may differ from adults. The exposure-response relationships in the paediatric population with BRAF V600E mutation-positive glioma are hypothesised by the applicant to be similar to that of the previously established exposure-response relationships in adult patients with a variety of BRAF V600- mutation positive solid tumours. This, however, cannot be ascertained. Not only are the tumour types different; moreover, there may be an impact of CNS drug distribution which renders the relation between plasma PK and the efficacy different. Overall though, for the current procedure there are efficacy- and safety data available and exposure-response analyses would only have had a supportive role with low impact on the overall benefit-risk assessment.

2.6.4. Conclusions on clinical pharmacology

The PK and PD of trametinib is generally well-described and it is overall considered acceptable.

The mechanism of action of dabrafenib and trametinib are well characterised in adults with V600 mutated oncological disease and the dose-selection has been done in line with the oncology paradigm targeting similar exposure as in adults.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- the MAH should submit a study investigating the effect of a low-fat/low-calorie meal following administration of the oral solution of trametinib and the dispersible tablet of dabrafenib.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

No formal dose-response studies have been carried out for the applied indications.

The applicant makes the assumption that therapeutic benefit in children would be achieved by targeting adult steady-state exposure, as observed in the approved indications of BRAF V600 mutation-positive tumours.

Thus, the basis for the dose selection were known exposure-response relationship in adult patients, and tolerability and exposure information obtained in paediatric Studies X2101 and A2102.

2.6.5.2. Main study

Title of study

Study CDRB436G2201: Study of Efficacy and Safety of Dabrafenib in Combination With Trametinib in Paediatric Patients With BRAF V600 Mutation Positive LGG or Relapsed or Refractory HGG Tumours.

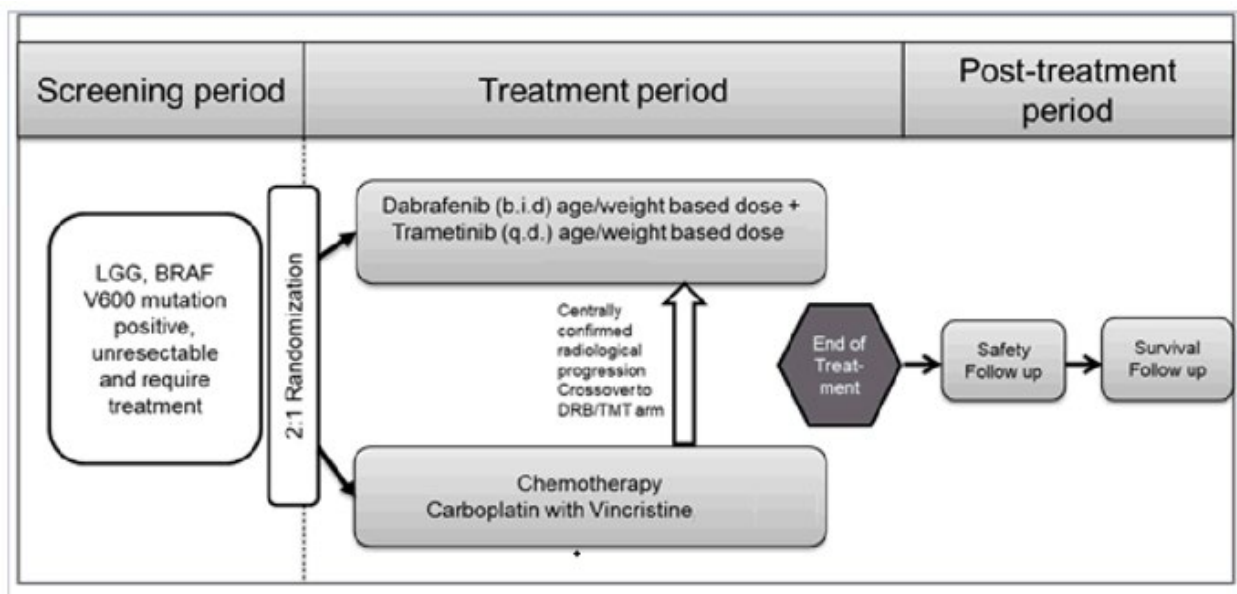
Methods

The pivotal study CDRB436G2201 (hereafter referred to as study G2201) combined two paediatric glioma cohorts into a single multi-centre, open-label, phase II study. Patients were enrolled at 58 centres across 20 countries.

The two cohorts consisted of paediatric patients with BRAF V600 mutation positive gliomas, with either low-grade glioma (the LGG cohort), or relapsed or refractory high-grade glioma (the HGG cohort).

- The LGG cohort was a 2:1 randomised comparison of dabrafenib with trametinib (D+T) versus chemotherapy carboplatin and vincristine (C+V) in chemotherapy naïve LGG patients.
- The HGG cohort had a single arm that evaluated the effect of dabrafenib with trametinib (D+T) in relapsed or refractory HGG patients in >2 line.

a) Study design for LGG cohort



b) Study design for HGG cohort

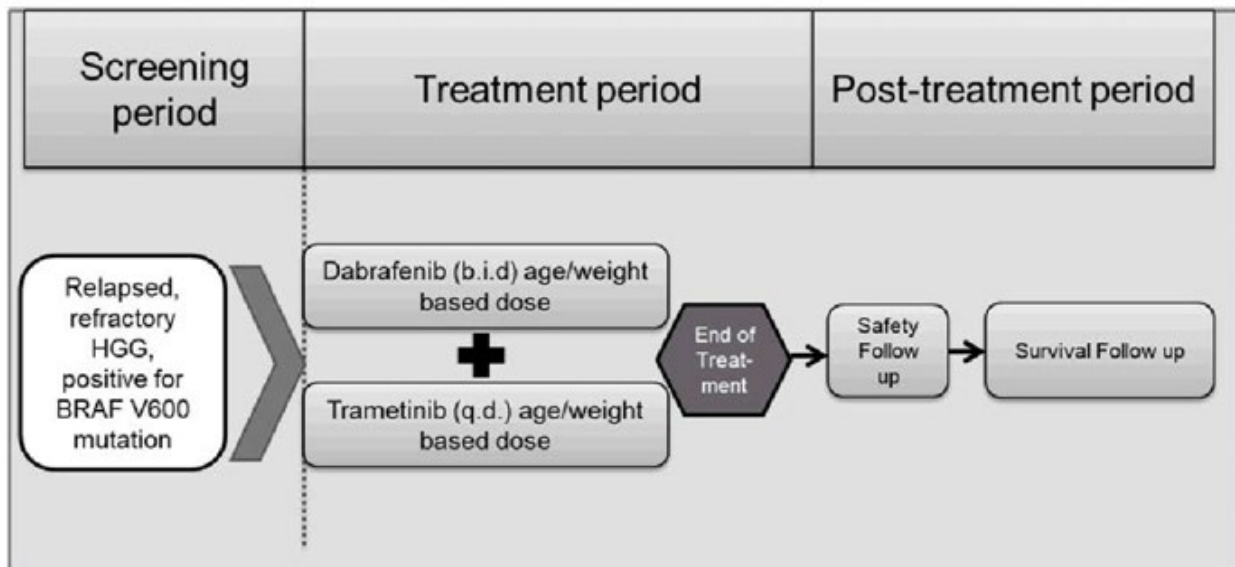


Figure 6. Study design for a) LGG cohort, and b) HGG cohort

- **Study Participants**

Key eligibility criteria;

- ≥ 12 months and < 18 years of age. Patients under 6 years old were to weigh at least 7 kg. Patients ≥ 6 years old were to weigh at least 10 kg at the time of enrolment.
- LGG or HGG as defined by WHO histological classification system, revised 2016.

LGG cohort only:

- Patients with progressive disease following surgical excision, or non-surgical candidates with necessity to begin systemic treatment because of a risk of neurological impairment with progression.

HGG cohort only:

- Relapsed, progressed, or failed to respond to frontline therapy.
- BRAF V600 mutation-positive tumour assessed locally, or at a Novartis designated central reference laboratory if local BRAF V600 testing was unavailable.
- If receiving glucocorticoids, patient was to be on a stable or weaning dose for at least 7 days prior to first dose of study treatment.

Key exclusion criteria;

- LGG patients
 - Any systemic anticancer therapy (chemotherapy, immunotherapy, biologic therapy or vaccine therapy) or investigational drugs prior to enrolment.
 - Radiotherapy to CNS glioma lesions at any point prior to enrolment.

- HGG patients
 - Cancer therapy (chemotherapy with delayed toxicity, immunotherapy, biologic therapy, vaccine therapy) or investigational drugs within 3 weeks preceding the first dose of study treatment.
 - Radiotherapy to CNS glioma lesions within 3 months prior to first dose of study treatment.
- **Treatments**

Dabrafenib with trametinib treatment (D+T) for both LGG and HGG cohort

Dabrafenib was administered orally, twice daily, and was dosed based on age and weight. Trametinib was administered orally, once daily in combination with the first daily dose of dabrafenib and was dosed based on age and weight.

In study G2201, the already available solid dose forms of dabrafenib and trametinib were considered suitable for approximating the intended mg/kg dose of each study drug for patients of sufficient weight. However, the liquid formulations were considered necessary to achieve the intended mg/kg dose for lower weight patients or those unable to reliably take the solid dose forms.

Formulation selection for dabrafenib in study G2201;

- Patients < 12 years old and ≥ 16 kg were to be administered either the dabrafenib capsules or dabrafenib dispersible tablets for oral suspension
- Patients ≥ 12 years old and ≥ 19 kg were to be administered either the dabrafenib capsules or dabrafenib dispersible tablets for oral suspension
- Patients < 12 years old and < 16 kg were to be administered dabrafenib dispersible tablets for oral suspension
- Patients ≥ 12 years old and < 19 kg were to be administered dabrafenib dispersible tablets for oral suspension

Formulation selection for trametinib in study G2201;

- Patients < 6 years old and < 26 kg were to be administered the trametinib oral solution
- Patients < 6 years old and ≥ 26 kg were to be administered either the trametinib oral solution or trametinib tablets
- Patients ≥ 6 years old and ≥ 10 kg < 33 kg were to be administered the trametinib oral solution
- Patients ≥ 6 years old and ≥ 33 kg were to be administered either the trametinib oral solution or the trametinib tablets

A dosing nomogram based on weight and/or age was used. The doses used for dabrafenib were 5.25 mg/kg/day (< 12 years old) and 4.5 mg/kg/day (≥ 12 years old) divided into 2 equal doses. The doses used for trametinib were 0.032 mg/kg/day (< 6 years old) and 0.025 mg/kg/day (≥ 6 years old).

Patients were to take D+T until no longer receiving clinical benefit as determined by the investigator, disease progression, death, unacceptable toxicity that precluded further treatment, start of new anticancer therapy, or the study was terminated by the Sponsor.

However, patients were permitted to continue D+T treatment beyond investigator-assessed, RANO-defined progressive disease, as long as they met the following criteria:

- Investigator assessed clear evidence of clinical benefit
- Tolerance of study treatment
- Continuation of study treatment was in the best interest of the patient as determined by the investigator
- Patient/legal guardian was willing to continue on the study and sign informed consent for treatment beyond progression.

In SmPC section 4.2 of both dabrafenib and trametinib, it is stated that dose modifications are necessary for only one of the two products in case of uveitis and RAS mutation positive non-cutaneous malignancies (*primarily related to dabrafenib*), and in case of left ventricular ejection fraction reduction, retinal vein occlusion, retinal pigment epithelial detachment and interstitial lung disease /pneumonitis (*primarily related to trametinib*). However, limited efficacy data on especially trametinib monotherapy are available. Thus, a warning on lack of efficacy data for monotherapy have been included in SmPC section 4.4.

In addition to study treatment, anti-cancer surgery was allowed in study G2201 after at least 36 months of treatment in the LGG cohort, and after at least 8 months on treatment in the HGG cohort, even without progression. Radiotherapy was allowed after at least a total of 36 months of treatment in both cohorts.

Carboplatin and vincristine (C+V) for LGG cohort only

Carboplatin with vincristine chemotherapy has been employed in the systemic treatment of paediatric patients with LGG for decades, and served as the standard of care treatment in several large studies (Ater 2012, Gnekow 2017). For the pivotal study G2201, the treatment regimen from COGA9952 was used for patients randomised to the comparator arm (Ater 2012).

C + V was administered as one course of induction (10 weeks of chemotherapy with 2 weeks of rest), followed by 8 cycles of maintenance chemotherapy. Each maintenance cycle was 6 weeks. The total planned duration of treatment with chemotherapy was therefore approximately 60 weeks.

Induction therapy;

- Carboplatin: 175 mg/m² as weekly i.v. infusion on Weeks 1 to 4, and Weeks 7 to 10.
- Vincristine: 1.5 mg/m² as weekly i.v. bolus infusion (0.05 mg/kg if child was <12 kg) (maximum dose of 2.0 mg) for 10 weeks.

Maintenance therapy;

Following induction therapy and two weeks of rest, maintenance therapy was to begin if peripheral blood counts were recovered. Each maintenance cycle was 6 weeks in duration and consisted of 4 weekly doses of carboplatin, and three weekly doses of vincristine given concomitantly with the first 3 weeks of carboplatin, followed by 2 weeks of rest. Maintenance continued for a total of 8 cycles.

Patients randomised to the carboplatin with vincristine treatment arm were allowed to cross over to receive dabrafenib in combination with trametinib after centrally confirmed RANO-defined disease progression.

- **Objectives**

The primary objective in the *LGG cohort* was to compare the anti-tumour activity of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by ORR by central independent assessment using the RANO criteria. Secondary objectives included the evaluation of ORR by investigator assessment, DOR by both investigator and central independent assessment, PFS by both investigator and central independent assessment, and OS.

The primary objective in the *HGG cohort* was to evaluate the anti-tumour activity of dabrafenib in combination with trametinib, as measured by ORR by central independent assessment using the Response Assessment in Neuro-Oncology (RANO) criteria. Secondary objectives included the evaluation of ORR by investigator assessment, DOR by investigator and central independent assessment, PFS by investigator and central independent assessment, and OS.

- **Outcomes/endpoints**

Selected endpoints in the LGG cohort

- ORR (primary endpoint) defined as the proportion of patients with a best overall confirmed CR or PR by blinded independent review per RANO criteria.
- DOR (secondary endpoint), calculated as the time from the date of the first documented confirmed response (CR or PR) to the first documented progression or death due to any cause, as assessed separately by investigator and central independent reviewer per RANO criteria.
- PFS (secondary endpoint), defined as time from date of randomization to progression or death due to any cause, as assessed separately by central independent reviewer and investigator per RANO criteria.
- OS (secondary endpoint), defined as the time from date of randomization to death due to any cause.
- CBR (clinical benefit rate) (secondary endpoint), proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of at least 24 weeks, as assessed separately by investigator and central independent reviewer per RANO criteria.

Selected endpoints in the HGG cohort

- ORR (primary endpoint), defined as the proportion of patients with a best overall confirmed CR or PR by independent assessment per RANO criteria.
- DOR (secondary endpoint), calculated as the time from the date of the first documented confirmed response (CR or PR) to the first documented progression or death due to any cause, as assessed separately by investigator and central independent reviewer per RANO criteria.
- PFS (secondary endpoint), defined as time from first dose of study treatment to progression or death due to any cause, as assessed separately by central independent reviewer and investigator per RANO criteria.
- OS (secondary endpoint), defined as the time from first dose of study treatment to death due to any cause.

The central RANO evaluation was conducted step-wise, first using only the radiologic data in a primary read, and then evaluated again including clinical data in a secondary read.

The RANO response criteria changed during the conduct of the studies with the introduction of RANO 2017 criteria. According to the applicant, the RANO response methods for HGG are indistinguishable

between RANO 2010 and 2017 criteria (Wen et al 2010, Wen et al 2017). The applicant has clarified that the primary efficacy endpoint (ORR) was based on RANO 2017 criteria for the LGG cohort, and on RANO 2010 criteria for the HGG cohort.

- **Sample size**

LGG cohort

To detect a 30% improvement in ORR based on central independent review response of 50% in the dabrafenib plus trametinib arm vs 20% in the carboplatin with vincristine arm (Lassaletta 2017 JCO) with at least 80% power, 102 patients are required to be randomised in the two treatment arms in a 2:1 ratio based on using a Maentel-Haenszel chi-squared test and one-sided $\alpha = 2.5\%$.

HGG cohort

Based on the exact binomial distribution, approximately 40 patients were to be enrolled if the study is not stopped for futility at the time of the interim analysis. The 95% CI, via the lower limit, is used to establish the levels of response which are exceeded by taking the combination therapy according to a robust standard of evidence (i.e., one-sided $\alpha=0.025$).

Due to the uncertainties regarding the historical control data there is no specific "success" threshold level that we can apply that the lower limit should be greater than to give robust evidence that dabrafenib and trametinib combination therapy is better than historical control; however, the study sample size gives reasonable operating characteristics for an illustrative threshold historical level of 20%, which is higher than the range expected based on the information given in the literature.

The study also aims to provide evidence that trametinib gives added value to the dabrafenib and trametinib combination over and above dabrafenib monotherapy treatment. Since a lower standard of evidence is usually required to show such added value, the lower limit of an 80% CI is used to identify the response rates which will be exceeded by taking the combination therapy based on a reduced level of evidence (one-sided α of 0.1). The number of patients in this trial give reasonable operating characteristics for an illustrative threshold level of 32%, which is the response rate observed in dabrafenib monotherapy patients in the study DRB436A2102 although based on limited data. Note that the 95% CIs can also be used to provide more robust evidence of the benefit of trametinib by looking at the lower limit compared to possible levels of dabrafenib monotherapy response.

For example, out of the 40 patients, with 14 responses (35%), the lower bound of 95% CI would be higher than 20%; with 18 responses (45%), the 80% CI would be higher than 32%; and with 20 responses (50%), the 95% CI would be higher than 32%.

HGG cohort was single-arm, powered to show the levels of response that exceed ORR rate in historical controls. Threshold used for historical control was ORR rate of:

- 20% which is higher than the applicant found in the literature for available therapies, and
- 32% which was used to denote a historical control of dabrafenib monotherapy.

For presentation of ORR levels above the 20% threshold, 95% CI was used. Regarding the indirect comparison to dabrafenib monotherapy (i.e., ORR of 32%), both 80% CI and 95% CI were considered. Operating characteristics were given in the Statistical Analysis Plan to illustrate potential outcomes. The indirect comparisons to historical control are considered only for the purpose of describing the sample size and not for hypothesis testing.

- **Randomisation and Blinding (masking)**

LGG cohort

Patients in the LGG cohort were randomised in a 2:1 ratio to dabrafenib with trametinib or carboplatin with vincristine. A patient randomization list was produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. No stratification was described for the randomization procedure which is acknowledged.

The LGG cohort is open label. Sponsor statisticians and statistical programmers were to remain blinded to the identity of the treatment from the time of randomization until database lock.

HGG cohort

All patients received the same treatment in the HGG cohort. Blinding was not applicable.

The study was open label for both cohorts. This may have affected study conduct and study subject disposition in the RCT. For example, there were 4 patients randomised to the control arm who did not receive randomised treatment due to patient/guardian or physician decision.

- **Statistical methods**

The data for the HGG and LGG cohorts were analysed independently with timing of analyses based on specific independent criteria for each cohort outlined in the study protocol.

The analysis cut-off date for the primary analysis of study data was established after all enrolled LGG patients have completed 32 weeks of treatment or had discontinued study; this was specified in the protocol amendment 2 in which the LGG cohort was added. The primary analysis was reported based on data cut-off date 23-Aug-2021.

Final analysis will be performed at the end of the study when all patients have been followed up for survival at least 2 years from last patient first treatment, except if consent is withdrawn, death, or patient is lost to follow-up or study discontinuation.

LGG cohort

Analysis sets

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

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

Evaluable set (Evaluable set-L) consisted of all evaluable patients in the FAS who had centrally confirmed measurable disease, centrally confirmed positive BRAFV600 mutation, an adequate tumour assessment at baseline, and a follow-up tumour assessment at least 8 weeks after starting treatment (unless disease progression is observed before that time) or had discontinued for any reason. An adequate tumour assessment at baseline refers to baseline measurable disease assessed by investigator and confirmed by central independent reviewer per RANO criteria. The evaluable set was used for sensitivity analyses.

Cross-over set (Cross-over set-L) comprised the subset of patients who were randomised to carboplatin with vincristine control arm and elected to cross-over to receive dabrafenib in combination

with trametinib treatment after centrally confirmed and RANO-defined disease progression. Only patients who received at least one dose of cross-over treatment were included in the cross-over set.

Primary analysis

ORR was defined as the proportion of patients with BOR of confirmed CR or PR according to RANO criteria. ORR was calculated using central independent review of tumour assessment data. Only tumour assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) was considered in the assessment of BOR.

The primary efficacy analysis in the LGG cohort was comparison of ORR between the two treatment arms, performed using a Mantel Haenszel chi-square test at one-sided 2.5% level of significance, based on the FAS. ORR was summarised using descriptive statistics (N, %) by treatment arm along with two-sided exact binomial 95% CIs (Clopper and Pearson 1934). The odds ratio (dabrafenib + trametinib vs carboplatin + vincristine) and its 95% CI were determined by logistic regression.

Primary estimand

The primary clinical question of interest is: what is the relative effect of the two treatment strategies in increasing the ORR by independent review as per RANO criteria in children and adolescent subjects with BRAFV600 mutant LGG with progressive disease, regardless of study treatment discontinuation and before start of any new anti-neoplastic therapy?

The justification for the primary estimand is that it will capture the treatment effect of the study drug even after treatment is discontinued but avoid potential confounding effects of any other new anti-neoplastic therapy.

The primary estimand is characterised by the following attributes:

- Population: all subjects randomised with BRAFV600 mutant LGG with progressive disease following surgical excision, or non-surgical candidates with necessity to begin first systemic treatment because of a risk of neurological impairment with progression.
- Primary Variable: BOR by independent review as per RANO criteria.
- Treatment: the randomised treatment (the investigational treatment dabrafenib plus trametinib or the control treatment vincristine plus carboplatin), regardless of treatment discontinuation.
- Handling of intercurrent events:

Intercurrent event	Strategy
Discontinuation of study treatment for any reason	Per treatment policy strategy, tumour assessment data collected after discontinuation of study treatment for any reason will be used to derive BOR. This includes subjects who were randomised but not treated.
Start of new anti-neoplastic therapy	Per while on treatment strategy, tumour assessments collected before start of new anti-neoplastic therapy will be used to derive BOR. Tumour assessments collected on/after the start of new therapy will not be considered for evaluation of BOR.

- Summary measure: proportion of subjects with BOR of a confirmed CR or PR by independent review as per RANO criteria between the treatment arms as assessed by the Mantel-Haenszel chi-squared test.

Sensitivity analyses for primary endpoint/estimand were performed using the evaluable set, with all other aspects of the estimand as defined above. Additionally, analyses with response as assessed by the investigator (instead of by central review) were done under the same estimand attributes.

Supplementary analysis for the primary estimand was performed where both pre-defined intercurrent events are handled using per treatment policy strategy.

Missing values

Patients with unknown or missing BOR were counted as non-responders in the analysis of ORR. If there was no baseline tumour assessment, all post-baseline overall lesion responses were expected to be 'Unknown'. If no valid post-baseline tumour assessments were available, the BOR was to be "Unknown". For the computation of ORR, these patients were included in the FAS and was counted as 'non-responders'. If a patient was determined to have non-measurable disease only, then the category of response could be expanded to include non-CR/non-PD.

Sensitivity analyses

The analysis of ORR was repeated using a stricter ITT approach i.e., including all response assessments irrespective of new anti-neoplastic therapy using the FAS. Response evaluations recorded after the initiation of new anti-neoplastic therapy were included in sensitivity analysis of ORR (i.e., the occurrence of new anti-neoplastic therapy was ignored for the analyses). The sensitivity analyses were performed based on both the investigator and independent review assessments using the FAS.

The ORR analysis was repeated based on radiographic response assessed by independent review by only incorporating the radiographic data which included the lesion measurements from target lesions, non-target lesions, and new lesion per RANO.

An assessment of the concordance between the central independent reviewer assessment and local investigator assessment of the BOR for each patient was provided.

Secondary endpoints

Duration of response (DOR) only applied to patients whose BOR was CR or PR according to RANO criteria. The start date was the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date was defined as the date of the first documented progression per RANO or death due to any cause. If a patient had not progressed or died or had received further anticancer therapy at the analysis cut-off date, DOR was censored at the date of the last adequate tumour evaluation before the cut-off date or before the start of the new anticancer therapy date, whichever was earlier.

PFS was calculated using RANO criteria based on investigators and central independent review of tumour assessments separately. If a patient had not progressed or died or had received any further anticancer therapy at the analysis cut-off date, PFS was censored at the date of the last adequate tumour evaluation date before the cut-off date or before the start of the new anticancer therapy date, whichever was earlier. Discontinuation due to disease progression without supporting evidence satisfying progression criteria per RANO was not considered disease progression for PFS derivation.

Table 10. Censoring rules for DOR and PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of randomization	Censored
Progression or death at or before next scheduled Assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim*	Date of last adequate assessment	Censored
New anticancer therapy (including cancer related surgery and radiotherapy) given prior to protocol defined progression (including patients who crossover from the control arm to the treatment arm)	Date of last adequate assessment on or prior to starting new anti-cancer therapy	Censored
Death before first PD assessment	Date of death	Event

* This refers to undocumented progression based on investigator claim only. Clinical Status will be considered as appropriate in the determination of progression per RANO criteria.

All deaths occurring on or before the cut-off date in the FAS were used in the OS analysis. If a patient was not known to have died at the time of analysis cut-off, OS was censored at the date of last contact.

The distribution of PFS and OS was estimated using the Kaplan-Meier method. The results were plotted graphically by treatment group. The median and 25th and 75th percentiles of PFS and OS along with 95% CIs were presented by treatment group. The hazard ratio for PFS and OS was calculated, along with its 95% CI, using a Cox model. A log-rank test at the one-sided 2.5% level of significance was used to compare the two treatment groups. The PFS and OS were formally tested at the time of primary analysis.

Clinical benefit rate (CBR) is defined as the proportion of patients with a BOR of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of 24 weeks.

Subgroup analysis

Efficacy analyses in subgroups were purely exploratory and intended to explore the consistency of treatment effect. Forest plot (n, odds ratio, 95% CI) was produced to graphically depict the treatment effect estimates in different subgroups. No inferential statistics (p-value) were produced for the subgroups. Subgroups mentioned in the SAP are by risk categories: radiographic progression as indication to treatment (Y/N), and gross total resection (Y/N).

Multiplicity

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

On treatments

Dose intensity (DI) and relative dose intensity (RDI) were summarised separately for each of the study treatment components, using the duration of exposure of each of the components. DI and RDI were summarised separately for induction and maintenance phase for carboplatin and vincristine.

The number of patients who had dose reductions, permanent discontinuations or interruptions, and the reasons, were summarised separately for each of the study treatment components.

HGG cohort

Analysis sets

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

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

Evaluable Set (Evaluable set-H) consisted of all evaluable patients in the FAS who had centrally confirmed HGG through histology, centrally confirmed positive BRAF V600 mutation, an adequate tumour assessment at baseline, a follow-up tumour assessment at least 8 weeks after starting treatment (unless disease progression was observed before that time) or had discontinued for any reason. An adequate tumour assessment at baseline refers to baseline measurable disease assessed by the investigator and confirmed by central independent reviewer per RANO criteria. The Evaluable set was used for sensitivity analyses.

Primary analysis

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

The point estimate and exact CIs (Clopper and Pearson 1934) of ORR were provided. The lower bound of the CIs was used to provide evidence that the true ORR is greater than a certain specific response rate. The 95% CI, via the lower limit, was used to establish the levels of response which were exceeded by taking the combination therapy according to a robust standard of evidence (i.e., one-sided $\alpha = 0.025$).

Intercurrent events of primary estimand for HGG cohort were handled as described in the table below:

Table 11. Handling of intercurrent events of primary estimand for HGG cohort

Intercurrent events	Strategy
Discontinuation of study treatment for any reason	Per treatment policy strategy, tumour assessment data collected after discontinuation of study treatment for any reason were used to derive BOR.
Start of new anti-neoplastic therapy	Per while on treatment strategy, tumour assessments collected before start of new anti-neoplastic therapy were used to derive BOR. Tumour assessments collected on/after the start of new therapy were not considered for evaluation of BOR.

Missing values

Patients with unknown or missing BOR were counted as failures. If there was no baseline tumour assessment, all post-baseline overall lesion responses were expected to be 'Unknown'. If no valid post-baseline tumour assessments were available, the BOR was "Unknown" unless progression was reported. For the computation of ORR, these patients were included in the FAS and counted as 'failures'.

Interim analysis

An interim analysis for futility was implemented to allow possible termination of recruitment in the HGG cohort in the event that there was insufficient efficacy. The patients for inclusion in the interim analysis were determined shortly after 16 patients in the FAS had been enrolled. The interim analysis was conducted when these patients had at least 20 weeks of follow-up or had withdrawn early. If the observed ORR assessed by the central independent reviewer was $\leq 25\%$, there could be a consideration to stop the HGG cohort due to insufficient efficacy. The final decision on whether to stop the HGG cohort also took into account all available study information at the IA cut-off including safety data and all efficacy endpoints.

At the time of data cut-off (24-Jul-2019), 6 of the 16 patients had ORR (best overall confirmed response of CR or PR). With a 37.5 % of ORR assessed by independent reviewer, the HGG cohort exceeded the 25% futility criteria for ORR. No new safety signals were observed in this interim analysis. Enrolment continued into the HGG cohort of the study. This futility analysis had no impact on the LGG cohort of this trial, which also continued enrolment. No formal interim analysis was planned for the LGG cohort.

The SAP governance

First SAP version was authored on 14 Mars 2018. The SAP was then updated on 20 September 2021, prior to the primary data base lock (DBL), to align with the protocol amendment 5. The most essential changes were following: clarification added that BOR is determined up to progression, addition of supportive analysis for randomised not treated subjects, addition of odds ratio for ORR, clarification that hierarchical testing will occur at the time of primary analysis, addition of analyses to describe the impact of COVID-19, addition of estimand language. The latest (current) version is dated 30 September 2021.

There was one futility interim analysis in the HGG cohort that was planned and performed. In the randomised LGG cohort, there was no interim analysis. The primary analysis was planned to be performed when all enrolled LGG patients have completed 32 weeks of treatment or had discontinued study, which is currently being reported based on the data cut-off date 23-Aug-2021 (this report). The study is still ongoing, with the final analysis to be performed when all patients have been followed up for survival at least 2 years.

The study is open label and the protocol has undergone five amendments. The SAP was updated twice during the course of the study. The first SAP version was authored at the time when the protocol amendment 2 was valid in which the randomised LGG cohort was added. Three protocol amendments later and shortly prior to the primary DBL, the SAP was updated.

The primary estimand for the ORR is described using the terminology of the ICH E9 (R1). Two key intercurrent events are foreseen: treatment discontinuations (handled using treatment policy) and start of new anti-neoplastic therapy (handled using while on treatment strategy). Supplementary estimand was analysed where both intercurrent events are treated according to treatment policy strategy.

Results

• Participant flow

LGG cohort

Table 12. Patient disposition in the LGG cohort

	D + T N=73 n (%)	C + V N=37 n (%)	All patients N=110 n (%)
Patient randomised	73 (100)	37 (100)	110 (100)
Treated	73 (100)	33 (89.2)	106 (96.4)
Not treated	0	4 (10.8)	4 (3.6)
Reason for not being treated			
Patient/guardian decision	0	3 (8.1)	3 (2.7)
Physician decision	0	1 (2.7)	1 (0.9)
Treatment ongoing¹	61 (83.6)	8 (21.6)	69 (62.7)
Discontinued treatment	12 (16.4)	25 (67.6)	37 (33.6)
Reason for discontinuation			
Progressive disease	5 (6.8)	9 (24.3)	14 (12.7)
Completed	0	9 (24.3)	9 (8.2)
Adverse event ²	3 (4.1)	6 (16.2)	9 (8.2)
Physician decision ³	2 (2.7)	0	2 (1.8)
New therapy for study indication ⁴	1 (1.4)	0	1 (0.9)
Protocol deviation ⁵	0	1 (2.7)	1 (0.9)
Patient/guardian decision ⁶	1 (1.4)	0	1 (0.9)
Post-treatment follow-up for patients who discontinued treatment			
Crossed-over to dabrafenib plus trametinib		9 (24.3)	9 (8.2)
Did not enter post-treatment follow-up	6 (8.2)	9 (24.3)	15 (13.6)
Entered post-treatment follow-up, ongoing *	5 (6.8)	13 (35.1)	18 (16.4)
Entered post-treatment follow-up, discontinued	1 (1.4)	3 (8.1)	4 (3.6)
Reason for discontinuation			
Completed	0	1 (2.7)	1 (0.9)
Physician decision	0	1 (2.7)	1 (0.9)
Progressive disease	0	1 (2.7)	1 (0.9)
Patient/guardian decision	1 (1.4)	0	1 (0.9)
Survival follow-up			
Did not enter Survival follow-up	1 (1.4)	11 (29.7)	12 (10.9)
Entered Survival follow-up	6 (8.2)	1 (2.7)	7 (6.4)
Alive	4 (5.5)	0	4 (3.6)
Unknown	2 (2.7)	1 (2.7)	3 (2.7)

¹Ongoing in randomised phase at the time of the DCO date 23-Aug-2021.

²Detailed narratives for patients who discontinued due to AEs are provided in [Section 14.3.3](#).

³Two patients in the D+T arm discontinued due to physician decision. One patient had PR as overall response by Investigator assessment on treatment for 2 years. The other patient had PR followed by SD as overall response by Investigator assessment on treatment for more than 2 years; this patient discontinued treatment as per Investigator's discussion with patient/family ([Listing 16.2.6-1.1L](#)).

⁴One patient in the D+T arm discontinued as the patient had radiotherapy ([Listing 16.2.4-4.4L](#)).

⁵One patient in the C+V arm discontinued due to a protocol deviation for I/E criteria – BRAF V600 mutation criteria was not met ([Listing 16.2.2-1.1L](#)). Further details are provided in [Section 10.1.2](#).

⁶One patient in the D+T arm discontinued due to patient/guardian decision; the patient was on treatment for more than 2 years; the patient had PR followed by PD and the patient's family decided to discontinue treatment ([Listing 16.2.6-1.1L](#)).

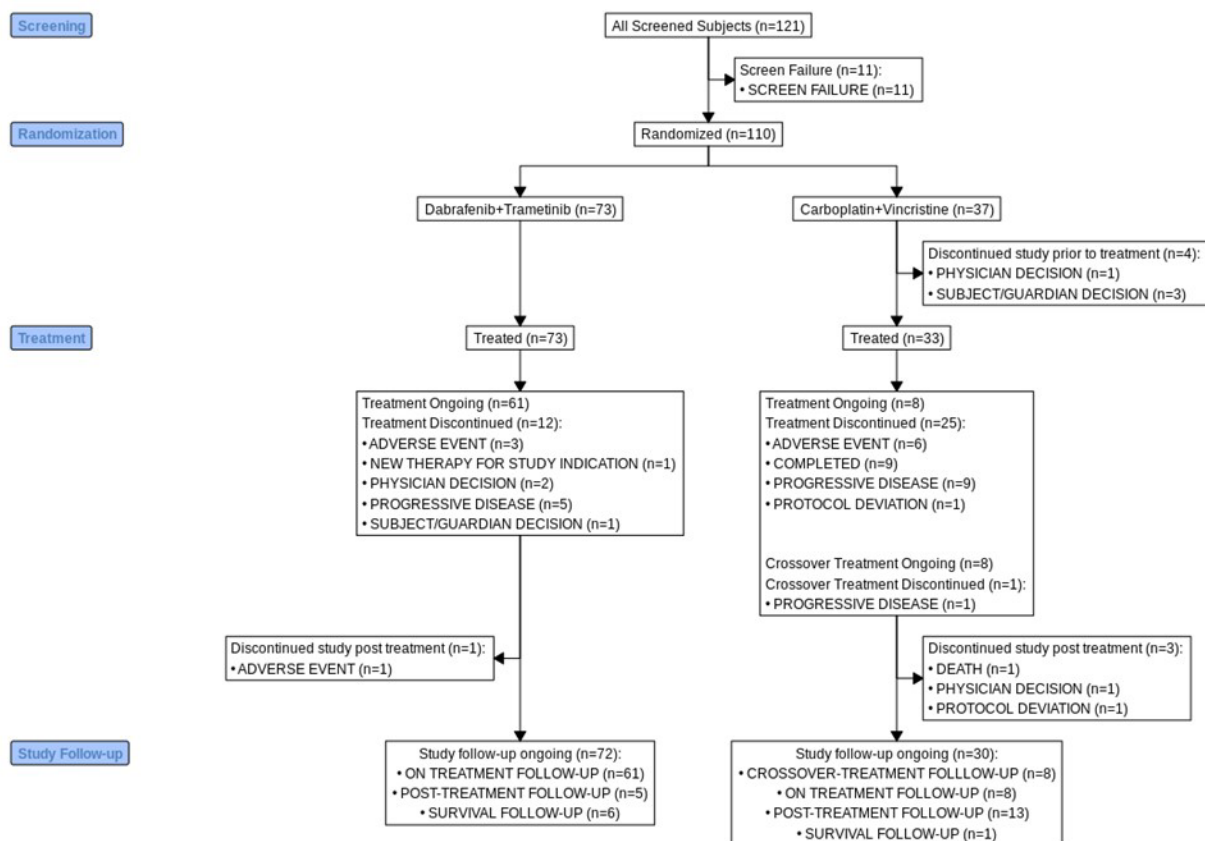


Figure 7. Consort diagram for LGG cohort of study G2201

At DCO date (23-Aug-2021), 69 patients (62.7%) had ongoing treatment (83.6% in D+T vs. 21.6% in C+V).

Patients in the D+T arm continued to receive treatment until disease progression or unacceptable toxicity (or until no longer receiving clinical benefit as determined by the investigator), while patients in the C+V arm received one course of induction followed by 8 cycles of maintenance chemotherapy with a maximum overall treatment duration of approximately 60 weeks. Nine patients (24.3%) in the C+V arm completed the treatment.

Cross-over to the D+T arm was allowed after centrally confirmed and RANO-defined disease progression. Nine 9 of the 37 patients in the C+V arm crossed-over to the D+T arm, of which 8 patients were ongoing in the cross-over phase at DCO date (23- Aug- 2021).

Table 13. Patient disposition in the HGG cohort

	All patients N = 41 n (%)
Patients treated	41 (100)
Treatment ongoing¹	21 (51.2)
No RANO progressive disease	19 (46.3)
Continuing post progressive disease	2 (4.9)
Discontinued treatment	20 (48.8)
Reason for discontinuation	
Progressive disease	16 (39.0)
Death	2 (4.9)
Adverse event ²	1 (2.4)
Physician decision ³	1 (2.4)
Post-treatment follow-up for patients who discontinued treatment	
Did not enter post-treatment follow-up	15 (36.6)
Entered post-treatment follow-up, ongoing ¹	2 (4.9)
Entered post-treatment follow-up, discontinued	3 (7.3)
Reason for discontinuation	
Death	3 (7.3)
Survival follow-up	
Did not enter Survival follow-up	7 (17.1)
Entered Survival follow-up	8 (19.5)
Alive	2 (4.9)
Dead	6 (14.6)

¹Ongoing at the time of the 23-Aug-2021 DCO date.

²Detailed narratives for patients who discontinue due to AEs are provided in [Section 14.3.3](#).

³The patient had progressive disease and the patient was advised to have surgery by the Investigator ([Listing 16.2.6-1.1H](#)).

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

As of the DCO date (23-Aug-2021), 21 patients (51.2%) had ongoing treatment.

It is noted that 2 patients (4.9%) continued treatment post-progression.

• Recruitment

Study period:

Study initiation date: 28-Dec-2017 (first patient first visit).

Data cut-off date: 23-Aug-2021 (the study is currently ongoing).

This submitted CSR presents the results of the primary analysis with a data cut-off date of 23-Aug-2021 when all patients had either completed at least 32 weeks of treatment (i.e. at least 24 weeks follow-up after the first post baseline tumour assessment) or had discontinued earlier.

Study centres:

The pivotal study G2201 was conducted in 58 centres across 20 countries; Argentina (1), Australia (2),

Belgium (1), Brazil (3), Canada (3), Czech Republic (2), Denmark (1), Finland (1), France (6), Germany (7), Israel (2), Italy (5), Japan (3), Netherlands (1), Russian Federation (1), Spain (4), Sweden (1), Switzerland (1), United Kingdom (3), United States (10).

- **Conduct of the study**

The submitted Clinical Study Report is version 3.0, dated 25-Jul-2022. The original study protocol (dated 02-Nov-2015) was amended 5 times, see selected key features of each amendment in the table below.

Table 14. Protocol amendments

Table 9-4	Protocol amendments
Version and date	Summary of key changes
Amendment 1 dated 07-Jun-2017	- Revised the investigational treatment regimen from dabrafenib monotherapy to include trametinib with dabrafenib for children and adolescents with BRAF V600 mutation-positive relapsed or refractory HGG - Guidance provided to the Sponsor by the FDA and CHMP, in addition to updated efficacy data from the ongoing dabrafenib monotherapy study (CDRB436A2102) supported the use of combination treatment in pediatric glioma clinical studies. - Safety related changes were also implemented to include: - Requirement to obtain informed consent/assent for patients who continued treatment beyond progression per RANO criteria. - Added ophthalmic examinations to follow any visual changes in patients receiving trametinib and dabrafenib combination therapy. - Updated dose modification guidance for combination treatment. - Revised cardiac toxicity monitoring and the conditions for re-starting study treatment per FDA advice. - Clarified that skeletal maturation monitoring of wrist or tibia could be assessed by X-ray or MRIs. - Added the collection of seizure AE on study treatment. - Updated the AESIs pertaining to dabrafenib and trametinib.
Amendment 2 dated 23-Feb-2018	- Added a new cohort of BRAF V600 mutant LGG children and adolescent patients whose tumor was unresectable and required systemic treatment. Additionally, the amendment also added a pediatric formulation of dabrafenib as a dispersible tablet. - The LGG cohort was added to enroll approximately 102 pediatric patients with BRAF V600 mutant LGG, randomized 2:1 dabrafenib with trametinib vs carboplatin plus vincristine, with overall response rate (PR+CR) as the primary endpoint. - In addition, taste questionnaires for trametinib and dabrafenib pediatric formulations were implemented for all patients who received the trametinib oral solution and/or dabrafenib oral suspension. The PROMIS PRO questionnaire was added for the LGG cohort of patients. Sparse PK collection was included for a subset of LGG patients.
Amendment 3 dated 07-Aug-2018	- Changed the age range of patients eligible to enroll in the study from ≥ 6 to < 18 years of age to ≥ 12 months to < 18 years of age. This change was possible as the recommended dose for the combination of dabrafenib with trametinib for patients between 12 months and 6 years of age had been determined. - The inclusion and exclusion criteria were updated to clarify the eligible population for the LGG cohort as patients with BRAF V600 mutant LGG, who either have progressive disease following surgical excision, or non-surgical candidates with necessity to begin first systemic treatment because of a risk of neurological impairment with progression. Further, the exclusion criteria specified that LGG patients who had any prior systemic anticancer therapy or antitumor radiotherapy were excluded. - The primary endpoint for the HGG cohort was changed from investigator assessment of ORR to central independent review of ORR. This change could lessen the potential for bias that could be introduced due to investigator assessment in a single arm study. Investigator assessment of ORR was therefore added as a secondary endpoint.
Amendment 4 dated 11-Mar-2019	- Added an additional interim analysis of key safety and pharmacokinetics (PK) data of the adolescent patients (ages ≥ 12 to < 18 years) in the HGG cohort to support a health authority request in the first half of 2019 for data in adolescent patients. - In addition, an exclusion criterion was added to exclude patients with history or current evidence of retinal vein occlusion and central serous retinopathy. This exclusion criteria is standard language for all studies with trametinib and was inadvertently omitted from previous versions of CDRB436G2201. - Optional CSF collection was removed. CSF samples were expected to be very limited (1/30 patients provided a sample), hence, the value of the analyses was limited.
Amendment 5 dated 26-Nov-2019	Added dose modification requirements for cases of severe cutaneous adverse reactions (SCARs) which had been reported during treatment with dabrafenib in combination with trametinib outside this clinical study.

In amendment 1, dated 07-June-2017, the investigational treatment was changed from dabrafenib monotherapy to dabrafenib + trametinib combination. This was in line with SAWP/CHMP advice given 2014. The first patient was enrolled in December 2017, after this amendment.

In amendment 2, dated 23-Feb-2018, the LGG cohort was added.

In amendment 3, dated 07-Aug-2018, the lower age range of eligible patients changed from ≥ 6 years, to ≥ 12 months, since the recommended dose for the combination of dabrafenib plus trametinib for patients between 12 months and 6 years had been determined. In addition, primary endpoint for the HGG cohort was changed from Investigator assessment to central Independent review, to lessen the potential for bias to be introduced.

It is noted that the majority of the patients in the LGG and HGG cohort were enrolled during amendment 4 and/or 5.

- **Baseline data**

LGG cohort

Table 15. Selected demographics and baseline characteristics in the LGG cohort

Demographic variable	D + T N=73	C + V N=37	All patients N=110
Age (years)			
n	73	37	110
Mean (SD)	9.3 (4.97)	8.8 (5.01)	9.1 (4.96)
Median	10.0	8.0	9.5
Q1-Q3	5.0-13.0	4.0-13.0	5.0-13.0
Min-Max	1-17	1-17	1-17
Age category-n (%)			
12 months - < 6 years	20 (27.4)	14 (37.8)	34 (30.9)
6 - <12 years	25 (34.2)	11 (29.7)	36 (32.7)
12 - <18 years	28 (38.4)	12 (32.4)	40 (36.4)
Sex-n (%)			
Female	44 (60.3)	22 (59.5)	66 (60.0)
Male	29 (39.7)	15 (40.5)	44 (40.0)
Race-n (%)			
White	55 (75.3)	25 (67.6)	80 (72.7)
Asian	5 (6.8)	3 (8.1)	8 (7.3)
Black or African American	2 (2.7)	3 (8.1)	5 (4.5)
Not reported	2 (2.7)	1 (2.7)	3 (2.7)
Unknown	6 (8.2)	4 (10.8)	10 (9.1)
Other	3 (4.1)	1 (2.7)	4 (3.6)
Ethnicity-n (%)			
Not Hispanic or Latino	48 (65.8)	17 (45.9)	65 (59.1)
Hispanic or Latino	8 (11.0)	4 (10.8)	12 (10.9)
Unknown	5 (6.8)	5 (13.5)	10 (9.1)
Not reported	12 (16.4)	11 (29.7)	23 (20.9)
Weight (kg)			
n	73	33	106
Mean (SD)	43.02 (26.364)	43.81 (26.527)	43.27 (26.291)
Median	36.50	38.20	36.75
Q1-Q3	22.30-61.80	22.40-60.60	22.30-61.80
Min-Max	7.8-115.0	9.0-110.3	7.8-115.0

Table 16. Disease characteristics in the LGG cohort

	D + T N=73	C + V N=37	All patients N=110
Disease history			
Pathology at initial diagnosis-n (%)			
Astrocytoma	1 (1.4)	1 (2.7)	2 (1.8)
Desmoplastic astrocytoma, NOS	0	1 (2.7)	1 (0.9)
Desmoplastic Infantile Astrocytoma	2 (2.7)	1 (2.7)	3 (2.7)
Diffuse Astrocytoma	1 (1.4)	1 (2.7)	2 (1.8)
Diffuse Glioma, Nos	2 (2.7)	0	2 (1.8)
Ganglioglioma	21 (28.8)	9 (24.3)	30 (27.3)
Glioneuronal, NOS	2 (2.7)	1 (2.7)	3 (2.7)
Infantile Desmoplastic GG	1 (1.4)	0	1 (0.9)
LGG, NOS	14 (19.2)	6 (16.2)	20 (18.2)
Pilocytic astrocytoma	22 (30.1)	12 (32.4)	34 (30.9)
Pleomorphic xanthoastrocytoma	6 (8.2)	4 (10.8)	10 (9.1)
Primitive neuroectodermal tumor	0	1 (2.7)	1 (0.9)
Missing	1 (1.4)	0	1 (0.9)
Histological grade at initial diagnosis - n (%)			
Grade 1	60 (82.2)	28 (75.7)	88 (80.0)
Grade 2	12 (16.4)	7 (18.9)	19 (17.3)
Grade 3	0	0	0
Grade 4	0	1 (2.7)	1 (0.9)
Missing	1 (1.4)	1 (2.7)	2 (1.8)
Time since initial diagnosis of primary site to study entry (months)			
n	72	33	105
Mean (SD)	15.6 (31.88)	6.6 (11.59)	12.8 (27.43)
Median	4.9	2.4	3.5
Q1-Q3	1.8-14.2	1.9-3.8	1.8-10.6
Min-Max	0.9-199.9	0.7-62.2	0.7-199.9
BRAF mutation status*			
V600E	70 (95.9)	35 (94.6)	105 (95.5)
Non-mutant	0	1 (2.7)	1 (0.9)
Other	3 (4.1)	0	3 (2.7)
Missing	0	1 (2.7)	1 (0.9)
Indication to treatment			
Blindness, one eye, low vision other eye	2 (2.7)	2 (5.4)	4 (3.6)
Clinical progression	21 (28.8)	7 (18.9)	28 (25.5)
Deterioration of visual acuity	19 (26.0)	11 (29.7)	30 (27.3)
Diencephalic syndrome of infancy	1 (1.4)	0	1 (0.9)
Neurologic symptoms	31 (42.5)	19 (51.4)	50 (45.5)
Nystagmus	9 (12.3)	5 (13.5)	14 (12.7)
Pressure effect of tumor mass	17 (23.3)	10 (27.0)	27 (24.5)
Radiological progression	44 (60.3)	15 (40.5)	59 (53.6)
Vision abnormal	22 (30.1)	19 (51.4)	41 (37.3)
Missing	1 (1.4)	0	1 (0.9)
Any metastatic sites			
Yes	7 (9.6)	2 (5.4)	9 (8.2)
No	66 (90.4)	35 (94.6)	101 (91.8)

*Local BRAF is presented when available otherwise central BRAF is presented.

One patient had grade 4 disease at diagnosis; this patient had primitive neuroectodermal tumor, termed LGG by Investigator and the patient was randomized to the C+V arm.

Of the 110 patients in the LGG cohort, 61 (55%) patients had BRAF V600 mutant status by both local and central assessments. Three patients had non-mutant BRAF V600 status centrally of which 2 patients had locally determined BRAF V600 status and 1 patient had missing status locally.

No patient in the LGG cohort had Neurofibromatosis type 1 syndrome.

The median duration of exposure to dabrafenib was 75.7 weeks (range: 2.71-149.7) and to trametinib was also 75.7 weeks (range: 2.71-149.7).

The median duration of exposure to carboplatin was 34.0 weeks (range: 12.0-70.1) and to vincristine was 35.3 weeks (range: 12.0-70.1).

Systemic corticosteroids (as clinically indicated) were used in 30.1% of patients in the D+T arm and 45.5% of patients in the C+V arm.

HGG cohort

Table 17. Selected demographics and baseline characteristics in the HGG cohort

Demographic variable	All patients N=41
Age (years)	
n	41
Mean (SD)	12.12 (4.451)
Median	13.00
Q1-Q3	10.00 - 16.00
Min-Max	2.0 - 17.0
Age category-n (%)	
12 months - < 6 years	5 (12.2)
6 - <12 years	10 (24.4)
12 - <18 years	26 (63.4)
Sex-n (%)	
Female	23 (56.1)
Male	18 (43.9)
Race-n (%)	
White	25 (61.0)
Asian	11 (26.8)
Black Or African American	1 (2.4)
Not Reported	1 (2.4)
Unknown	3 (7.3)
Ethnicity-n (%)	
Not Hispanic Or Latino	26 (63.4)
Hispanic Or Latino	5 (12.2)
Not Reported	7 (17.1)
Unknown	3 (7.3)
Weight (kg)	
n	41
Mean (SD)	49.82 (27.381)
Median	44.90
Q1-Q3	33.20 - 57.40
Min-Max	11.3 - 155.6

Table 18. Selected disease characteristic in the HGG cohort, per institution at diagnosis

Disease history	All patients N=41
Pathology at initial diagnosis - n (%)	
Anaplastic astrocytoma	3 (7.3)
Anaplastic ganglioglioma	2 (4.9)
Anaplastic pilocytic astrocytoma	1 (2.4)
Anaplastic pleomorphic xanthoastrocytoma	6 (14.6)
Diffuse midline glioma (H3K27M Mutated)	2 (4.9)
Diffuse midline glioma, NOS	1 (2.4)
Epitheloid glioblastoma multiforme	1 (2.4)
Ganglioglioma	1 (2.4)
Glioblastoma multiforme	13 (31.7)
HGG, NOS	4 (9.8)
LGG, NOS	1 (2.4)
Oligodendroglioma	1 (2.4)
Pleomorphic Xanthoastrocytoma	4 (9.8)
Unknown	1 (2.4)
Missing	0
Histological grade at initial diagnosis - n (%)	
Grade 1	3 (7.3)
Grade 2	4 (9.8)
Grade 3	13 (31.7)
Grade 4	20 (48.8)
Missing	1 (2.4)
Time since initial diagnosis of primary site to study entry (months)	
n	41
Mean (SD)	30.5 (38.89)
Median	17.4
Q1-Q3	8.3-30.4
Min-Max	2.7-174.3
BRAF mutation status	
V600E ¹	41 (100)

¹Local BRAF is presented when available otherwise central BRAF is presented

Thirty-one patients (75.6%) had BRAF V600 mutant status by both local and central assessments. Five patients with missing local mutation status were enrolled with centrally determined BRAF V600E status at the time of screening. Of the remaining 5 patients, 4 patient samples could not be analysed centrally due to insufficient or not evaluable, and 1 was non-mutant centrally. All these 5 patients were enrolled by locally determined BRAF V600 status.

All patients except one (97.6%) had prior surgery, with the majority of patients (61.0%) with residual disease. In total, 90.2% of patients underwent prior radiotherapy mostly in the adjuvant setting (48.8%), and 80.5% of patients had received chemotherapy mostly in the adjuvant setting (51.2%).

No patient in the HGG cohort had Neurofibromatosis type 1 syndrome.

The median duration of exposure to both dabrafenib and trametinib was 72.7 weeks (range: 1.3-172.1) at the time of DCO.

Twenty patients (48.8%) received systemic corticosteroids (as clinically indicated).

- **Numbers analysed**

LGG cohort

All 110 LGG patients were included in the **FAS-L**.

HGG cohort

All 41 HGG patients were included in the **FAS-H**.

- **Outcomes and estimation**

Results of the primary analysis with a data cut-off date of 23-Aug- 2021.

LGG cohort

- **Primary endpoint**

Table 19. ORR by independent review in FAS-L

	D+T N=73		C+V N = 37		Odds ratio between treatment groups		p-values (one- sided) ³
	n (%)	95% CI ¹	n (%)	95% CI ¹	OR ²	95% CI ²	
Best overall response							
Complete Response (CR)	2 (2.7)		1 (2.7)				
Partial Response (PR)	32 (43.8)		3 (8.1)				
Stable Disease (SD) ⁴	30 (41.1)		15 (40.5)				
Progressive Disease (PD)	8 (11.0)		12 (32.4)				
Unknown (UNK)	1 (1.4)		6 (16.2)				
Overall Response Rate (ORR: CR+PR)	34 (46.6)	(34.8, 58.6)	4 (10.8)	(3.0, 25.4)	7.19	(2.3, 22.4)	<0.001
Clinical Benefit Rate (CBR: CR+PR+SD⁵)	63 (86.3)	(76.2, 93.2)	17 (45.9)	(29.5, 63.1)	7.41	(2.9, 18.8)	<0.001

N: The total number of patients in the treatment group. It is the denominator for percentage (%) calculation.

n: Number of patients who are at the corresponding category.

¹The exact binomial 95% CI (Clopper and Pearson 1934).

²Odds ratio (D+T vs C+V) and 95% confidence interval are from a logistic regression with treatment as the only covariate. Odds ratio > 1 favors D+T.

³The p-value is computed from chi-square test (Mantel-Haenszel) at a one-sided 2.5% level of significance

⁴SD: Response SD for 16 weeks or longer is recorded at 15 weeks or later (i.e. ≥ 105 days) from randomization date.

⁵SD: Response SD for 24 weeks or longer is recorded at 23 weeks or later (i.e. ≥ 161 days) from randomization date.

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

CR were reported in 2 patients (2.7%) in the D+T arm and 1 patient (2.7%) in the C+V arm.

The treatment outcomes for ORR in the chemotherapy C+V arm are considered to be in line with historical expectations in patients with BRAF mutated LGG (Lassaletta et al 2017, Nobre et al 2020, Ater et al 2012).

- **Secondary endpoints**

ORR as determined per Investigator was 54.8% (95% CI: 42.7, 66.5) in the D+T arm and 13.5% (95% CI: 4.5, 28.8) in C+V arm, with an odds ratio of 7.76 (95% CI: 2.7, 22.2), which is consistent with the ORR observed per Independent review. The overall concordance rate of BOR between independent review and investigator assessment was 66.4%. More progression events were identified by Independent review than by local investigator in both treatment arms, the Independent review identified more frequent increases of at least 25% from nadir measurements than the Investigator.

Preplanned supportive and sensitivity analyses of ORR were overall consistent with the primary analysis, which indicates robustness of the ORR results. Further, a sensitivity analysis of ORR for patients randomised to the chemotherapy C+V arm but not treated (n=4) was performed, and results were still statistically significant in favor of D+T arm also when the 4 patients who discontinued prior to receiving treatment were considered to be responders.

In addition, ORR analysis by Independent review using only the radiographic data (but not including clinical status and steroid use data that may introduce bias) is consistent with the primary ORR analysis using full RANO criteria, which supports the robustness in the RANO criteria.

Table 20. Supportive analyses of ORR.

D+T			C+V		Odds ratio between treatment groups	
	n (%)	95% CI ¹	n (%)	95% CI ¹	OR ²	95% CI ¹
Independent review						
Sensitivity analyses: new anticancer therapy (FAS-L)						
N	73		37			
Overall Response Rate (ORR: CR+PR)	34 (46.6)	(34.8, 58.6)	4 (10.8)	(3.0, 25.4)	7.19	(2.3, 22.4)
Evaluable set-L						
N	49		19			
Overall Response Rate (ORR: CR+PR)	21 (42.9)	(28.8, 57.8)	2 (10.5)	(1.3, 33.1)	6.37	(1.3, 30.7)
Radiographic response FAS-L						
N	73		37			
Overall Response Rate (ORR: CR+PR)	34 (46.6)	(34.8, 58.6)	4 (10.8)	(3.0, 25.4)	7.19	(2.3, 22.4)
Radiographic response Evaluable set-L						
N	49		19			
Overall Response Rate (ORR: CR+PR)	21 (42.9)	(28.8, 57.8)	2 (10.5)	(1.3, 33.1)	6.37	(1.3, 30.7)
Investigator assessment						
Sensitivity analyses: new anticancer therapy (FAS-L)						
N	73		37			
Overall Response Rate (ORR: CR+PR)	40 (54.8)	(42.7, 66.5)	6 (16.2)	(6.2, 32.0)	6.26	(2.3, 16.8)
Evaluable set-L						
N	49		19			
Overall Response Rate (ORR: CR+PR)	28 (57.1)	(42.2, 71.2)	3 (15.8)	(3.4, 39.6)	7.11	(1.8, 27.6)

¹The exact binomial 95% CI (Clopper and Pearson 1934).

²Odds ratio (D+T vs C+V) and 95% CI are from a logistic regression with treatment as the only covariate. Odds ratio > 1 favors D+T.

Median PFS per Independent review of 20.1 months (95% CI: 12.8, NE) in the D+T arm and 7.4 months (95% CI: 3.6, 11.8) in the C+V arm, with HR 0.31 (95% CI: 0.17, 0.55), which indicates a clinically relevant efficacy of treatment with D+T in patients with LGG who require first line systemic therapy.

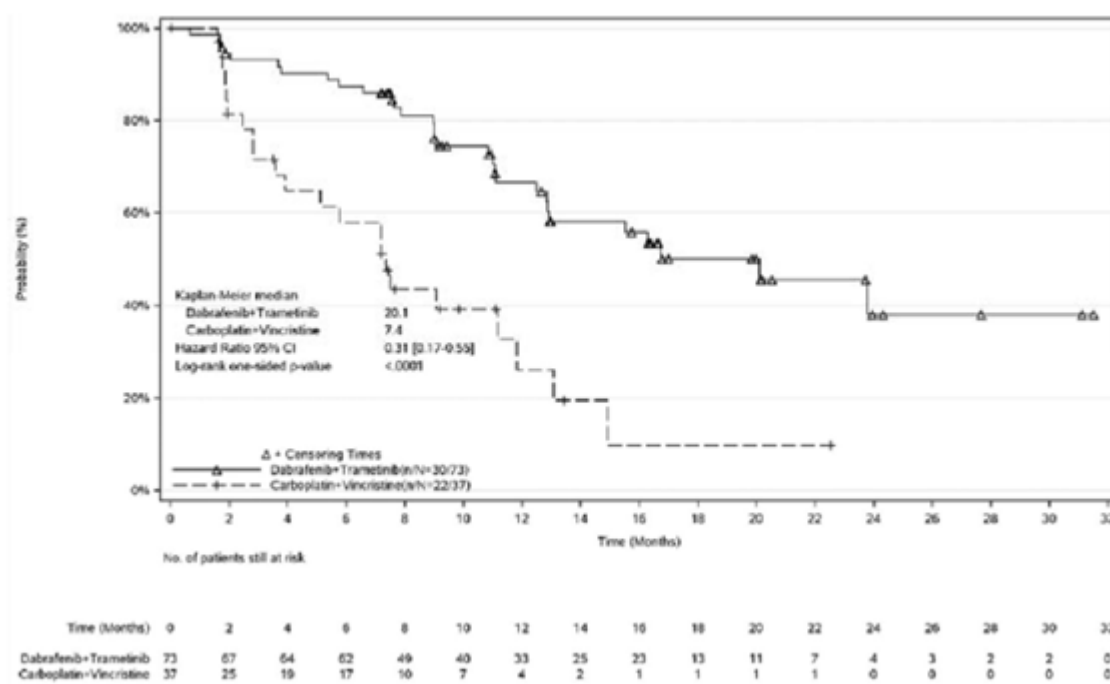


Figure 8. Kaplan-Meier plot of PFS based on independent review and using RANO criteria (FAS-L)

Table 21. Reasons for censoring in the PFS analysis based on Independent review

	Dabrafenib+Trametinib N=73 n (%)	Carboplatin+Vincristine N=37 n (%)
Reason of censoring		
Number of subjects censored	43 (58.9)	15 (40.5)
Reason of censoring		
Ongoing without event (1)	40 (54.8)	8 (21.6)
Lost to follow-up (2)	0	0
Withdrew consent	0	3 (8.1)
Initiation of new cancer therapy	1 (1.4)	2 (5.4)
Event after >=2 missing tumor assessments	1 (1.4)	0
Adequate assessment no longer available (3)	1 (1.4)	2 (5.4)

- (1)Subjects without event and had adequate follow-up as of data cut-off
 - (2)Recorded on the End of treatment CRF, Study evaluation completion CRF or defined as not adequately followed as of the cut-off
 - (3)If the time interval is larger than the interval of 2 missing tumor assessments with no event observed or without adequate baseline assessments

PFS as determined per Investigator was also in favour of the D+T arm compared to the chemotherapy C+V arm, HR 0.37 (95% CI: 0.14, 0.93). In line with ORR assessment, there were fewer PFS events identified by Investigator assessment than by Independent review.

Results of preplanned supportive analyses of PFS were overall consistent with the PFS results per Independent review.

Among patients with confirmed CR or PR, the median DOR per Independent review was 20.3 months (95% CI: 12.0, NE) in the D+T arm while the median DOR was not estimable in the C+V arm.

Using descriptive statistics, among patients with confirmed response (CR or PR), the median TTR was 3.6 months (range: 1.6-13.0) vs. 3.8 months (range: 3.7-5.3) by Independent review in the D+T arm vs. the chemotherapy C+V arm, respectively.

CBR was 86.3% vs. 45.9% in the D+T arm compared to the C+V arm, by Independent review.

With a median follow-up of 18.9 months (range: 7.9-35.4) in the LGG cohort, OS data are immature with no deaths in the D+T arm and 1 death in the chemotherapy C+V arm.

Only 9 patients were in the cross-over phase, and showed an ORR of 33.3% (95% CI: 7.5, 70.1), which needs to be interpreted with caution due to the limited number of patients.

HGG cohort

- **Primary endpoint**

Table 22. ORR per independent review

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

N: The total number of patients in the treatment group. It is the denominator for percentage (%) calculation.

n: Number of patients who are at the corresponding category.

¹SD: Response SD for 16 weeks or longer is recorded at 15 weeks or later (i.e. ≥ 105 days) from treatment start date.

²SD: Response SD for 24 weeks or longer is recorded at 23 weeks or later (i.e. ≥ 161 days) from treatment start date.

The exact binomial 95% CI/80% CI (Clopper and Pearson 1934) is presented.

The pre-defined success criteria of ORR per Independent review in the HGG cohort was met, with an ORR of 56.1%, (95% CI: 39.7, 71.5, 80% CI: 44.9, 66.8). The lower bound of the 95% CI for D+T treatment ORR exceeded the 20% rate prespecified in the study protocol based on the historical rates of ORR for patients with molecularly unselected relapsed refractory pHGG (5-12%) treated with the best available therapy.

CR was reported in 12 patients (29.3%) and PR in 11 patients (26.8%).

The protocol specified a waiting period of at least 3 months beyond prior given radiotherapy, which was accepted by the SAWP. In 36 of the 37 patients that had received radiotherapy prior to study entry, the irradiation occurred more than 3 months before start of study treatment. One patient received prior radiotherapy less than 3 months before study treatment, and received the first dose of study treatment after a duration of >2 months since the radiotherapy. As per Independent review, the patient had SD on Day 46 and was noted to progress from Day 107 with BOR of PD. Overall, prior given radiotherapy to patients in the HGG cohort is not considered likely to have an impact on the efficacy conclusions.

- **Secondary endpoints**

ORR as determined per Investigator assessment was 58.5% (95% CI: 42.1, 73.7; 80% CI: 47.3, 69.1). The concordance rate of BOR between Independent review and Investigator assessment was 73.2%.

Preplanned supportive and sensitivity analyses of ORR demonstrated overall consistency of the ORR results per Independent review.

ORR analysis by Independent review using only the radiographic response, (but not including clinical status and steroid use data that may introduce bias) is consistent with the primary ORR analysis using full RANO criteria, which is considered to support the robustness in the RANO criteria.

Table 23. Supportive analyses of ORR

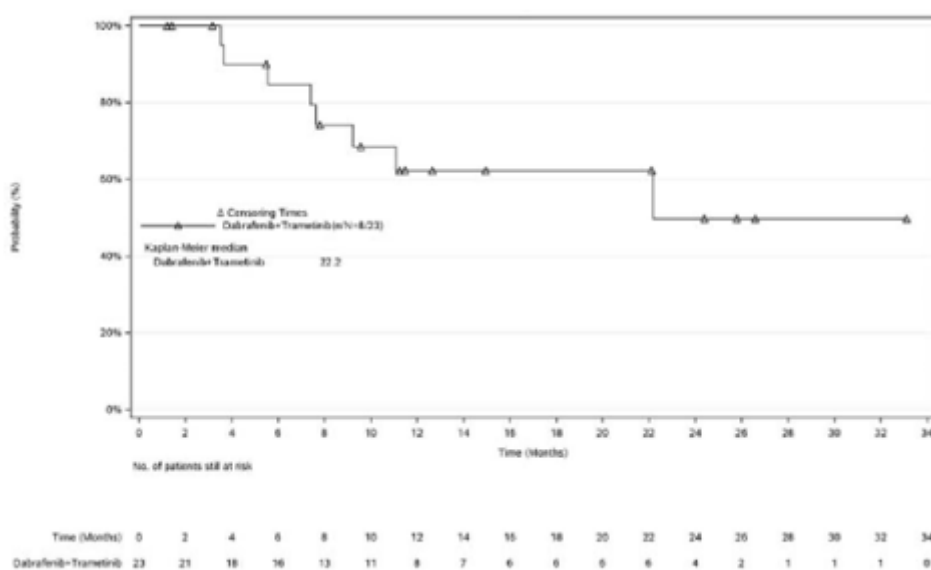
	N (%)	D+T	95% CI
Independent review			
Sensitivity analyses: new anticancer therapy (FAS-H)			
N		41	
Overall Response Rate (ORR: CR+PR)	23 (56.1)		(39.7, 71.5)
Evaluable set-H			
N		27	
Overall Response Rate (ORR: CR+PR)	17 (63.0)		(42.4, 80.6)
Radiographic response FAS-H			
N		41	
Overall Response Rate (ORR: CR+PR)	23 (56.1)		(39.7, 71.5)
Radiographic response Evaluable set-H			
N		27	
Overall Response Rate (ORR: CR+PR)	17 (63.0)		(42.4, 80.6)
Investigator assessment			
Sensitivity analyses: new anticancer therapy (FAS-H)			
N		41	
Overall Response Rate (ORR: CR+PR)	24 (58.5)		(42.1, 73.7)
Evaluable set-H			
N		27	
Overall Response Rate (ORR: CR+PR)	17 (63.0)		(42.4, 80.6)

¹The exact binomial 95% CI (Clopper and Pearson 1934).

Source: Table 14.2-1.3.1H, Table 14.2-1.5H, Table 14.2-1.4H, Table 14.2-1.6H, Table 14.2-1.1.2H, Table 14.2-1.3.2H

The median DOR of 22.2 months (95% CI: 7.6, NE) per Independent review indicates a clinically relevant efficacy of treatment with D+T in second line treatment of HGG patients.

Figure 9. KM plot of DOR per independent review (FAS-H).

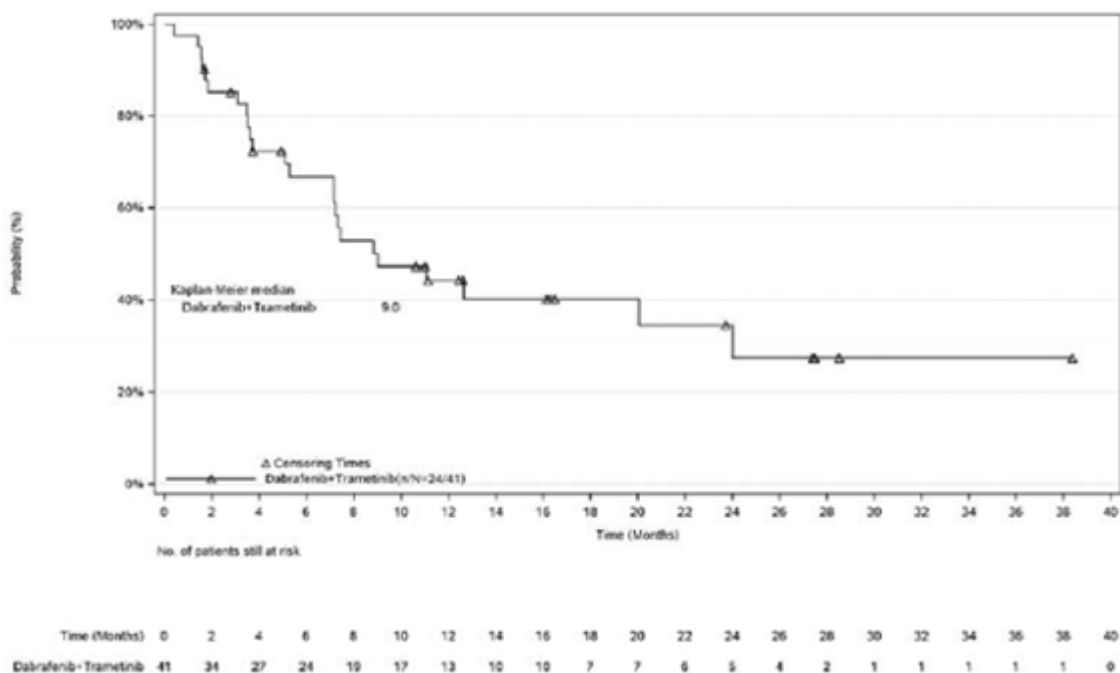


The CBR was 65.9% (95% CI: 49.4, 79.9) per Independent review.

Among patients who responded (CR+PR), the median TTR per Independent review was 1.9 months (range: 1.0, 10.9).

Median PFS was 9.0 months (95% CI: 5.3, 24.0) per Independent review and 17.1 months (95% CI: 12.5, NE) per Investigator assessment.

Figure 10. Kaplan-Meier plot of PFS per independent review (FAS-H).



With a median follow-up of 25.1 months (range: 11.7-41.1) in the HGG cohort, median OS was 32.8 months (95% CI: 19.2, NE). Fourteen patients (34.1%) died and 27 patients (65.9%) were censored

at the time of the DCO date. The OS data are immature at the time of this primary analysis. The estimated OS rates at 12 and 24 months were 76.3% (95% CI: 59.3, 86.9) and 58.6% (95% CI: 37.6, 74.7).

- **Ancillary analyses**

N/A

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24. Summary of efficacy for study G2201, LGG cohort

Title: 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)	
Study identifier	CDRB436G2201 EudraCT number 2015-004015-20 www.clinicaltrials.gov NCT02684058
Design	LGG cohort; randomised, open-label, phase II, cross-over, multi-centre First patient first visit 28-Dec-2017, the study is currently ongoing.
	Duration of main phase:
	<i>Dabrafenib + trametinib (D+T) arm;</i> administered orally, daily, treatment continued until progression, unacceptable toxicity, or loss of clinical benefit as determined by the Investigator.
	<i>Carboplatin + vincristine (C+V) arm;</i> administered intravenously, one course of induction for 10 weeks, followed by 8 cycles of maintenance chemotherapy, each maintenance cycle was 6 weeks. Treatment continued for the prescribed number of cycles as tolerated, or until progression or unacceptable toxicity.
	Duration of Run-in phase:
	NA.
	Duration of Extension phase:
	<i>D+T arm;</i> treatment continued indefinitely as appropriate, as outlined above.
	<i>C+V arm;</i> the maximum total planned duration of treatment was 60 weeks.
Hypothesis	Statistical hypothesis; $H_{01}: ORR_t \leq ORR_c$ vs. $H_{A1}: ORR_t > ORR_c$. Comparison of ORR between the two treatment arms, where ORR_t is the ORR in the D+T arm, and ORR_c is the ORR in the C+V arm.

Title: 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)

Study identifier	CDRB436G2201 EudraCT number 2015-004015-20 www.clinicaltrials.gov NCT02684058			
Treatments groups	LGG D+T arm	Dabrafenib (D) was administered orally, twice daily, dosed based on age and weight. Trametinib (T) was administered orally, once daily in combination with dabrafenib, dosed based on age and weight. D+T was given continuously until progression, unacceptable toxicity, or loss of clinical benefit as determined by the Investigator.		
	LGG C+V arm	One course of induction in which Carboplatin (175 mg/m2) was given weekly on Weeks 1 to 4, and Weeks 7 to 10, and Vincristine (1.5 mg/m2, 0.05 mg/kg if <12 kg, maximum dose of 2.0 mg) was given weekly for 10 weeks. Then followed 8 cycles of maintenance chemotherapy. Each maintenance cycle was 6 weeks in duration and consisted of 4 weekly doses of carboplatin, and three weekly doses of vincristine given concomitantly with the first 3 weeks of carboplatin		
Endpoints and definitions	Primary; Overall response rate	ORR	The proportion of patients with a best overall confirmed CR or PR by blinded independent review per RANO criteria.	
	Secondary; Progression-free survival	PFS	The time from date of randomization to progression or death due to any cause, as assessed separately by central independent reviewer and investigator per RANO criteria.	
	Secondary; Overall survival	OS	The time from date of randomization to death due to any cause.	
Database lock	Data cut-off date: 23-Aug-2021			
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	The primary population for efficacy analyses was FAS-L, which comprised all patients to whom study treatment had been assigned by randomization regardless of whether or not treatment was administered. The primary analysis was conducted as all treated patients had either completed at least 32 weeks of treatment or discontinued earlier.			
Descriptive statistics and estimate variability	Treatment group	LGG D+T arm	LGG C+V arm	<i>Effect estimate per comparison</i>

Title: 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)				
Study identifier	CDRB436G2201 EudraCT number 2015-004015-20 www.clinicaltrials.gov NCT02684058			
	Number of subject	73	37	
	ORR, % (n)	46.6% (34)	10.8% (4)	Odds ratio 7.19 (95% CI: 2.3, 22.4)
	(95% CI)	(34.8, 58.6)	(3.0, 25.4)	1-sided p <0.001
	Median PFS (months)	20.1	7.4	HR 0.31 (95% CI: 0.17, 0.55)
	(95% CI)	(12.8, NE)	(3.6, 11.8)	1-sided p <0.001
	Median OS*	NE	NE	NE
Notes	*OS data are currently very immature with no deaths in the targeted therapy (D+T) arm and 1 death in the chemotherapy (C+V) arm.			

Table 25. Summary of efficacy for study G2201, HGG cohort

Title: 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)		
Study identifier	CDRB436G2201 EudraCT number 2015-004015-20 www.clinicaltrials.gov NCT02684058	
Design	HGG cohort; single-arm, open-label, phase II, multi-centre First patient first visit 28-Dec-2017, the study is currently ongoing.	
	Duration of main phase:	<i>Dabrafenib + trametinib (D+T)</i> ; administered orally, daily, treatment continued until progression, unacceptable toxicity, or loss of clinical benefit as determined by the Investigator.
	Duration of Run-in phase:	NA.
	Duration of Extension phase:	<i>D+T arm</i> ; treatment continued indefinitely as appropriate, as outlined above.
Hypothesis	The HGG cohort was single-arm, powered to show the levels of response that exceed ORR rate in historical controls. Threshold used for historical control was ORR rate of 20% which is higher than the applicant found in the literature for available therapies.	

Title: 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)			
Study identifier	CDRB436G2201 EudraCT number 2015-004015-20 www.clinicaltrials.gov NCT02684058		
Treatments groups	HGG D+T treatment	Dabrafenib (D) was administered orally, twice daily, dosed based on age and weight. Trametinib (T) was administered orally, once daily in combination with dabrafenib, dosed based on age and weight. D+T was given continuously until progression, unacceptable toxicity, or loss of clinical benefit as determined by the Investigator.	
Endpoints and definitions	Primary; Overall response rate	ORR	The proportion of patients with a best overall confirmed CR or PR by independent assessment per RANO criteria.
	Secondary: Duration of response	DOR	The time from the date of the first documented confirmed response (CR or PR) to the first documented progression or death due to any cause, as assessed separately by investigator and central independent reviewer per RANO criteria.
Database lock	Data cut-off date: 23-Aug-2021		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	FAS-H comprised all patients to whom study treatment had been assigned and who received at least one dose of study treatment. The primary analysis was conducted as all treated patients had either completed at least 32 weeks of treatment or discontinued earlier.		
Descriptive statistics and estimate variability	Treatment group	HGG D+T	NA
	Number of subject	41	-
	ORR, % (n)	56.1% (23)	-
	(95% CI)	(39.7, 71.5)	
	Median DOR (months)	22.2	-
(95% CI)	(7.6, NE)		
Notes	-		

2.6.5.3. Clinical studies in special populations

N/A

2.6.5.4. *In vitro* biomarker test for patient selection for efficacy

As part of the screening in study G2201, all patients needed available tumour samples (either FFPE blocks or slides) for the local determination of the BRAF V600 mutation status. Tumour tissue must then be available and subsequently provided to Novartis for central confirmatory testing of BRAF mutational status. Retrospective central BRAF V600 mutation testing, proceeded by the bioMerieux THxID- BRAF kit, was performed at the Novartis-designated central laboratory and was required for all patients.

The bioMerieux THxID is CE marked for the detection of BRAF V600E and V600K mutations in melanoma, which was the first disease in which this oncogene was targeted.

The bioMerieux THxID BRAF assay is an allele-specific PCR performed on DNA extracted from FFPE tumour tissue. The assay was designed to detect the BRAF V600E and V600K mutations with high sensitivity (down to 5% V600E and V600K sequence in a background of wild-type sequence using DNA extracted from FFPE tissue). Of the specimens from the non-clinical and clinical trials (n=876) that were mutation positive by the THxID BRAF assay and subsequently were sequenced using the reference method (bi-directional Sanger sequencing), the specificity of the assay was 94%.

Based on the results of all evaluable samples with a valid BRAF V600E result, a bridging study from the validated BRAF V600E central test to an *in vitro* companion diagnostic (CDx) device is planned to support the development of a CDx for the intended population of BRAF V600E mutation-positive glioma patients. Notified Body review of the proposed CDx is expected for Q4 2023 to meet the regulatory obligation of the Regulation EC No 2017/746 on IVDR. The rationale for choice of predictive biomarker and validated test is acknowledged. Moreover, CE marking for use in glioma is anticipated by Q4 2023.

2.6.5.5. *Analysis performed across trials (pooled analyses and meta-analysis)*

N/A

2.6.5.6. *Supportive study(ies)*

The applicant submitted two Phase I/II studies in paediatric patients for supportive efficacy data for dabrafenib and/or trametinib.

- Study A2102 investigated dabrafenib monotherapy in 85 children and adolescent patients with advanced BRAF V600-positive solid tumours (including 68 patients with glioma).
- Study X2101 enrolled 139 children and adolescents with refractory or recurrent solid tumours, including 49 patients with BRAFV600 mutation-positive LGG treated with either trametinib monotherapy (n=13) or with dabrafenib plus trametinib combination therapy (n=36).

Table 26. Overview of supportive studies for LGG and HGG cohort

Studies	Supportive studies	
	Study A2102-pediatric patients (dabrafenib monotherapy)	Study X2101-pediatric patients (trametinib monotherapy and D+T)
Study purpose	To determine the safety, tolerability, pharmacokinetics, and clinical activity of oral dabrafenib	To investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of trametinib monotherapy and D+T combination
Study Status	Completed (LPLV 04-Dec-2020)	Completed (LPLV 29-Dec-2020)
Study design	Phase I/IIa, 2-part, multicenter, single-arm, open-label study. Part 1: Dose escalation using a modified Rolling 6 Design Part 2: Expansion	Phase I/II, 4 part, multicenter, open-label study. Part A: trametinib monotherapy dose escalation Part B: monotherapy disease cohort expansion Part C: limited dose escalation phase of D+T in BRAF V600 mutant tumors Part D: cohort expansion phase of D+T in BRAF V600 mutant LGG and LCH
Study Population	Pediatric patients (≥ 12 months and < 18 years of age) with advanced BRAF V600 mutation-positive tumors	Pediatric patients with refractory or recurrent tumors with presumed MAPK pathway activation. For Parts A and B, additionally patients were required to have a solid tumor. For Parts B, C, and D, additionally patients were required to have a BRAFV600 mutant tumor. Parts A and B: ≥ 1 month and < 18 years of age Parts C and D: ≥ 12 months and < 18 years of age
Treatment dosages	Dabrafenib: 1.5 to 2.625 mg/kg bid (capped at 150 mg bid)	Dabrafenib: 1.125, 1.315, 2.250 or 2.625 mg/kg bid (capped at 150 mg bid) Trametinib: 0.0125, 0.025, 0.032, or 0.040 mg/kg qd (capped at 2 mg/day)
Number of patients enrolled and treated	85 enrolled and treated	139 enrolled and treated (trametinib monotherapy: 91; D+T: 48)

All paediatric glioma patients included in studies A2102 and X2101 had received at least one prior standard treatment regimen. Patients had disease that was relapsed/refractory to potential standard curative treatment regimens. Measurable disease was not required for inclusion into A2102 or X2101.

2.6.5.6.1. Supportive LGG efficacy data

A total of 82 patients with LGG were reported, of which 33 patients received dabrafenib monotherapy in Study A210, and 13 patients received trametinib monotherapy and 36 patients received D+T combination therapy in Study X2101.

Study A2102

The ORR in the LGG cohort treated with monotherapy dabrafenib in second line (n=33) was 39.4% (95% CI: 22.9, 57.9) as per independent review (RANO 2017), and the median PFS was 18.5 months (95% CI 13.0-38.7).

Study X2101

The ORR in LGG patients treated with D+T in second line (n=36) was 25% (95% CI: 12.1, 42.2) as per Independent reviewer (RANO 2017 criteria), and the median PFS was 36.9 months (95% CI 36.0-NR).

The ORR in LGG patients treated with monotherapy trametinib in second line (n=13) was 15.4% (95% CI: 1.9, 45.4) as per independent reviewer (RANO 2017 criteria), and the median PFS was 16.4 months (95% CI 3.2-NR).

Table 27. Efficacy results across studies G2201, X2101, and A2101

	Study G2201	Study X2101		Study A2102
	FAS	All treated population		All treated population
	D+T, First line	D+T, Second line	T, Second line	D, Second line
	n = 73	n = 36	n = 13	n = 33
ORR (CR+PR)	34 (46.6)	9 (25.0)	2 (15.4)	13 (39.4)
95% CI	(34.8, 58.6)	(12.1, 42.2)	(1.9, 45.4)	(22.9, 57.9)
DOR				
No. of events - n (%)	10 (29.4)	2 (22.2)	0	8 (24.2)
No. of censored	24 (70.6)	7 (77.8)	2 (100)	5 (15.2)
Percentiles (months) (95% CI)				
50th	20.3 (12.0, NE)	33.6 (11.2, NR)	NR (NR, NR)	12.8 (9.3, NR)
PFS				
No. of PFS events - n (%)	30 (41.1)	10 (27.8)	5 (38.5)	16 (48.5)
No. censored - n (%)	43 (58.9)	26 (72.2)	8 (61.5)	17 (51.5)
Percentiles (months) for				
PFS (95% CI)				
50th	20.1 (12.8, NE)	36.9 (36.0, NR)	16.4 (3.2, NR)	18.5 (13.0, 38.7)
Kaplan-Meier event-free estimates (95% CI)				
12 months	0.67 (0.53, 0.77)	0.8 (0.7, 0.9)	0.6 (0.3, 0.8)	0.7 (0.5, 0.9)

ORR after monotherapy dabrafenib in second line was observed to be 39.4% in study A2102, while treatment with D+T in second line resulted in an ORR of 25% in study X2101. ORR in the LGG cohort in the pivotal study G2201 was 46.6% after treatment with D+T in first line.

2.6.5.6.2. Supportive HGG efficacy data

A total of 35 patients with HGG were included from Study A2102, of which all patients received dabrafenib monotherapy.

The ORR in the HGG cohort treated with monotherapy dabrafenib (n=35) was 45.7% (95% CI: 28.8, 63.4) as per independent review (RANO 2010), and the median DOR was 25.9 months (95% CI: 5.6, NR).

2.6.5.6.3. Managed access programme (MAP) in paediatric glioma

Outside of the clinical trial setting, access to D+T combination therapy was also available via the Novartis MAP. Between Nov-2016 and Nov-2021, 110 paediatric patients with low or high grade glioma with a BRAF V600 mutation were recorded as having received access to D+T across 19 countries. The median age was 6.9 years (range: 0.4-18.0).

While no formal efficacy evaluation can be performed in a managed access programme, treatment duration (derived from resupply request dates) indicates a degree of benefit, since resupply requests are contingent on the physician confirming continued benefit.

The estimated median duration of treatment was 14.8 months for LGG and 8.4 months for HGG.

The descriptive data from patients in the managed access programme is not considered to have a significant impact on the overall efficacy conclusions in the current application.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Data to support the sought indications are derived from the multi-centre, open-label, phase II study G2201, conducted in 58 centres across 20 countries. It was a study comprised of two cohorts, to evaluate the effect of dabrafenib in combination with trametinib in paediatric low-grade glioma (LGG cohort), or high-grade glioma (HGG cohort).

There was no attempt to disentangle the effects of MEK and BRAF inhibition (isolate the efficacy of each component). It is notable that the add-on efficacy has been shown in the treatment of melanoma. Moreover, the addition of a MEK inhibitor (the less active component of the treatment) includes overall tolerability of the regimen, particularly with respect to dermatological adverse effects. This effect is considered independent of the treatment indication, and due to the interaction of signalling pathways. Therefore, the lack of study of each component is acceptable.

Overall, the study entry criteria define a population appropriate for the proposed treatment. Moreover, the LGG cohort represents an RCT with a relevant comparator, whereas for the HGG cohort there are no relevant treatment options to which patients could have been randomised.

Depending on age and weight, patients could be administered either the liquid formulations of dabrafenib and trametinib, or the solid formulations of the products that are currently approved for the treatment of adult patients with BRAFV600 mutant tumours. Even though the respective final (to be marketed) liquid formulations were included in the pivotal study G2201, only a minority of patients actually received those, in the group 6 years and older.

No formal dose-response studies have been carried out for the applied indications. The assumption that the therapeutic benefit in children would be achieved by targeting adult steady-state exposure (as observed in the approved indications of BRAF V600 mutation-positive tumours in adults) was questionable. The therapeutic range in paediatric patients has been identified on the exposure range from the 5th to 95th percentile of the observed exposure in study G2201.

The applicant states that monotherapy of dabrafenib and trametinib, respectively, have been studied and demonstrate ORR rates which point towards a continued benefit by temporary monotherapy, in case that an AE is primarily related to either dabrafenib or trametinib, and continued treatment with only one of the products is necessary. However, limited clinical efficacy data on especially trametinib monotherapy are available. Thus, a warning on lack of efficacy data for monotherapy has been included in SmPC section 4.4.

Carboplatin plus vincristine (C+V), which constituted the comparator arm in the LGG cohort, has been used in the treatment of paediatric LGG for several years. There are multiple treatment schedules for administering carboplatin with vincristine in first systemic therapy of paediatric LGG, the most widely utilised are the COGA9952 protocol (Ater 2012) and the SIOP-LGG-2004 protocol (Gnekow 2017). For the pivotal study G2201, the treatment regimen from COGA9952 was used for patients randomised to the comparator arm. C + V was administered as one course of induction for 10 weeks, followed by 8

cycles of maintenance chemotherapy, each maintenance cycle was 6 weeks. The total planned duration of C+V was approximately 60 weeks. The rationale for choice of comparator arm in the LGG cohort is acknowledged.

In addition to study treatment, anti-cancer surgery was allowed after at least 36 months of treatment in the LGG cohort, and after at least 8 months on treatment in the HGG cohort, even without progression. Radiotherapy was allowed after at least a total of 36 months of treatment in both cohorts. All of the main efficacy analyses were performed using only response assessments obtained prior to the start of new anticancer therapy such as radiotherapy or surgery. Results of sensitivity analyses for duration of response and progression-free survival, in which response assessments after new anticancer therapy were also considered, were similar to the main efficacy analyses. Thus, the adjunctive radiotherapy or surgery are considered to not have an impact on the reliability of the isolation of treatment effect of D+T.

The primary estimand for ORR in both LGG and HGG cohort is described using the terminology of the ICH E9 (R1). Two key intercurrent events are foreseen: treatment discontinuations (handled using treatment policy) and start of new anti-neoplastic therapy (handled using while on treatment strategy, i.e., tumour assessments collected on/after the start of new therapy are not considered for evaluation of BOR). Supplementary estimand was analysed where both intercurrent events are treated according to treatment policy strategy. The estimand approach is considered acceptable.

The primary endpoint for both LGG and HGG cohort was ORR, by blinded independent review per RANO criteria in the LGG cohort, and by independent assessment per RANO criteria in the HGG cohort. Secondary endpoints for both cohorts included DOR, PFS, and OS. It is notable that this is the first time that RANO-criteria are used as the primary basis for approval of a medicinal product in the EU.

The central RANO evaluation was conducted step-wise, first using only the radiologic data in a primary read, and then evaluated again including clinical data in a secondary read.

The primary efficacy endpoint (ORR) was based on RANO 2017 criteria for the LGG cohort, and on RANO 2010 criteria for the HGG cohort.

According to Wen et al 2017, response assessment in LGG patients using RANO criteria can result in complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), but also in minor response (MR) if the perpendicular diameters of the tumour lesion has decreased between 25%-50%. The response assessment criterion MR was not used, on the advice of the study steering committee. Instead, such responses were included in the SD category, which seems appropriate.

According to the applicant, for efficacy assessment contrast enhanced brain MRI was preferred. However, the applicant states that if MRI contrast was contraindicated, CT with or without contrast was allowed, but highly discouraged. The applicant has clarified that only one patient had a second evaluation performed by emergency CT, which was the final response assessment for this patient, and determined as non-evaluable. This will not influence the B/R assessment and is thus considered acceptable.

The concordance between investigator and independent review for BOR and PFS estimates is considered very low and the differences also seems to be inconsistent across experimental arms. However, this is primarily a result of the 4 patients on the C+V arm in the LGG cohort that have response of 'unknown' only because they withdrew from study prior to any treatment on study and the independent and investigator determined responses are both defined as 'unknown', which has the effect of increasing the apparent % concordance in the C+V arm. Further, regarding the discordance between investigator and independent determined PFS in the LGG cohort, the applicant argues that the rigorous definition of progression as a 25% increase in the sum of the products of the biperpendicular diameters over nadir measurements did not seem to be adhered to by the investigators while it was

adhered to by the independent determination. This resulted in earlier determination of progression by independent versus investigator evaluations. It is noted that the hazard ratio for the treatment effect on PFS was similar for both independent determination and investigator determination. Thus, the applicant has provided an acceptable explanation for the discordance between investigator and independent assessment.

The HGG cohort was single-arm, powered to show the levels of response that exceed ORR rate in historical controls. Threshold used for indirect historical control was ORR rate of 20% (95% CI), which is higher than the applicant found in the literature for available therapies. Concerning the HGG cohort, the statistical approach is not sufficiently justified in terms of the clinical relevance and the outstanding character of proposed cut-offs. As the applicant's historical control was not accepted as a benchmark for inferring efficacy, the regulatory evaluation of ORR is not made in relation to this.

The LGG cohort was adequately powered to detect a 30% improvement in ORR when response rate in the control group (carboplatin + vincristine) is 20%. Of note, the observed ORR for the C + V arm in this study was 10.8%. For the LGG cohort, the primary endpoint ORR and the secondary endpoints PFS and OS were tested hierarchically to control the overall Type I error rate at the level corresponding to 5% two-sided. However, it was not indicated in the hierarchical procedure which type of the assessment of PFS (Independent review or Investigator) that was to be formally tested. The applicant clarified that only IRC-assessed PFS was intended for formal testing, although this was not clearly written in the SAP. For transparency, the applicant has performed the analysis also for investigator-assessed PFS, which is statistically significant, and thus constitutes a supportive sensitivity analysis.

Methodologically the study appears to be quite straight forward. LGG and HGG are independently analysed cohorts, using conventional analysis methods, and with traditional definitions of safety and full analysis set. Of note, the ITT approach in the analysis sets has been considered relevant for the presentations in the SmPC section 5.1 for both cohorts. The study was open label and the protocol has undergone five amendments. The SAP was updated twice during the course of the study. The first SAP version was authored at the time when the protocol amendment 2 was valid in which the randomised LGG cohort was added. Three protocol amendments later and shortly prior to the primary DBL, the SAP was updated. With an open label design, doubts about data driven choices made in the planned statistical analyses and in the protocol amendments cannot be excluded. However, no crucial changes deviating from the protocol amendment 2 were identified that would impact the primary and key secondary endpoints, interim analyses, or multiple testing procedure. Also, the primary endpoint is assessed by central independent review of tumour assessment data and analysed using conventional statistical methods. Therefore, the late updates of the SAP are not judged to be of a major concern. The five amendments performed during this open label study are not considered to challenge the integrity of the study. It is noted that the majority of the patients in the LGG and HGG cohort were enrolled during amendment 4 and/or 5.

Further, the reported protocol deviations are not considered to impact the overall efficacy conclusions in the LGG or HGG cohort. However, it is noted that 'treatment deviations' are reported in 18.2% of LGG patients, and 34.1% of HGG patients. The dosing of dabrafenib BID, but trametinib only once daily, could be considered challenging for guardians to handle, with regard to dosing errors. The applicant has clarified that 'Treatment deviations' included (i) dosing that did not follow protocol specified dose interruptions/adjustments, and (ii) dosing errors. The treatment deviations reported in G2201 were predominantly due to not interrupted dosing despite protocol guidance for events of pyrexia. There were three cases of dosing errors, all in adolescents; one took three doses of dabrafenib in one day, the other two took two doses of trametinib in one day. Thus, the number of dosing errors are considered to be low in study G2201.

Of note, numerous other interruptions in the planned treatment and study conduct were noted, such as dose interruptions and dose modifications, covid-19 pandemic, antineoplastic therapies, concomitant therapies, etc. These events have not been defined as intercurrent events; this is in accordance with the oncology study design paradigm.

The analysis cut-off date for the primary analysis of study data was established after all enrolled LGG patients have completed 32 weeks of treatment or had discontinued study; this was specified in the protocol amendment 2 in which the LGG cohort was added. The primary analysis was reported based on data cut-off date 23-Aug-2021. The study is still ongoing, with the final analysis to be performed when all patients have been followed up for survival at least 2 years.

The timing of primary analyses was based on specific independent criteria for each cohort but that, for simplicity, one single cut-off date was used for both cohorts. Deviation from the pre-specified analysis time point is not optimal, particularly in open-label studies. However, the data cut-off was changed only for the HGG cohort, which is of minor relevance as for this cohort, no comparison to a control group was made and the hypothesis test against the chosen threshold is not of major relevance for regulatory decision making.

Efficacy data and additional analyses

LGG cohort

In total, 110 patients entered the LGG cohort and were randomised in a 2:1 ratio to the experimental D+T arm (n=73) or the comparator chemotherapy C+V arm (n=37).

At DCO date (23-Aug-2021), 69 patients (62.7%) had ongoing treatment (83.6% in D+T vs. 21.6% in C+V arm). The most common reason for discontinuation was progressive disease, n=5 (6.8%) in the D+T arm and n=9 (24.3%) in the C+V arm.

The Kaplan-Meier curves for time to treatment discontinuation and time to end of follow-up for response have been provided during the assessment. The issue was raised to understand whether there is a possible bias due to different length of the period where a response could be observed. More patients from the control arm of the LGG cohort discontinued treatment earlier or were followed for a shorter period for response. However, one reason for shorter follow-up was treatment discontinuation due to disease progression (n=9) where response can anyway no longer be expected; study discontinuation (n=5) and start of new anticancer therapy (n=3) were also more frequent as reason for end of follow-up for response in the control arm but the influence of these factors for ORR was assessed in sensitivity analyses showing consistent conclusions. Further, due to the low number of patients with new anti-cancer therapy, the complete follow-up of these patients and the provided sensitivity analyses, it can be concluded that starting new anti-cancer therapy had no relevant influence on the overall efficacy results in the LGG cohort.

Overall, demographic characteristics were reasonably well-balanced between the D+T and the C+V chemotherapy arm given the small size of the control arm.

It is noted that corticosteroids have been used in 30.1% of patients in the D+T arm and 45.5% of patients in the C+V arm. The applicant has clarified that the use of systemic corticosteroids (as well as changes in clinical status) was made available to independent reviewer, following response assessment based solely on radiographic data. Further, the applicant clarified that in each of the 6 patients assigned to the C+V arm where systemic corticosteroid use was commenced/increased about the time of first determination of progressive disease, there was also other evidence of progression for that patient. Thus, increased dose of systemic corticosteroid was not the only reason for determination of progressive disease in any subject with LGG assigned to the C+V arm. Overall, the use of corticosteroids is not considered to have had an impact on the overall LGG efficacy conclusions.

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

CR were reported in 2 patients (2.7%) in the D+T arm and 1 patient (2.7%) in the C+V arm.

The outcome for ORR in the chemotherapy C+V arm is considered to be in line with historical expectations in patients with BRAF mutated LGG (Lassaletta et al 2017, Nobre et al 2020, Ater et al 2012).

ORR per investigator was consistent with the ORR observed per Independent review. Also, preplanned supportive and sensitivity analyses of ORR were overall consistent with the primary analysis and indicate robustness of the ORR results. Sensitivity analysis that considered response scenarios for the 4 patients who discontinued prior to receiving treatment were performed, and the results are still statistically significant in favour of D+T. Notably, missing data was considered as non-response. As more data were missing in the control group, the analysis might be anti-conservative. As sensitivity analyses, an analysis similarly to the analysis of not treated patients (i.e., considering different response scenarios for these patients) was provided. Even in the most extreme scenario which is very unlikely (where all patients with 6 unknown responses in the C+V arm were considered as responders, and the 1 patient with unknown response in the D+T arm was considered as a non-responder), the results remained favourable to the D+T arm with a statistically significant difference.

ORR analysis by Independent review using only the radiographic data (but not including clinical status and steroid use data that may introduce bias) is consistent with the primary ORR analysis using full RANO criteria. Given that the RANO criteria include not only radiological assessment, but also the assumption that a response requires stable clinical disease without increased corticosteroids, this is reassuring with regards to the robustness of these response criteria.

A median PFS of 20.1 months (95% CI: 12.8, NE) in the D+T arm versus 7.4 months (95% CI: 3.6, 11.8) in the C+V arm, with HR 0.31 (95% CI: 0.17, 0.55) per Independent review, further supports a clinically relevant efficacy of treatment with D+T in patients with LGG who require first line systemic therapy.

With regards to analysis of PFS and DOR in the LGG cohort, data were censored at the last adequate tumour assessment in case of the following: absence of event, the event occurred after a new anticancer therapy, or the event occurred after two or more missing tumour assessments. This follows the FDA's recommended censoring rules. In accordance with the EMA guideline on anticancer medicinal products, an analysis of PFS was also performed for events that occurred after a new anticancer therapy, or after two or more missing tumour assessments, are considered as events (instead of being censored); with this approach the results are similar to the main PFS analysis.

Also, when all informative censoring is replaced with an event in analyses of PFS by IRC and investigator assessment, the results are similar to the main PFS analysis. In the worst-case imputation scenario, in which all informative censoring is imputed with event on day 1 in D+T arm and replaced with censoring at the last observed duration of follow-up in the study in C+V arm, the result shows trend in favour of the D+T arm.

As the odds ratio is difficult to interpret, particularly in terms of clinical relevance, the treatment effect in terms of difference in ORR's has been provided with the corresponding 95% CI (using the exact method and Newcombe's method) and included in the SmPC section 5.1 in addition to the presentation of the odds ratio. The applicant proposed to present only exact 95% CI which is acceptable.

With a median follow-up of 18.9 months (range: 7.9-35.4) in the LGG cohort, OS data are immature with no deaths in the D+T arm and 1 death in the chemotherapy C+V arm.

Considering the immaturity of the secondary endpoints, the applicant has committed to deliver the final analysis of study G2201, which will include the final analysis of LGG cohort, including analyses of DoR, PFS and OS (minimum 2-year OS data). The final analysis will be performed when all patients have been followed for at least two years. The last patient last visit on study G2201 is expected to occur in Q2 2023, and therefore the final CSR could be submitted in Q4 2023. Updated survival data from study G2201 is included as a proposed Post-authorisation measure (REC).

The supportive studies A2102 or X2101 included a small number of patients having previously received systemic therapy. The interpretability of these studies is limited by small numbers and other study design weaknesses. Still, they indicate the activity of trametinib/dabrafenib also in second-line treatment.

HGG cohort

It is noted that corticosteroids have been used in 48.8% of patients in the HGG cohort. The applicant has explained that most use of steroids was at or after the time of PD. Further, the applicant points out that RANO responses require stable or reduced steroid as a requirement for PR and absence of steroid use to qualify for CR. Overall, corticosteroid treatment is not considered to have had an impact on the reliability of the isolation of treatment effect in the single-arm HGG cohort.

The pre-defined success criteria of ORR per Independent review (primary endpoint) in the HGG cohort was met, with a clinically relevant ORR of 56.1%, (95% CI: 39.7, 71.5, 80% CI: 44.9, 66.8). The lower bound of the 95% CI for D+T treatment ORR exceeded the 20% rate prespecified in the study protocol based on the historical rates of ORR for patients with molecularly unselected relapsed refractory HGG (5-12%) treated with standard available therapy. The study design is considered to isolate the drug effect of D+T treatment, under the assumption that at least three months had passed since prior radiation (see below), and that no concomitant active therapies were given. CR was reported in 12 patients (29.3%) and PR in 11 patients (26.8%).

Preplanned supportive and sensitivity analyses of ORR demonstrated overall consistency of the ORR results, which indicates robustness of the ORR results.

ORR analysis by Independent review using only the radiographic data (but not including clinical status and steroid use data that may introduce bias) is consistent with the primary ORR analysis using full RANO criteria. This is reassuring with respect to the robustness and interpretability of results.

The protocol specified a waiting period of at least 3 months beyond prior given radiotherapy, which was accepted by the SAWP. In 36 of the 37 patients that had received radiotherapy prior to study entry, the irradiation occurred more than 3 months before start of study treatment. One patient received prior radiotherapy less than 3 months before study treatment, this patient had one day of radiotherapy, and received the first dose of study treatment after a duration of at least >2 months since the radiotherapy. This patient had SD on Day 46 and was noted to progress from Day 107 with BOR of PD. Overall, prior given radiotherapy to patients in the HGG cohort is not considered likely to have an impact on the efficacy conclusions.

The median DOR of 22.2 months (95% CI: 7.6, NE) indicates a clinically meaningful efficacy of treatment with D+T in second line treatment of relapsed or refractory HGG patients.

Considering the immaturity of the secondary endpoints, the applicant has committed to deliver the final analysis of study G2201 post approval as a recommendation, which will include the final analysis of the HGG cohort, including analyses of DoR, PFS and OS. The time dependent endpoints of, PFS and

OS cannot be interpreted in the context of a single-arm trial, and are therefore not presented in section 5.1 of the SmPC.

Overall, the additional study A2102, cannot be considered informative for the overall efficacy conclusions for the HGG cohort, due to the study design as single-arm trial with dose escalation, and the treatment with only monotherapy dabrafenib to a limited number of patients, and the included patients who were not required to have measurable disease.

2.6.7. Conclusions on the clinical efficacy

The clinical relevance of efficacy in paediatric patients with BRAF mutated LGG treated with dabrafenib plus trametinib in first line systemic therapy is supported by sufficiently robust ORR data and a substantial PFS benefit as reported from the randomised LGG cohort in study G2201.

In addition, a clinically relevant ORR and a clinically meaningful response duration is reported after treatment with dabrafenib plus trametinib in paediatric patients with relapsed or refractory BRAF mutated HGG. Despite the single-arm study design and limited sample size, activity is evident and can be isolated, which is deemed relevant in this scenario where there are no satisfactory treatment options.

The CHMP considers the following measures necessary to address issues related to efficacy:

- the MAH should submit the final survival data delivery from pivotal study G2201, LGG and HGG cohorts.

2.6.8. Clinical safety

The applicant has submitted an integrated safety analysis using data from the pivotal study CDRB436G2201 (hereafter referred to as study G2201) and study CTMT212X2101 (hereafter referred to as Study X2101) at the initial data cut-off dates of 23 August 2021 and 29 December 2020 (study completion) respectively.

Table 28. Brief overview of source studies in paediatric patients

	Main study	Supportive studies	
Studies	Study G2201–pediatric patients (D+T)	Study A2102–pediatric patients (dabrafenib monotherapy)	Study X2101–pediatric patients (trametinib monotherapy and D+T)
Study purpose	To assess the clinical efficacy and safety of D+T	To determine the safety, tolerability, pharmacokinetics, and clinical activity of oral dabrafenib	To Investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of trametinib monotherapy and D+T combination
Study Status	Ongoing (data cut-off: 23-Aug-2021)	Completed (LPLV 04-Dec-2020)	Completed (LPLV 29-Dec-2020)
Study design	Phase II, 2-cohort, open-label, multicenter study. HGG cohort: single arm (D+T) LGG cohort: 2:1 randomized comparison of D+T to chemotherapy	Phase I/IIa, 2-part, multicenter, single-arm, open-label study. Part 1: Dose escalation using a modified Rolling 6 Design Part 2: Expansion	Phase I/II, 4 part, multicenter, open-label study. Part A: trametinib monotherapy dose escalation Part B: monotherapy disease cohort expansion Part C: limited dose escalation phase of D+T in BRAF V600 mutant tumors Part D: cohort expansion phase of D+T in BRAF V600 mutant LGG and LCH
Study Population	Pediatric patients (≥ 12 months and < 18 years of age) with BRAF V600 mutation-positive LGG or relapsed or refractory BRAF V600 mutation-positive HGG	Pediatric patients (≥ 12 months and < 18 years of age) with advanced BRAF V600 mutation-positive tumors	Pediatric patients with refractory or recurrent tumors with presumed MAPK pathway activation. For Parts A and B, additionally patients were required to have a solid tumor. For Parts B, C, and D, additionally patients were required to have a BRAFV600 mutant tumor. Parts A and B: ≥ 1 month and < 18 years of age Parts C and D: ≥ 12 months and < 18 years of age
Treatment dosages	Dabrafenib: 2.25 or 2.625 mg/kg bid (capped at 150 mg bid) Trametinib 0.025 or 0.032 mg/kg qd (capped at 2 mg) Carboplatin 175 mg/m ² Vincristine 1.5 mg/m ²	Dabrafenib: 1.5 to 2.625 mg/kg bid (capped at 150 mg bid)	Dabrafenib: 1.125, 1.315, 2.250 or 2.625 mg/kg bid (capped at 150 mg bid) Trametinib: 0.0125, 0.025, 0.032, or 0.040 mg/kg qd (capped at 2 mg/day)
Number of patients enrolled and treated	151 enrolled, 147 treated (D+T: 114; carboplatin + vincristine: 33)	85 enrolled and treated	139 enrolled and treated (trametinib monotherapy: 91; D+T: 48)
Source: [Study G2201], [Study A2102] and [Study X2101]			

The safety assessment is focused on the patients treated with dabrafenib + trametinib combination therapy in the pivotal study G2201 (n=114).

The individual doses in study G2201 were age and weight dependent. Dabrafenib was dosed orally at 2.625 mg/kg twice daily for ages <12 years and at 2.5 mg/kg for ages ≥ 12 years and was capped at 150 mg twice daily. Trametinib was dosed orally at 0.032 mg/kg once daily for ages <6 years and at 0.025 mg/kg at ages ≥ 6 years and was capped at 2 mg once daily. These doses are close, but not identical, to the proposed doses in the SmPC, where doses are only weight dependent and varies between 2.2 and 2.9 mg/kg twice daily for dabrafenib.

Data from study X2101 (parts C +D, n= 48) is used for support regarding safety issues. Study X2101 contained a limited dose escalation phase and a cohort expansion phase and thus included both higher and lower doses of dabrafenib and trametinib than the current proposed ones. When applicable, comparisons will be made with the safety profile of carboplatin + vincristine in study G2201 (n=33).

Study G2201:

Low-grade glioma (LGG) cohort; n=73 patients randomised to dabrafenib + trametinib (D+T) and n=33 patients randomised to standard of care chemotherapy with carboplatin + vincristine (C+V)

Nine patients in the C+V arm crossed over to the D+T arm

High-grade glioma (HGG) cohort; all 41 patients received D+T treatment

For the patients in the LGG cohort of study G2201 who crossed over from C+V to D+T, the on-treatment period started on the first day of D+T.

A **combination therapy pool** (also called the safety analysis set) consisting of safety data from a total of 171 patients treated with D+T (n=123 from study G2201; n=48 from study X2101), was constructed for safety comparisons. This population included n=4 children aged <2 years, n=39 aged 2 to <6 years, n=54 aged 6 to <12 years, and n=74 aged 12 to <18 years.

Apart from the proposed liquid formulations of D+T, currently approved solid formulations of dabrafenib (Tafinlar) capsules (50 and 75 mg) and trametinib (Mekinist) tablets (0.5 and 2 mg) were

also used in the studies. The proposed liquid formulations were mainly administered to patients <6 years of age. No safety analysis by formulation received was presented.

2.6.8.1. Patient exposure

Table 29. Summary of patient exposure from clinical studies

	Monotherapy / Combination	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
Placebo-controlled		0	0	0	0
Active-controlled	Combination	110	82	82	76
Open studies	Monotherapy	85	85	65	58
	Combination	89	89	84	69
Post marketing		0	0	0	0
Compassionate use	Combination	110	N/A	N/A	N/A

*Defined as at least 26 weeks duration of exposure. N/A = not available

The row 'Active-controlled studies' includes patients from the LGG cohort in study G2201. The rows for 'Open studies' include patients receiving dabrafenib monotherapy in study DRB436A2101, and patients receiving D+T combination therapy in the HGG cohort in study G2201 as well as in supporting study X2101 parts C and D. The compassionate use exposure only reports the number of paediatric patients for whom monotherapy or combination therapy was requested; as the exposure or duration of exposure in the managed access programme can only indirectly be inferred from the physician resupply requests, the numbers of patients exposed/exposed to the proposed dose range/with long term data in the compassionate use programme cannot be determined.

2.6.8.1.1. LGG cohort

In the pivotal study, the median daily dose of dabrafenib was 4.74 mg/kg and the median daily dose of trametinib was 0.026 mg/kg, with a median relative dose intensity of 100% for both substances. The median daily dose in the specified dabrafenib age groups <12 years (5.16 mg/kg) and ≥12 years (4.26 mg/kg) and trametinib age groups <6 years (0.032 mg/kg) and ≥6 years (0.025 mg/kg) were close to the intended dose per protocol.

The median duration of exposure to dabrafenib as well as trametinib was 75.7 weeks. The majority (64.4%) of patients received dabrafenib and trametinib for ≥56 weeks. The median duration of exposure to carboplatin was 34.0 weeks and to vincristine 35.3 weeks.

In accordance with the study protocol, patients in the D+T arm continued to receive study treatment until disease progression, while patients in the C+V arm received one course of induction (10 weeks of chemotherapy with two weeks of rest) followed by up to eight cycles of maintenance chemotherapy (each maintenance cycle was six weeks). This is considered to be a standard procedure and overall acceptable.

The doses of dabrafenib and trametinib used in the study were weight and age dependent, as specified in the study protocol. In the proposed posology the doses are only weight dependent, with narrow dosing steps.

2.6.8.1.2. HGG cohort

The median daily dose of dabrafenib was 4.39 mg/kg/day and of trametinib was 0.024 mg/kg, with a median relative dose intensity of 100%. The median daily dose in the specified dabrafenib age groups <12 years (4.92 mg/kg) and ≥ 12 years (4.17 mg/kg) and in the specified trametinib age groups <6 years (0.033 mg/kg) and ≥ 6 years (0.024 mg/kg) were close to the intended dose per protocol.

The median duration of exposure to both dabrafenib and trametinib was 72.7 weeks at the time of DCO with 21 patients continuing treatment. The majority (56.1%) of patients received dabrafenib and trametinib for ≥ 56 weeks.

2.6.8.1.3. Combination therapy pool

In the combination therapy pool, a total of 171 patients were exposed to D+T, with a median duration of exposure of 76.9 weeks (range 1.3-228.1) for dabrafenib and 75.7 weeks for trametinib (range 1.3-228.1). The majority of patients received dabrafenib and trametinib for 48 weeks or longer (72.5% and 71.3% respectively). The median daily dose was 4.7 mg/kg for dabrafenib and 0.025 mg/kg for trametinib.

2.6.8.2. Adverse events

AEs overview

Adverse Events (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 as the studies were performed at various times. To produce the summary of clinical safety analyses, lower-level terms from all studies were mapped to MedDRA version 24.0, which was the version used for the pivotal Study G2201, while the CTCAE grading version used was the same as in the original studies.

LGG cohort

Table 30. Overview of adverse events – LGG cohort

	D+T N=73		C+V N=33		D+T vs C+V Risk difference	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades	Grade ≥ 3
Adverse events	73 (100.0)	34 (46.6)	33 (100.0)	31 (93.9)	NE	-47.4
Treatment-related	67 (91.8)	19 (26.0)	32 (97.0)	29 (87.9)	-5.2	-61.9
SAEs	29 (39.7)	20 (27.4)	13 (39.4)	7 (21.2)	0.3	6.2
Treatment-related	10 (13.7)	4 (5.5)	8 (24.2)	4 (12.1)	-10.5	-6.6
Fatal SAEs	0	0	0	0	NE	NE
Treatment-related	0	0	0	0	NE	NE
AEs leading to discontinuation	3 (4.1)	2 (2.7)	6 (18.2)	3 (9.1)	-14.1	-6.4
Treatment-related	3 (4.1)	2 (2.7)	6 (18.2)	3 (9.1)	-14.1	-6.4
AEs leading to dose adjustment/interruption	58 (79.5)	27 (37.0)	26 (78.8)	19 (57.6)	0.7	-20.6
AEs requiring additional therapy	72 (98.6)	22 (30.1)	32 (97.0)	22 (66.7)	1.7	-36.5

Table 31. Adverse events by system organ class – LGG cohort (Study No. CDRB436G2201)

Primary system organ class	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33		Dabrafenib+Trametinib vs Carboplatin+Vincristine Risk Difference (95% CI)	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of subjects with at least one event	73 (100.0)	34 (46.6)	33 (100.0)	31 (93.9)	NE (NE, NE)	-47.4 (-61.4, -33.3)
Blood and lymphatic system disorders	21 (28.8)	7 (9.6)	25 (75.8)	15 (45.5)	-47.0 (-64.9, -29.1)	-35.9 (-54.1, -17.6)
Cardiac disorders	3 (4.1)	1 (1.4)	2 (6.1)	0	-2.0 (-11.3, 7.4)	1.4 (-1.3, 4.0)
Ear and labyrinth disorders	12 (16.4)	1 (1.4)	3 (9.1)	0	7.3 (-5.6, 20.3)	1.4 (-1.3, 4.0)
Endocrine disorders	4 (5.5)	0	1 (3.0)	0	2.4 (-5.4, 10.3)	NE (NE, NE)
Eye disorders	16 (21.9)	0	5 (15.2)	1 (3.0)	6.8 (-8.7, 22.2)	-3.0 (-8.9, 2.8)
Gastrointestinal disorders	52 (71.2)	3 (4.1)	26 (78.8)	4 (12.1)	-7.6 (-24.9, 9.8)	-8.0 (-20.0, 4.0)
General disorders and administration site conditions	59 (80.8)	6 (8.2)	19 (57.6)	1 (3.0)	23.2 (4.1, 42.4)	5.2 (-3.4, 13.8)
Immune system disorders	3 (4.1)	0	5 (15.2)	1 (3.0)	-11.0 (-24.1, 2.0)	-3.0 (-8.9, 2.8)
Infections and infestations	46 (63.0)	9 (12.3)	14 (42.4)	3 (9.1)	20.6 (0.4, 40.8)	3.2 (-9.1, 15.6)
Injury, poisoning and procedural complications	22 (30.1)	2 (2.7)	12 (36.4)	2 (6.1)	-6.2 (-25.7, 13.3)	-3.3 (-12.3, 5.6)
Investigations	38 (52.1)	16 (21.9)	22 (66.7)	18 (54.5)	-14.6 (-34.4, 5.1)	-32.6 (-52.1, -13.2)
Metabolism and nutrition disorders	14 (19.2)	2 (2.7)	15 (45.5)	2 (6.1)	-26.3 (-45.5, -7.0)	-3.3 (-12.3, 5.6)
Musculoskeletal and connective tissue disorders	28 (38.4)	0	12 (36.4)	0	2.0 (-17.9, 21.8)	NE (NE, NE)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (15.1)	0	0	0	15.1 (6.9, 23.3)	NE (NE, NE)
Nervous system disorders	43 (58.9)	9 (12.3)	22 (66.7)	5 (15.2)	-7.8 (-27.4, 11.9)	-2.8 (-17.2, 11.5)
Psychiatric disorders	7 (9.6)	0	5 (15.2)	1 (3.0)	-5.6 (-19.5, 8.4)	-3.0 (-8.9, 2.8)
Renal and urinary disorders	6 (8.2)	1 (1.4)	3 (9.1)	0	-0.9 (-12.5, 10.8)	1.4 (-1.3, 4.0)
Reproductive system and breast disorders	5 (6.8)	0	2 (6.1)	0	0.8 (-9.2, 10.8)	NE (NE, NE)
Respiratory, thoracic and mediastinal disorders	28 (38.4)	3 (4.1)	13 (39.4)	1 (3.0)	-1.0 (-21.1, 19.0)	1.1 (-6.3, 8.5)
Skin and subcutaneous tissue disorders	56 (76.7)	2 (2.7)	15 (45.5)	2 (6.1)	31.3 (11.7, 50.8)	-3.3 (-12.3, 5.6)
Surgical and medical procedures	1 (1.4)	0	0	0	1.4 (-1.3, 4.0)	NE (NE, NE)
Vascular disorders	6 (8.2)	0	3 (9.1)	2 (6.1)	-0.9 (-12.5, 10.8)	-6.1 (-14.2, 2.1)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for a SOC is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.03.

HGG cohort

Table 32. Overview of adverse events – HGG cohort

Category	All patients N=41		
	All grades n (%)	Grade 3/4/5 n (%)	Grade 5 n (%)
Adverse events	41 (100.0)	28 (68.3)	3 (7.3)
Treatment-related	34 (82.9)	11 (26.8)	0
SAEs	25 (61.0)	22 (53.7)	3 (7.3)
Treatment-related	7 (17.1)	6 (14.6)	0
Fatal SAEs	3 (7.3)	3 (7.3)	3 (7.3)
Treatment-related	0	0	0
AEs leading to discontinuation	2 (4.9)	0	0
Treatment-related	1 (2.4)	0	0
AEs leading to dose adjustment/interruption	26 (63.4)	14 (34.1)	2 (4.9)
AEs requiring additional therapy	39 (95.1)	23 (56.1)	1 (2.4)

Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.03.
Source: [Study G2201-Table 14.3.1-1.1H]

Table 33. Adverse events by system organ class - HGG cohort (Study No. CDRB436G2201)

Primary system organ class	All subjects N=41	
	All Grades n (%)	Grade ≥3 n (%)
Number of subjects with at least one event	41 (100)	28 (68.3)
Skin and subcutaneous tissue disorders	33 (80.5)	1 (2.4)
Gastrointestinal disorders	26 (63.4)	6 (14.6)
General disorders and administration site conditions	26 (63.4)	4 (9.8)
Infections and infestations	25 (61.0)	5 (12.2)
Nervous system disorders	25 (61.0)	11 (26.8)
Investigations	17 (41.5)	5 (12.2)
Respiratory, thoracic and mediastinal disorders	16 (39.0)	2 (4.9)
Musculoskeletal and connective tissue disorders	12 (29.3)	1 (2.4)
Metabolism and nutrition disorders	11 (26.8)	2 (4.9)
Eye disorders	10 (24.4)	2 (4.9)
Injury, poisoning and procedural complications	9 (22.0)	1 (2.4)
Blood and lymphatic system disorders	8 (19.5)	2 (4.9)
Psychiatric disorders	7 (17.1)	3 (7.3)
Vascular disorders	5 (12.2)	2 (4.9)
Cardiac disorders	4 (9.8)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (9.8)	0
Immune system disorders	3 (7.3)	0
Reproductive system and breast disorders	3 (7.3)	1 (2.4)
Ear and labyrinth disorders	2 (4.9)	0
Renal and urinary disorders	2 (4.9)	1 (2.4)
Endocrine disorders	1 (2.4)	0
Hepatobiliary disorders	1 (2.4)	0
Product issues	1 (2.4)	0

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for a SOC is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.03.

Combination therapy pool

Of the patients in the combination therapy pool, 98.8% experienced at least one AE (regardless of study drug relationship). Grade ≥ 3 AEs were reported in 57.3% of patients. AEs leading to treatment discontinuation were reported in 7.6% of the patients.

Overall, the frequency and distribution of AEs in the pivotal study and in the combination therapy pool are in line with what is expected with BRAF and MEK inhibitor treatment.

AEs in the SOC category `neoplasm benign, malignant, and unspecified (including cysts and polyps) were reported in 21 patients (12.3%), of which seven had melanocytic naevi. These cases were either confounded or the diagnosis was revised upon histopathological analysis. The applicant will continue to monitor cases post-marketing through routine pharmacovigilance activities and in potential future clinical studies.

The applicant has reported data on the median time to onset for the most common AEs ($\geq 20\%$). The majority of these AEs have a median time to onset less than three months. Several ADRs within the SOC of eye disorders did, however, have a later median time to onset; visual impairment (7.62 months [range 6.93-8.31]), uveitis (8.31 months [range 3.02-23.75]) and retinal detachment (23.49 months [range 23.49-23.49]). Of note, the ADR retinal detachment only appeared in one subject. With this information at hand, it is considered important that clinicians are made aware of the potential late time to onset of ocular side-effects. This is now reflected in the SmPC sections 4.2, 4.4 and 4.8.

Adverse events by preferred term

LGG cohort

Table 34. abbreviated by the rapporteur. Adverse events (>10% in any treatment arm) by preferred term - LGG cohort

Preferred term	D + T N=73		C + V N=33		D + T vs. C + V Risk difference	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades	Grade ≥3
Number of patients with at least one event	73 (100.0)	34 (46.6)	33 (100.0)	31 (93.9)	NE	-47.4
Pyrexia	50 (68.5)	6 (8.2)	6 (18.2)	1 (3.0)	50.3	5.2
Headache	34 (46.6)	1 (1.4)	9 (27.3)	1 (3.0)	19.3	-1.7
Vomiting	25 (34.2)	1 (1.4)	16 (48.5)	1 (3.0)	-14.2	-1.7
Fatigue	23 (31.5)	0 (0.0)	10 (30.3)	0 (0.0)	1.2	NE
Diarrhoea	21 (28.8)	0 (0.0)	6 (18.2)	2 (6.1)	10.6	-6.1
Dry skin	19 (26.0)	0 (0.0)	1 (3.0)	0 (0.0)	23.0	NE
Nausea	18 (24.7)	0 (0.0)	15 (45.5)	0 (0.0)	-20.8	NE
Epistaxis	15 (20.5)	0 (0.0)	1 (3.0)	0 (0.0)	17.5	NE
Rash	14 (19.2)	1 (1.4)	3 (9.1)	1 (3.0)	10.1	-1.7
Abdominal pain	12 (16.4)	0 (0.0)	7 (21.2)	0 (0.0)	-4.8	NE
Anaemia	11 (15.1)	0 (0.0)	20 (60.6)	8 (24.2)	-45.5	-24.2
Upper respiratory tract infection	11 (15.1)	0 (0.0)	2 (6.1)	0 (0.0)	9.0	NE
Weight increased	11 (15.1)	5 (6.8)	0 (0.0)	0 (0.0)	15.1	6.8
Alanine aminotransferase increased	10 (13.7)	4 (5.5)	9 (27.3)	3 (9.1)	-13.6	-3.6
Neutropenia	10 (13.7)	7 (9.6)	10 (30.3)	10 (30.3)	-16.6	-20.7
Neutrophil count decreased	10 (13.7)	4 (5.5)	16 (48.5)	16 (48.5)	-34.8	-43.0
Pain in extremity	10 (13.7)	0 (0.0)	3 (9.1)	0 (0.0)	4.6	NE
Constipation	9 (12.3)	0 (0.0)	12 (36.4)	0 (0.0)	-24.0	NE
Dermatitis acneiform	9 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	12.3	NE
Eczema	9 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	12.3	NE
Rash maculo-papular	9 (12.3)	1 (1.4)	1 (3.0)	0 (0.0)	9.3	1.4

Numbers (n) represent counts of patients. A patient with multiple severity grades for an AE is only counted under the maximum grade.

MedDRA version 24.0, CTCAE version 4.03.

Source: [Study G2201-Table 14.3.1-2.2L]

Table 35. Adverse events (>10%) by preferred term - HGG cohort

Preferred term	All patients N=41	
	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with at least one event	41 (100)	28 (68.3)
Pyrexia	21 (51.2)	1 (2.4)
Headache	14 (34.1)	4 (9.8)
Dry skin	13 (31.7)	0
Vomiting	12 (29.3)	2 (4.9)
Diarrhoea	10 (24.4)	1 (2.4)
Rash	9 (22.0)	1 (2.4)
Nausea	8 (19.5)	0
Cough	7 (17.1)	0
Upper respiratory tract infection	7 (17.1)	0
Epistaxis	6 (14.6)	0
Fatigue	6 (14.6)	0
Neutropenia	6 (14.6)	1 (2.4)
Rash maculo-papular	6 (14.6)	0
Abdominal pain	5 (12.2)	0
Constipation	5 (12.2)	0
Erythema	5 (12.2)	0
Oropharyngeal pain	5 (12.2)	0
Weight increased	5 (12.2)	0
White blood cell count decreased	5 (12.2)	1 (2.4)

Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.03.
Source: [Study G2201-Table 14.3.1-2.2H]

The AEs reported in ≥20% of patients by PT in the HGG cohort were generally consistent with those in the LGG cohort D+T arm.

Combination therapy pool

The most common AEs by PT reported in paediatric patients in the pivotal study and in the combination therapy pool are in line with the known safety profiles of dabrafenib and trametinib monotherapy respectively.

Adverse events by age

In the age subgroup <6 years, AEs in nervous system disorders (37.2%), musculoskeletal and connective tissue disorders (23.2%), and eye disorders (18.6%) were reported at lower frequencies compared to patients ≥6 years of age (65.6%, 40.6%, and 27.3% for the respective SOC). The incidence of AEs in gastrointestinal disorders and investigations was slightly higher in patients <6 years of age (79.1% and 62.8% respectively) compared to patients ≥6 years of age (69.5% and 53.1% respectively).

For AEs by PT, pyrexia was the most commonly reported AE across age subgroups and reported at higher frequency in patients <6 years of age (74.4%) compared to patients ≥6 years of age (61.7%), but with comparable severity. Also, rash maculopapular was more common among the younger children (23.2% vs. 14.8% among patients ≥6 years). As noted above, the slightly higher frequency of AEs under the gastrointestinal disorders SOC in younger compared to older patients was primarily driven by higher incidences of vomiting (48.8% for patients <6 years vs. 34.4% for patients ≥6 years) and diarrhoea (34.9% vs. 28.1%). Headache was reported at a lower frequency in patients <6 years of

age vs. patients ≥ 6 years of age (16.3% vs. 46.9%), with grade ≥ 3 reported only for patients 12 to <18 years ($n=5$).

Treatment related adverse events

LGG cohort

The AEs suspected to be study treatment related occurred at similar frequencies in the D+T and C+V arms (91.8% vs. 97.0%), but the incidence of grade ≥ 3 AEs suspected to be study treatment related were reported less frequently in the D+T arm compared to the C+V arm (26.0% vs. 87.9%). Pyrexia (42.5%) was the only AE suspected to be study treatment related with a reported incidence $\geq 20\%$ in the D+T arm compared to the C+V arm (12.1%).

HGG cohort

AEs suspected to be study treatment related were reported in 34/41 (82.9%) patients in the HGG cohort, with 11 patients (26.8%) experiencing grade ≥ 3 AEs. The most frequently reported AEs ($\geq 10\%$ incidence) suspected to be study treatment related were pyrexia (39.0%), dry skin (22.0%), rash (17.1%), and rash maculo-papular (12.2%).

The data on treatment related AEs in the HGG cohort are in line with the data from the LGG cohort D+T arm.

Combination therapy pool

No additional data were provided in the combination therapy pool, which, thus, are in line with the data in the LGG and HGG cohorts respectively.

Severity of adverse events

In the LGG cohort D+T arm, grade 3 AEs were reported for $n=34$ (46.6%) of the patients experiencing at least one event. The most common grade 3 AEs were 'Blood and lymphatic disorders' ($n=7$ [9.6%], all due to neutropenia), 'General disorders and administration' ($n=6$ [8.2%], all due to pyrexia), 'Infections and infestations' ($n=8$ [11%], distributed across several different infections of which only urinary tract infection was reported for >1 patient), 'Investigations' ($n=16$ [21.9%], mainly due to weight increased [6.8%], ALT increased [5.5%], and neutrophil count decreased [5.5%], and 'Nervous system disorders' ($n=9$ [12.3%], with syncope [4.1%] and hydrocephalus [2.7%] being the most common). Grade 4 AEs were reported in three patients (4.1%), distributed across 'Infections and infestations' (one laryngitis and one toxic shock syndrome), and 'Investigations' (one CPK increased). There were no grade 5 AEs reported for the LGG cohort.

Overall, in the LGG cohort grade ≥ 3 AEs were reported in 46.6% of the patients in the D+T arm and in 93.9% of the patients in the C+V arm. Grade ≥ 3 weight increased, and pyrexia events were reported more frequently in the D+T arm, while in the C+V arm there was an increased risk of grade ≥ 3 haematological toxicities. Hypersensitivity, infusion related reaction and neuropathy (peripheral motor and peripheral sensory) AEs were reported only in the C+V arm, and at least one event of each was grade ≥ 3 .

In the HGG cohort, grade 3 AEs were reported for $n=27$ (65.9%) of the patients. The most commonly reported grade 3 AEs were 'Nervous system disorders' (19.5%, of which headache was the most common [$n=4$, 9.8%] and seizures [$n=2$, 4.9%]), 'GI disorders' (14.6%, mainly due to vomiting

[n=2, 4.9%]), 'Infections and infestations' as well as 'Investigations' (n=5, 12.2% each). Most of the reported grade 3 AEs occurred in one patient each. Grade 4 AEs were reported for n=8, (19.5%) of the patients, with 'Investigations' (n=3, 7.3%) being the most common and mainly due to laboratory abnormalities. Grade 5 AEs were reported for three (7.3%) of the patients, distributed across 'Infections and infestations' (encephalomyelitis), 'Nervous system disorders' (intracranial pressure increased), and 'Respiratory, thoracic, and mediastinal disorders' (apnoea). Overall, headache (9.8%) was the most commonly (>5%) reported grade ≥ 3 AE in the HGG cohort.

Pyrexia (8.8%), neutropenia (7.6%), neutrophil count decreased (7.6%), and ALT increased (5.3%) were the most commonly (>5% incidence) reported grade ≥ 3 AEs in the combination therapy pool.

Adverse events leading to dose modification and dose interruption

LGG cohort

In the LGG cohort D+T arm, most of the patients had at least one dose reduction and/or interruption of dabrafenib or trametinib treatment (80.8% vs. 75.3% respectively). The numbers are similar to those in the C+V arm (81.8% for carboplatin and 75.8% for vincristine, respectively). The main reasons for dose reduction and interruption, regardless of substance, were AEs, which led to dose adjustment and/or interruption in 79.5% of the patients in the D+T arm and in 78.8% of the patients in the C+V arm.

The most frequently reported AEs leading to dose adjustment and/or interruption (with differences of $\geq 10\%$ between D+T and C+V arms) were pyrexia (+53.4%), neutrophil count decreased (−24.5%), platelet count decreased (−18.2%), neutropenia (−14.4%), infusion related reaction, and peripheral sensory neuropathy (−12.1% each).

Cardiac disorders and vascular disorders (embolism), which have been reported for both dabrafenib and trametinib, were uncommon reasons for dose reduction or interruption of D+T treatment (one patient/1.4% each). Eye disorders, which have been reported for both dabrafenib treatment (uveitis) and trametinib treatment (visual impairment), were also uncommon reasons for dose reduction or interruption of D+T treatment (one patient/1.4%). However, gastrointestinal disorders, mainly related to trametinib treatment, were reported as reasons for dose modification or interruption in 11 patients (15.1%). One case (1.4%) was a grade ≥ 3 event.

In general, dose reduction of dabrafenib was more common than for trametinib (61.6% vs. 19.2% at least one dose reduction of dabrafenib vs. trametinib respectively), while dose interruptions were equally frequent (76.7% vs. 72.6% at least one dose interruption of dabrafenib vs. trametinib respectively).

Dose discontinuations were less frequent in the D+T arm (17.8% for both dabrafenib and trametinib) compared to the C+V arm (78.8% for carboplatin and 75.8% for vincristine respectively). In both treatment arms, progressive disease was the most common reason for dose discontinuation (6.8% for dabrafenib and trametinib vs. 27.3% for both carboplatin and vincristine, respectively). AE as reason for dose discontinuation occurred in 4.1% of the patients for dabrafenib and trametinib respectively.

HGG cohort

As in the LGG cohort, dose reduction of dabrafenib occurred more frequently than dose reduction of trametinib (46.3 vs. 24.4% at least one dose reduction of dabrafenib vs. trametinib respectively). The most common reason for dose reduction and/or interruption was AE. Dose interruptions (63.4 vs. 68.3% at least one dose interruption of dabrafenib vs. trametinib respectively) were equally distributed. The most frequently reported AEs leading to dose adjustment and/or interruption (occurring in $\geq 5\%$ of patients) were pyrexia (36.6%) and headache (9.8%).

Also, in line with the data from the LGG cohort D+T arm, cardiac disorders, vascular disorders, and eye disorders were uncommon reasons for dose reduction or interruption of D+T treatment (one patient/2.4% each). Gastrointestinal disorders were reported as a reason for dose modification or interruption in five patients (12.1%), of which three cases (7.3%) were grade ≥ 3 events.

Dose discontinuations were more frequent in the HGG cohort (48.8%) compared to the LGG cohort D+T arm, but as in the LGG cohort D+T arm the main reason was progressive disease (36.6%) and not AEs (2.4%). This is in line with the expected poor prognosis for HGG.

Combination therapy pool

Dose reductions due to AEs occurred in 25/171 patients (14.6%) and dose interruptions occurred in 121/171 (70.8%) in the combination therapy pool. The most frequently reported AE leading to dose reduction was pyrexia (eight patients/4.7%). The most frequently reported AEs leading to dose interruptions ($>5\%$ incidence) were pyrexia (49.7%) and vomiting (9.4%). Dose interruptions and subsequent dose reductions were stipulated in the study protocols to manage AEs, including pyrexia events. Overall, the data on dose reductions and interruptions are in line with those in the LGG and HGG cohorts respectively.

adverse events of special interest (AESIs)

General AESIs

Adverse events of special interest (AESI) are collections of AE PTs that have been identified as meriting enhanced data presentation due to their possible clinical impact, based on development experience predominantly in adult clinical trials. Each AESI is composed of a selected group of AE PTs that are of specific clinical interest in connection with dabrafenib and trametinib treatment. The AESI groupings are defined at programme level based on the current safety information available for D+T. AESIs were identified for this combination based on a clinical review of a comprehensive list of MedDRA terms. Categories of AESI included bleeding events, cardiac related events, hepatic disorders, hyperglycaemia, hypersensitivity, hypertension, new primary/secondary malignancy, neutropenia, ocular events, pancreatitis, pneumonitis and interstitial lung disease, pre-renal and intrinsic renal failure, pyrexia, skin toxicities, uveitis, and venous thromboembolism.

The AESIs for the paediatric population included potential effects on growth and development.

Table 36. Overview of AESIs - LGG cohort

Safety topics	D+T N=73		C+V N=33	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Bleeding events	20 (27.4)	0	4 (12.1)	0
Cardiac-related events	3 (4.1)	1 (1.4)	0	0
Hepatic disorders	15 (20.5)	5 (6.8)	10 (30.3)	4 (12.1)
Hyperglycemia	2 (2.7)	0	2 (6.1)	0
Hypersensitivity	11 (15.1)	0	8 (24.2)	2 (6.1)
Hypertension	0	0	1 (3.0)	1 (3.0)
Neutropenia	18 (24.7)	10 (13.7)	27 (81.8)	25 (75.8)
Ocular events	7 (9.6)	0	1 (3.0)	0
Pancreatitis	3 (4.1)	1 (1.4)	0	0
Pneumonitis and interstitial lung disease	1 (1.4)	0	0	0
Pyrexia	50 (68.5)	6 (8.2)	7 (21.2)	1 (3.0)
Skin toxicities	53 (72.6)	2 (2.7)	11 (33.3)	1 (3.0)
Uveitis	2 (2.7)	0	0	0
Venous thromboembolism	1 (1.4)	0	1 (3.0)	0

Numbers (n) represent counts of patients.
 A patient with multiple severity grades for an AE is only counted under the maximum grade.
 MedDRA version 24.0, CTCAE version 4.03. Case Retrieval Strategy version released 10-Oct-2021(Dabrafenib) and 10-Jul-2021(Trametinib).
 Source: [Table 14.3.1-3.1L](#)

In the D+T arm, bleeding events (27.4%), hepatic disorders (20.5%), neutropenia (24.7%), and, above all, pyrexia (68.5%) and skin toxicities (72.6%) were among the most frequently occurring AESIs. Most of the AESIs were grade 1-2 events. In the C+V arm, neutropenia (81.8%) and hepatic disorders (30.3%) were the most frequently occurring AESIs. This is in line with what is expected of the respective treatments.

Of note, ocular events (9.6%), mainly related to trametinib treatment, and uveitis (2.7%), mainly related to dabrafenib treatment, occurred more frequently in the D+T than in the C+V arm (3.0% ocular events and not cases of uveitis reported).

HGG cohort

Table 37. Overview of AESIs - HGG cohort

Safety topic	All patients N=41	
	All grades n (%)	Grade ≥ 3 n (%)
Skin toxicities	34 (82.9)	1 (2.4)
Pyrexia	21 (51.2)	2 (4.9)
Bleeding events	12 (29.3)	2 (4.9)
Neutropenia	12 (29.3)	3 (7.3)
Ocular events	6 (14.6)	0
Hypersensitivity	5 (12.2)	0
Cardiac related events	4 (9.8)	1 (2.4)
Hepatic disorders	3 (7.3)	1 (2.4)
Hypertension	3 (7.3)	1 (2.4)
Hyperglycemia	1 (2.4)	0
Pancreatitis	1 (2.4)	1 (2.4)

Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.03, Case Retrieval Strategy version released 10-Oct-2021 (dabrafenib), 07-Oct-2021 (trametinib).
Source: [Table 14.3.1-3.1H](#)

The incidence of AESIs in the HGG cohort was in line with the incidence reported in the LGG cohort D+T arm.

Combination therapy pool

Among the AESIs, skin toxicities (78.9%), pyrexia (67.3%), neutropenia (28.1%), bleeding events (27.5%), and hepatic disorders related events (20.5%) were reported in ≥20% of patients in the combination therapy pool. Grade ≥3 events (with incidence ≥10%) were reported for neutropenia in 14.6% of patients. Grade 4 AESIs were reported for neutropenia (six patients) and pancreatitis (one patient). There were no reported AESIs grade 5 in the combination therapy pool. The presented AESI data in the combination therapy pool are in line with the data reported in the LGG cohort D+T arm and the HGG cohort.

Growth and bone age

LGG cohort

Treatment with D+T over six months did neither significantly impact gain in height, nor result in any significant acceleration or deceleration for estimated adjusted average growth of height SDS and did not seem to impact bone age. However, weight gain in D+T was greater than expected based on age specific norms (i.e., positive weight velocity SDS). The proportion of patients on the D+T arm with notably high weight gain during their first 6 months of treatment was 48.5%.

One patient discontinued D+T at Day 220 for grade 3 related weight gain, while an additional patient required dose interruption and subsequent dose reduction due to related grade 3 weight gain.

The effects of D+T on skeletal maturation are considered important potential risks. The long-term follow-up study CDRB36G2401 (study G2401) will capture long-term data on paediatric patients treated with D+T combination therapy, including effects on growth and development, potential delayed cardiac effects or new primary malignancies. All participants in study G2201 will be offered participation in study G2401. Information is now included in section 4.8 of the SmPC, with a cross reference to section 5.3, that data on growth and skeletal maturation are currently lacking.

HGG cohort

Fifteen of 36 (41.7%) patients with weight data available at six months on treatment had notably high weight gain at this time point. None of the patients in the HGG cohort discontinued D+T due to grade 3 related weight gain. D+T treatment did not seem to impact bone age.

Combination therapy pool

Treatment with D+T over six months did not significantly impact gain in height for the patients in the combination therapy pool. However, weight gain in D+T was greater than expected based on age specific norms.

Puberty

Most patients in the LGG and HGG cohorts as well as in the combination therapy pool had normal progression through the stages of maturation while on treatment. Three patients in the LGG cohort and two patients in the HGG cohort respectively were identified with premature puberty. None of the patients had delayed onset of puberty.

Reproductive toxicity

Currently, there is a knowledge gap on the effects of dabrafenib and trametinib monotherapy on reproductive toxicity in adult and paediatric human patients. The potential risk of D+T effects on reproduction is addressed in the RMP.

Renal toxicity

Based on animal renal toxicity data, children <1 year of age are excluded from clinical trials with D+T and, hence, from treatment with these substances.

2.6.8.3. Serious adverse event/deaths/other significant events

SAEs

LGG cohort

Table 38. Serious adverse events by preferred term – LGG cohort (Study No. CDRB436G2201)

Preferred term	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33		Dabrafenib+Trametinib vs Carboplatin+Vincristine Risk Difference (95% CI)	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of subjects with at least one event	29 (39.7)	20 (27.4)	13 (39.4)	7 (21.2)	0.3 (-19.8, 20.4)	6.2 (-11.1, 23.5)
Pyrexia	10 (13.7)	4 (5.5)	6 (18.2)	1 (3.0)	-4.5 (-19.8, 10.9)	2.4 (-5.4, 10.3)
Vomiting	3 (4.1)	1 (1.4)	0 (0.0)	0 (0.0)	4.1 (-0.4, 8.7)	1.4 (-1.3, 4.0)
Apnoea	2 (2.7)	2 (2.7)	0 (0.0)	0 (0.0)	2.7 (-1.0, 6.5)	2.7 (-1.0, 6.5)
Hydrocephalus	2 (2.7)	2 (2.7)	0 (0.0)	0 (0.0)	2.7 (-1.0, 6.5)	2.7 (-1.0, 6.5)
Procedural complication	2 (2.7)	2 (2.7)	0 (0.0)	0 (0.0)	2.7 (-1.0, 6.5)	2.7 (-1.0, 6.5)
Seizure	2 (2.7)	1 (1.4)	0 (0.0)	0 (0.0)	2.7 (-1.0, 6.5)	1.4 (-1.3, 4.0)
Tonsillitis	2 (2.7)	1 (1.4)	0 (0.0)	0 (0.0)	2.7 (-1.0, 6.5)	1.4 (-1.3, 4.0)
Urinary tract infection	2 (2.7)	2 (2.7)	0 (0.0)	0 (0.0)	2.7 (-1.0, 6.5)	2.7 (-1.0, 6.5)
Aspiration	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1.4 (-1.3, 4.0)	NE (NE, NE)
Bacterial sepsis	1 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)	1.4 (-1.3, 4.0)	1.4 (-1.3, 4.0)
Bronchitis	1 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)	1.4 (-1.3, 4.0)	1.4 (-1.3, 4.0)
Cerebral ventricle dilatation	1 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)	1.4 (-1.3, 4.0)	1.4 (-1.3, 4.0)
Dehydration	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1.4 (-1.3, 4.0)	NE (NE, NE)
Detachment of retinal pigment epithelium	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1.4 (-1.3, 4.0)	NE (NE, NE)
Device related infection	1 (1.4)	1 (1.4)	1 (3.0)	1 (3.0)	-1.7 (-8.1, 4.8)	-1.7 (-8.1, 4.8)
Embolism	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1.4 (-1.3, 4.0)	NE (NE, NE)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.03.

In the LGG cohort, the incidence of SAEs was overall comparable between the D+T and the C+V arms (39.7% vs. 39.4% respectively). Pyrexia was the most frequently (incidence ≥5%) reported SAE in both groups (13.7% vs. 18.2% respectively). SAEs not displayed in the table above all occurred in ≤1 patient each. Grade ≥3 SAEs were reported in 27.4% of the patients in the D+T arm and 21.1% of the patients in the C+V arm respectively.

HGG cohort

Table 39. Serious adverse events by preferred term - HGG cohort (Study No. CDRB436G2201)

Preferred term	All subjects N=41	
	All Grades n (%)	Grade ≥ 3 n (%)
Number of subjects with at least one event	25 (61.0)	22 (53.7)
Headache	3 (7.3)	2 (4.9)
Pyrexia	3 (7.3)	1 (2.4)
General physical health deterioration	2 (4.9)	2 (4.9)
Intracranial pressure increased	2 (4.9)	2 (4.9)
Agitation	1 (2.4)	1 (2.4)
Altered state of consciousness	1 (2.4)	0
Anxiety	1 (2.4)	1 (2.4)
Apnoea	1 (2.4)	1 (2.4)
Atelectasis	1 (2.4)	1 (2.4)
Brain abscess	1 (2.4)	1 (2.4)
C-reactive protein increased	1 (2.4)	1 (2.4)
Cerebral haemorrhage	1 (2.4)	0
Confusional state	1 (2.4)	1 (2.4)
Depressed level of consciousness	1 (2.4)	0
Dysarthria	1 (2.4)	0
Encephalomyelitis	1 (2.4)	1 (2.4)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.03.

SAEs were reported in 25/41 patients (61.0%), of which 22 patients (53.7%) had grade ≥ 3 SAEs. Three were fatal (not treatment related).

The most frequently reported SAEs (occurring in $\geq 5\%$ of patients) were headache and pyrexia (7.3% each). Except for the SAEs of general physical health deterioration and intracranial pressure increased (4.9% each), all other SAEs (including those not displayed in the table above) were reported in ≤ 1 patient each.

The incidence of SAEs, including grade ≥ 3 SAEs, was higher in the HGG cohort (61.0%) compared to the LGG cohort (39.7%). This is in line with the previously discussed general data on AEs in the HGG and LGG cohort D+T arm. Since the HGG cohort only consists of 41 patients, these numbers should be interpreted with caution. As for the LGG cohort, pyrexia was the most commonly reported SAE in the HGG cohort.

Combination therapy pool

The SAEs in the combination therapy pool are in line with the data reported in the LGG cohort D+T arm and the HGG cohort.

Deaths

A total of 18 deaths were reported across the three paediatric studies (total N=371) in this submission; 15 of these were treated with D+T in Study G2201, and three were treated with dabrafenib or trametinib monotherapy in the supporting monotherapy studies.

Six of the 15 deaths in patients who received D+T combination therapy in study G2201 were on-treatment deaths. Four patients died due to the underlying disease (one patient in the LGG cross-over cohort and three patients in the HGG cohort) and two patients in the HGG cohort died secondary to other causes.

2.6.8.4. Laboratory findings

Haematology

Haematological toxicity was less frequent and less severe in the LGG cohort D+T arm compared to the C+V arm. Apart from neutrophils decreased (16.4%) and lymphocytes decreased (1.4%) there were no other grade 3/4 haematologic AEs in the D+T arm.

The haematologic toxicity in the HGG cohort was generally consistent with that in the LGG cohort D+T arm. Apart from neutrophils decreased (14.6%) and lymphocytes decreased (12.2%) other grade 3/4 haematologic AEs were uncommon (<5%).

No additional data are provided in the combination therapy pool.

Clinical chemistry

The incidence of increase in liver enzymes, bilirubin, and most assessed blood electrolytes (including grade 3/4 events) was higher in the C+V than in the D+T arm. The exceptions were increase in ALP (60.3%) and magnesium (35.6%), which were higher in the D+T than in the C+V arm. Magnesium decrease is a known side-effect of platinum containing chemotherapy.

Overall, the biochemistry abnormalities in the HGG cohort were consistent with those in the LGG cohort D+T arm.

Overall, no clinically meaningful changes in liver enzymes were noted in the paediatric population.

'Blood creatinine increased' was reported more frequently among children <6 years of age compared in children ≥6 years of age, which is in line with a similar trend in study A2102 with dabrafenib monotherapy. In study G2201, there were four cases of increased creatinine reported in patients <6 years of age. They were all grade 1 or 2 without any accompanying clinical renal dysfunction.

Vital signs and physical findings

Systolic blood pressure

In the LGG cohort, clinically notable high systolic blood pressure (SBP) was reported in 26 patients (35.6%) in the D+T arm and 10 patients (30.3%) in the C+V arm. Clinically notable low SBP was reported in 15 patients (20.5%) only in the D+T arm.

In the HGG cohort, clinically notable high SBP occurred in 11 patients (26.8%), low SBP in 10 patients (24.4%).

Electrocardiograms

In dedicated thorough QT studies in adult patients, dabrafenib has been associated with a minor not clinically significant QT effect, whereas trametinib was devoid of cardiac repolarization effects.

In the LGG cohort, two patients (2.8%) in the D+T arm had increase in QTcF >60 ms from baseline. One patient in the D+T and one in the C+V arm respectively had new QTcF between >450 and ≤480 ms. None of the three patients that received D+T had cardiac-related AEs reported. One patient in the D+T arm had an AE of electrocardiogram T wave abnormal reported (grade 2, suspected to be study drug related). No action with the study treatment was taken and the AE was resolving at the time of the data cut-off date.

In the HGG cohort, two patients (5.0%) had an increase in QTcF of >60 ms post-baseline and one patient had new QRS >120 ms post-baseline. One patient had an AE of ECG prolongation reported (grade 1, not suspected to be treatment related) that led to study treatment interruption. The AE resolved in three days.

Echocardiogram

Decreased LVEF has been reported in adult patients receiving trametinib monotherapy, with a median time to first occurrence of left ventricular dysfunction, cardiac failure and LVEF decrease of 2-5 months. Combination therapy with BRAF/MEK inhibitors is associated with a more than 3-fold increase in risk of LVEF decrease compared with BRAF inhibitor monotherapy, and in adult patients receiving D+T combination therapy the incidence of decreased LVEF is 6%. Most of the cases were asymptomatic and reversible. Therefore, LVEF was monitored in the paediatric patient population following the label recommendation to regularly monitor the LVEF before initiating BRAF/MEK inhibition in adult patients.

LVEF was decreased by at least 10% and resulting in less than low limit of normal in seven patients (9.9%) in the LGG cohort D+T arm. Of these, LVEF decreased by at least 20% in three patients. Four of the seven patients had LVEF decrease resolved while on study and none of the patients had any cardiac-related AEs.

One patient (2.6%) in the HGG cohort had LVEF decreased by at least 10% and resulting in less than low limit of normal on study. The case was not resolved at the time of the data cut-off date.

Patients with LVEF lower than the institutional lower limit of normal were not included in the trials.

Visual assessments

In the LGG cohort, ocular related AESIs were reported in seven patients (9.6%) in the D+T arm, of which five had treatment related AESIs. None were considered grade ≥ 3 AESI. One ocular related AESI of detachment of retinal pigment epithelium was considered serious. None of the ocular related AESIs required treatment discontinuation or dose modification. There were no differences between the D+T and C+V arms respectively in changes in visual acuity over time. Most patients in both arms had stable visual acuity on-treatment.

In the HGG cohort, six patients (14.6%) had ocular related AESIs, of which none were serious nor led to study treatment discontinuation. There were no differences in change in visual acuity over time. Most patients had stable visual acuity on-treatment.

Overall, the ocular AESIs were varying and relatively few. None were grade ≥ 3 AESIS. The need for awareness of new visual disturbances and subsequent ophthalmologic assessments is addressed in SmPC section 4.4.

Concomitant medication

In the LGG cohort D+T arm, 30.1% of the patients received one or more systemic corticosteroids, of which dexamethasone (13.7%) and hydrocortisone (11.0%) were the most commonly used substances (compared to 39.4% systemic corticosteroid use overall in the LGG cohort C+V arm with 21.2% and 18.2% for dexamethasone and hydrocortisone respectively). Systemic corticosteroids were either started prior to and continued during the study or started on or within 30 days of end of treatment.

In the HGG cohort, 41.5% of the patients received one or more systemic corticosteroids, and as in the LGG cohort, dexamethasone (34.1%) and hydrocortisone (14.6%) were the most commonly used substances. The frequency of systemic corticosteroid use is relatively higher in the HGG than in the LGG cohort.

The data in the combination therapy pool are in line with the data in the LGG and HGG cohorts respectively.

2.6.8.5. Safety in special populations

The EMA requested table pertaining to age cohorts (age <65, 65-74, 75-84, and 85+) is not considered relevant due to the age distribution of the target population.

2.6.8.6. Safety related to drug-drug interactions and other interactions

Please refer to the Pharmacokinetics section.

2.6.8.7. Discontinuation due to adverse events

LGG cohort

Table 40. Adverse events leading to discontinuation of study treatment by preferred term - LGG cohort (Study No. CDRB436G2201)

Preferred term	D + T N=73		C + V N=33		D + T vs C + V Risk difference	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades	Grade ≥3
Number of patients with at least one event	3 (4.1)	2 (2.7)	6 (18.2)	3 (9.1)	-14.1	-6.4
Chills	1 (1.4)	0	0	0	1.4	NE
Fatigue	1 (1.4)	0	0	0	1.4	NE
Pyrexia	1 (1.4)	1 (1.4)	0	0	1.4	1.4
Weight increased	1 (1.4)	1 (1.4)	0	0	1.4	1.4
Headache	1 (1.4)	0	1 (3.0)	1 (3.0)	-1.7	-3.0
Neutropenia	0	0	1 (3.0)	1 (3.0)	-3.0	-3.0
Eyelid ptosis	0	0	1 (3.0)	0	-3.0	NE
Hypersensitivity	0	0	1 (3.0)	0	-3.0	NE
Infusion related reaction	0	0	2 (6.1)	0	-6.1	NE
Dizziness	0	0	1 (3.0)	1 (3.0)	-3.0	-3.0
Peripheral motor neuropathy	0	0	1 (3.0)	1 (3.0)	-3.0	-3.0
Urticaria	0	0	1 (3.0)	1 (3.0)	-3.0	-3.0

Numbers (n) represent counts of patients.

A patient with multiple severity grades for an AE is only counted under the maximum grade.

MedDRA version 24.0, CTCAE version 4.03.

Source: [Table 14.3.1-2.9L](#)

Treatment discontinuation due to AEs was less frequent in the D+T than in the C+V arm (4.1% vs. 18.2% respectively). All AEs leading to treatment discontinuation occurred at a frequency of one patient each, except infusion related reaction which led to treatment discontinuation in two patients in the C+V arm. One patient in the LGG cohort D+T arm discontinued study treatment due to the new paediatric ADR weight increased.

HGG cohort

Table 41. Adverse events leading to discontinuation of study treatment by preferred term - HGG cohort (Study No. CDRB436G2201)

Preferred term	All patients N=41	
	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with at least one event	2 (4.9)	0
Rash	2 (4.9)	0

Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.03.
Source: Table 14.3.1-2.9H

Treatment discontinuation due to AEs occurred in two patients (4.9%) in the HGG cohort. Both cases regarded rash, and none were grade ≥ 3 .

Combination therapy pool

AEs leading to treatment discontinuation in the combination therapy pool occurred in 13/171 (7.6%). From an oncology perspective, the discontinuation rate due to AEs for D+T combination therapy is considered low and indicates a favourable tolerability of the combination treatment with D+T.

2.6.8.8. Updates of AE reports after Data cut off (DCO)

During a routine GCP inspection it was revealed that AE reports had been changed after primary DCO of 23 August 2021. As requested, the applicant has provided the final cleaned data set from final data base lock (DBL) on 03 July 2023. The applicant has re-run all relevant AE data outputs based on the final cleaned data set from final DBL, using the primary analysis cut-off date. Updated AE tables and listings have been provided.

The analysis of the safety dataset was performed comparing all AE entries in the primary analysis reporting period for changes in 12 key data fields: Dictionary-Derived Term; Start Date/Time of Adverse Event; End Date/Time of Adverse Event; Serious Event; Causality; Action taken to investigational treatment (4 data fields, one each for dabrafenib, trametinib, and – for LGG only – carboplatin and vincristine); Other Action Taken; Outcome of Adverse Event; and Standard Toxicity Grade.

The MAH has confirmed that AE data could only be updated by site staff, and that changes would usually be triggered by monitoring queries. The justification for each change has always been captured in the clinical data base by the Investigator at the time of the update via a mandatory drop-down field for the main reason for the change and an optional comment field in case the investigator needed to provide additional information.

Overall, the updates have only resulted in minor changes to the individual reported AEs, AE frequencies, and the AE summary.

LGG cohort

In the LGG cohort, the duration of exposure to dabrafenib was changed for two patients who were on D + T treatment, which resulted in a somewhat shorter median duration of exposure to dabrafenib of 74.0 weeks (compared with the originally reported 75.3 weeks) for the entire patient cohort. The median duration of exposure to trametinib remained unchanged.

In total, 144/2,231 AE records in the LGG cohort were changed between primary and final analysis. These 144 AE records corresponded to 210 data field modifications, translating to approximately 1.0% of all AE data fields. The majority (n=86) of the changed AE records impacted one data field each. The most common change made to an AE was update of the outcome of the AE to "Recovered/Resolved", (n=84 cases, 66 in the D+T arm and 18 in the C+V arm). The second most common change was update of the end date of the AE from "missing" to "now having an end date" (n=48 cases, 34 in the D+T arm and 14 in the C+V arm). No AE was upgraded from non-serious to serious. Two AEs (both in the C+V arm) had their grade increased, one from grade 1 to grade 2, and one from grade 1 to grade 3. The AE which increased to grade 3 was for "neutrophil count decreased", and that patient already had a grade 3 AE with the same PT reported in the primary CSR. After update, one treatment related SAE was no longer considered treatment related (D+T arm), whereas one more treatment-related AE was reported to have resulted in treatment discontinuation (C+V arm). In the cleaned data set, AEs grade 3 were reported for 35 patients (47.9%) compared to 34 patients (46.6%) in the primary application.

For AEs by PT, it is noted that one additional patient had an AE of weight increased reported. Overall, the changes to AEs by PT in the cleaned data set were considered minor. Among the most frequently reported AEs in the LGG cohort D+T arm, *e.g.*, AE pyrexia was changed from 68.5% to 69.9%, AE headache from 46.6% to 47.9%, AE diarrhoea from 28.8% to 31.5%, and AE epistaxis from 20.5% to 21.9%, corresponding to changes for 1-2 patients/AE. The changes to AE frequencies were similar in the C+V arm.

An additional 104 AE records with a start date prior to the primary DCO were added to the study data base following the primary CSR DBL. There were 62 new AE records added for 21 patients in the D+T arm, and 42 new AE records added for six patients in the C+V arm. None of the new AE records were SAEs, 79 were grade 1 (46 D+T, 33 C+V), 20 were grade 2 (14 D+T, six C+V), four were grade 3 (two D+T, two C+V), and one was grade 4 (C + V arm). Ten AE entries in the LGG cohort were no longer present in the primary analysis database at the time of the final DBL but remained visible in the audit trail. Among these 10 events, none were SAEs, and all were grade 1 or 2.

The AE changes are summarised below.

Table 42. Summary of changes to data fields in AE records between primary and final data base lock in the LGG cohort

Field	D+T	C+V	Total
Total number of fields changed	153	57	210
Outcome of Adverse Event	69	20	89
Updated to recovered/resolved	66	18	84
Updated to not recovered/resolved	3	2	5
End Date/Time of Adverse Event	40	23	63
Updated from missing to having an end date	34	14	48
End date now earlier	5	1	6
End date now later	1	8	9
Causality	12	5	17
Changed to related	8	3	11
Changed to unrelated	4	2	6
Dictionary-Derived Term	9	2	11
Dictionary-derived term	9	2	11
Start Date/Time of Adverse Event	11	4	15
Start date now earlier	7	1	8
Start date now later	4	3	7
Other Action Taken	8	1	9
Updated to concomitant medication or non-drug therapy given	8	1	9
Action taken to investigational treatment	4	0	4
Updated to drug interrupted	3	0	3
Updated to dose not changed	1	0	1
Standard Toxicity Grade	0	2	2
Grade 1 to Grade 2	0	1	0
Grade 1 to Grade 3	0	1	0
Serious Event	0	0	0

HGG cohort

In the HGG cohort, 44/766 AE records were changed between primary and final analysis. These 44 AE records corresponded to 68 data field modifications, translating to approximately 1.0% of all AE data fields. The majority (n=27) of the changed AE records impacted one data field each. The most common change made to an AE was update of the outcome of the AE to "Recovered/Resolved", (n=9 cases). The second most common change was update of the end date of the AE from "missing" to "now having an end date" (n=8 cases). One AE of paresis in one patient was upgraded to "serious" due to hospitalisation of the patient. This did, however, not impact the SAE summary tables since the same patient already had another SAE of paresis reported. Three AEs had their grade increased, two from grade 1 to grade 2, and one from grade 2 to grade 3. The AE which increased to grade 3 was for "amylase increased", and that patient already had a grade 4 AE with the same PT reported in the primary CSR. One AE of headache in one patient was downgraded from serious to non-serious. This patient had another SAE with the same start date reported. Originally this other SAE had a PT of general physical health deterioration, but this was updated to syncope by the time of the final DBL. After update, one additional AE was considered treatment related, but one AE less was considered leading to dose adjustment/interruption.

For AEs by PT, it is noted that one additional patient had an AE of weight increased reported. As opposed to the primary report, in the cleaned data set no patients experiencing increased weight were reported to be on systemic corticosteroids. As for the LGG cohort D+T arm, the changes to AEs by PT in the cleaned data set were considered minor. Among the most frequently reported AEs in the HGG cohort, e.g., AE headache was changed from 34.1% to 36.6% and AE nausea from 19.5% to 22.0%, corresponding to a change for one patient/AE.

An additional 28 AE records with a start date prior to the primary DCO were added to the study data base following the primary CSR DBL. None were SAEs, 19 were grade 1, eight were grade 2, and one

was grade 4. Three AE entries in the HGG cohort were deleted following the primary CSR data base lock but remained visible in the audit trail. The AE changes are summarised below.

Table 43. Summary of changes to data fields in AE records between primary and final data base lock in the HGG cohort

Field	Total
Total number of fields changed	68
End Date/Time of Adverse Event	15
Updated from missing to having an end date	8
End date now earlier	4
End date now later	3
Outcome of Adverse Event	11
Updated to recovered/resolved	9
Updated to recovering/resolving	2
Dictionary-Derived Term	8
Dictionary-derived term	8
Start Date/Time of Adverse Event	8
Start date now earlier	5
Start date now later	3
Causality	7
Changed to unrelated	6
Changed to related	1
Other Action Taken	7
Updated to concomitant medication or non-drug therapy not given	5
Updated to concomitant medication or non-drug therapy given	2
Action taken to investigational treatment	6
Updated to dose not changed	5
Updated to drug interrupted	1
Standard Toxicity Grade	4
Grade 1 to Grade 2	2
Grade 2 to Grade 1	1
Grade 2 to Grade 3	1
Serious Event	2
Changed from non-serious to serious	1
Changed from serious to non-serious	1

2.6.8.9. Adverse drug reaction (ADR) summary as included in the SmPC

ADR

According to the applicant, ADR identification for D+T combination therapy in paediatric patients was based on the ADR definition in the adult population in a large phase III safety data pool. Any paediatric AE that was listed as an adult ADR for D+T combination treatment (for all indications) was identified as a paediatric ADR. All treatment emergent AEs (*i.e.*, not only AEs suspected to be related to study drug by the investigator), which did not qualify as ADRs in the adult population, were screened to detect potential paediatric ADR candidates.

Identified potential paediatric ADRs:

- Any paediatric AEs, which were identified as an ADR from the ADR lists of competitors (vemurafenib, encorafenib, cobimetinib + vemurafenib (combination), binimetinib + encorafenib (combination), selumetinib).
- Any paediatric AEs that were part of developmental toxicities or fertility toxicities.
- Any AE that was a designated medical event.
- Any AE that did not fulfil above criteria but appeared in at least three patients in the paediatric combination therapy pool.

The potential paediatric ADR candidates were reviewed by the sponsor to assess the plausibility of a causal association with D and T. The criteria for causal association included consistency with the mechanism of action of the drugs, the known safety profile of other drugs with similar mechanism of action (*i.e.*, listed for vemurafenib, encorafenib, cobimetinib + vemurafenib [combination], binimetinib + encorafenib [combination], or selumetinib), temporal relationship to study drugs, dechallenge, and re-challenge effect. The frequency of the identified paediatric ADRs was calculated based on the pooled safety population of 171 patients who received D+T combination therapy.

Tabulated list of adverse reactions

Adverse reactions in the integrated paediatric safety population are listed below by MedDRA system organ class ranked by frequency using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), very rare ($< 1/10\ 000$) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 44. Adverse reactions reported in the integrated paediatric safety population of trametinib in combination with dabrafenib (n=171)

Infections and infestations	
Very common	Paronychia
Common	Urinary tract infection, cellulitis, nasopharyngitis* ¹
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	
Common	Skin papilloma
Blood and lymphatic system disorders	
Very common	Neutropenia* ² , anaemia, leukopenia*
Common	Thrombocytopenia*
Immune system disorders	
Common	Hypersensitivity
Metabolism and nutrition disorders	
Common	Dehydration, decreased appetite
Nervous system disorders	
Very common	Headache, dizziness* ³
Eye disorders	
Common	Vision blurred, visual impairment, uveitis* ⁴
Uncommon	Retinal detachment, periorbital oedema
Cardiac disorders	
Common	Ejection fraction decreased, bradycardia*
Vascular disorders	
Very common	Haemorrhage* ⁵
Common	Hypertension, hypotension
Respiratory, thoracic, and mediastinal disorders	
Very common	Cough*
Common	Dyspnoea
Gastrointestinal disorders	
Very common	Abdominal pain*, constipation, diarrhoea, nausea, vomiting
Common	Pancreatitis, stomatitis
Uncommon	Colitis*
Skin and subcutaneous tissue disorders	
Very common	Dermatitis acneiform* ⁶ , dry skin* ⁷ , pruritus, rash* ⁸ , erythema
Common	Dermatitis exfoliative generalised* ⁹ , alopecia, palmar-plantar erythrodysesthesia syndrome, folliculitis, skin lesion, panniculitis, hyperkeratosis
Uncommon	Skin fissures, night sweats, hyperhidrosis

Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, pain in extremity
Common	Myalgia*, muscle spasms* ¹⁰
General disorders and administration site conditions	
Very common	Pyrexia*, fatigue* ¹¹ , weight increased
Common	Mucosal inflammation, face oedema*, chills, oedema peripheral, influenza-like illness
Investigations	
Very common	Transaminases increased* ¹²
Common	Hyponatraemia, hypophosphataemia, hyperglycaemia, blood alkaline phosphatase increased, gammaglutamyltransferase increased, blood creatine phosphokinase increased
*Denotes grouped term of two or more MedDRA preferred terms that were considered clinically similar. 1 nasopharyngitis includes pharyngitis 2 neutropenia includes neutrophil count decreased and febrile neutropenia 3 dizziness includes vertigo 4 uveitis includes iridocyclitis 5 haemorrhage includes epistaxis, haematuria, contusion, haematoma, international normalised ratio increased, anal haemorrhage, catheter site haemorrhage, cerebral haemorrhage, ecchymosis, extradural haematoma, gastrointestinal haemorrhage, haematochezia, petechiae, post-procedural haemorrhage, rectal haemorrhage, red blood cell count decreased, upper gastrointestinal haemorrhage and uterine haemorrhage 6 dermatitis acneiform includes acne and acne pustular 7 dry skin includes xerosis and xeroderma 8 rash includes rash maculo-papular, rash pustular, rash erythematous, rash papular, rash macular 9 dermatitis exfoliative generalised includes skin exfoliation and dermatitis exfoliative 10 muscle spasms include musculoskeletal stiffness 11 fatigue includes malaise and asthenia 12 transaminases increased includes aspartate aminotransferase (AST) increased and alanine aminotransferase (ALT) increased	

Description of selected adverse reactions

Weight increased

Weight increase has only been reported in the paediatric population. It was reported as an adverse reaction in 16% of paediatric patients including Grade 3 cases in 4.7% of patients, with a discontinuation rate of 0.6% of patients. The median time to onset of the first occurrence of the reported weight increase in paediatric patients receiving trametinib in combination with dabrafenib was 3.1 months. Weight increase from baseline of ≥ 2 BMI (body mass index)-for-age percentile categories was observed in 29.8% of patients.

Haemorrhage

Haemorrhagic events were observed in 30% of paediatric patients, with Grade 3 events occurring in 1.2% of patients. The most frequent haemorrhagic event (epistaxis) was reported in 18% of paediatric patients. The median time to onset of the first occurrence of haemorrhagic events in paediatric patients was 2.4 months. Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages, occurred in adult patients taking trametinib in combination with dabrafenib.

Left ventricular ejection fraction (LVEF) reduction/Left ventricular dysfunction

Decreased LVEF has been reported in 5.3% of paediatric patients, with Grade 3 events occurring in <1% of patients. The median time to onset for the first occurrence of LVEF decrease was around one month. In clinical studies in adult patients, the median time to first occurrence of left ventricular

dysfunction, cardiac failure and LVEF decrease was between 2 to 5 months. Patients with LVEF lower than the institutional lower limit of normal were not included in clinical studies with trametinib.

Pyrexia

Pyrexia has been reported in clinical studies with trametinib as monotherapy and in combination with dabrafenib; however, the incidence and severity of pyrexia are increased with the combination therapy. Pyrexia was reported in 65% of paediatric patients, with Grade 3 events occurring in 8.8% of patients.

Hepatic events

Hepatic adverse reactions have been reported in adult and paediatric clinical studies with trametinib in combination with dabrafenib. In the paediatric safety population, increased ALT and AST were very common, reported in 12.3% and 15.2% of patients, respectively. The hepatic adverse reactions of increased ALT and AST were the most common events in adult patients, the majority of these events were either Grade 1 or 2. For trametinib monotherapy, more than 90% of these liver events occurred within the first 6 months of treatment. Liver events were detected in clinical studies with monitoring every four weeks.

Blood pressure changes

Hypertension was reported in 2.3% of paediatric patients, with Grade 3 events occurring in 1.2% of patients. The median time to onset of the first occurrence of hypertension in paediatric patients was 5.4 months.

Hypotension was reported in 3.5% of paediatric patients, with Grade ≥ 3 events occurring in 2.3% of patients. The median time to onset of the first occurrence of hypotension in paediatric patients was 1.5 months.

Visual impairment

In paediatric patients treated with trametinib in combination with dabrafenib, ophthalmological reactions, including uveitis 1.8% and iridocyclitis 1.2%, have been reported. Grade 3 uveitis occurred in <1% of paediatric patients. Retinal pigment epithelial detachment (RPED) occurred in <1% of paediatric patients. Disorders associated with visual disturbances, including RPED and RVO, have also been observed with trametinib in adult patients. Symptoms such as blurred vision, decreased acuity and other visual disturbances have been reported in adult clinical studies with trametinib.

Rash

Rash has been observed in about 47% of paediatric patients in trametinib and dabrafenib combination studies in the integrated safety population. The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions.

Rhabdomyolysis

Rhabdomyolysis has been reported in adult patients taking trametinib.

Pancreatitis

Pancreatitis was reported in 1.2% of paediatric patients, with <1% of patients with Grade 3 severity.

Renal failure

Renal failure has been reported with trametinib in combination with dabrafenib. Renal failure due to pyrexia-associated pre-renal azotaemia or granulomatous nephritis was uncommon in adult patients;

however, trametinib has not been studied in patients with renal insufficiency (defined as creatinine $>1.5 \times \text{ULN}$).

2.6.9. Discussion on clinical safety

The proposed liquid formulations of D+T were mainly administered to patients <6 years of age, *i.e.*, to a limited number of patients (exact number not provided). Currently approved solid formulations of dabrafenib (Tafinlar) capsules and trametinib (Mekinist) tablets were provided to the majority of patients (exact number not provided). Thus, the safety profile of the liquid formulations is almost exclusively derived from data on the, numerically limited, <6 years of age subgroup. The proposed dabrafenib dispersible tablets and trametinib powder for oral solution were considered clinically comparable to the respective capsule/tablet formulations. No safety analysis by formulation received is provided. The safety data of the sought administration form is limited but considered sufficiently comprehensive to characterise the safety profile of D+T, at least in the short-term perspective given the rarity of the disease. Also, given the rarity of the disease, the size of the safety database is considered sufficiently comprehensive to characterise the safety profile of D+T, at least in the short-term perspective.

Dosing errors were reported for only three paediatric patients (one in the LGG cohort and two in the HGG cohort, respectively) and the administration instructions in the product information is considered sufficiently adequate. Medication errors will be monitored through routine pharmacovigilance and included as a standard safety topic in the respective PSURs.

In the LGG cohort D+T arm in study G2201, the median duration of exposure to D+T was 75.7 weeks (range 2.71-149.71). Of the patients in the LGG cohort, 64.4% received D+T for ≥ 56 weeks. The median duration of exposure to carboplatin was 34.0 weeks (range 12.0-70.14) and to vincristine 35.3 weeks (range 12.0-70.14). In the HGG cohort, the median exposure to D+T was 72.7 weeks (range 1.3-172.1). Twenty-one (51.2%) patients in the HGG cohort were still on treatment at DCO. Overall, 56.1% of the patients in the HGG cohort received D+T for ≥ 56 weeks.

In order to address the important potential risk regarding the long-term safety in patients <18 years old (including potential adverse effects on skeletal maturation and sexual maturation), the applicant should submit the final data from the pivotal study (REC) as well as from the expansion study CDRB436G2401 (a category 3 study in the RMP) as post-authorisation measures (REC and MEA respectively).

AEs overview: All patients in the D+T as well as the C+V arm in the LGG cohort experienced at least one AE. Overall, the number of grade ≥ 3 AEs was higher in the C+V arm (93.9%) compared to the D+T arm (46.6%), especially regarding blood and lymphatic system disorders. This is in line with what is expected for chemotherapy regimens like C+V. Similarly, in the HGG cohort, all patients experienced at least one AE. Of these, 68.3% were grade ≥ 3 , which is higher than for the LGG cohort D+T treated patients (46.6%). However, no firm conclusions about a real difference in tolerability can be drawn given the limited number of patients in the HGG cohort that also carries a more aggressive disease.

Skin and subcutaneous tissue disorders were among the most frequent AEs in both the LGG cohort D+T arm (all grades 76.6%) and the HGG cohort (all grades 80.5%). As for Tafinlar and Mekinist (see SmPC), these are well-known side effects of dabrafenib and trametinib monotherapies and D+T combination therapy; this is reflected in the Spexotras SmPC section 4.8. Nervous system disorders were among the most frequent grade ≥ 3 AEs in both the LGG cohort D+T arm (12.3%) and the HGG cohort (26.8%).

Overall, the frequency and distribution of AEs are in line with what is expected with BRAF and MEK inhibitor treatment and the data are supported by that from the combination therapy pool. Although the number of AEs leading to dose adjustment/interruption in the D+T arms is high, the number of AEs leading to discontinuation is relatively low (LGG cohort 4.1%, HGG cohort 4.9%) indicating a manageable toxicity profile. The median time to onset for the most common AEs ($\geq 20\%$) as well as ADRs was in general less than three months, although individual cases presented with a time to first occurrence of >20 months. Several ADRs within the SOC of eye disorders did have a later median time to onset and it is considered important that clinicians are made aware of the potential late time to onset of ocular side-effects. Information regarding time to onset of ocular side-effects has been included in the SmPC section 4.4 as follow: Ophthalmological reactions, including uveitis and iridocyclitis, have been reported in paediatric patients taking dabrafenib in combination with trametinib, in some cases with a time to onset of several months. In clinical studies in adult patients treated with dabrafenib, ophthalmological reactions, including uveitis, iridocyclitis and iritis, have been reported. Patients should be routinely monitored for visual signs and symptoms (such as change in vision, photophobia and eye pain) while on therapy.

No dose modifications are required as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, withhold dabrafenib until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level. No dose modification of trametinib is required when taken in combination with dabrafenib following diagnosis of uveitis.

RPED and RVO may occur with dabrafenib in combination with trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib following diagnosis of RVO or RPED.

AEs by preferred term: In both the LGG cohort D+T arm and the HGG cohort, pyrexia (68.5% in the LGG cohort vs. 51.2% in the HGG cohort), headache (46.6% vs. 34.1%), vomiting (34.2% vs. 29.3%), diarrhoea (28.8% vs. 24.4%), dry skin (26.0% vs. 31.7%), and epistaxis (20.5% vs. 14.6%) were among the most frequent AEs.

In the C+V arm, well-known chemotherapy side-effects such as anaemia (60.6%), neutrophil count decreased (48.5%), vomiting (48.5%), nausea (45.5%), white blood cell count decreased (36.4%), platelet count decreased (30.3%), and neutropenia (30.3%) were among the most frequently reported AEs.

Pyrexia is a well-known side effect of both dabrafenib and trametinib, and both the incidence and severity are increased with combination therapy (as reflected in section 4.4 of the SmPC). Fever has been reported in adult and paediatric clinical studies with dabrafenib. Serious non-infectious febrile events were defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency of pre-renal origin in patients with normal baseline renal function. In paediatric patients who received dabrafenib in combination with trametinib, the median time to onset for the first occurrence of pyrexia was 1.3 months. In adult patients with unresectable or metastatic melanoma who received dabrafenib in combination with trametinib and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy and approximately one third of the patients had 3 or more events. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care.

Therapy with dabrafenib and trametinib should be interrupted if the patient's temperature is $\geq 38^{\circ}\text{C}$. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with antipyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which antipyretics are insufficient. Patients should be evaluated for signs and symptoms of infection. Therapy can be restarted once the fever resolves. If fever is associated with other severe signs or symptoms, therapy should be restarted at a reduced dose once fever resolves and as clinically appropriate.

Furthermore, dry skin, rash, rash maculo-papular, dermatitis acneiform, and eczema are well-known and frequent side effects of combination treatment with D+T (reflected in section 4.4 of the SmPC). The majority of the events were grade 1-2 AEs.

Weight increased is considered a new ADR in the paediatric population. In the initial application, weight increased was reported in 11 patients (15.1%) in the LGG cohort D+T arm and in five patients (12.2%) in the HGG cohort. Likewise, in the initial application four patients (one in the HGG cohort and three in the LGG cohort D+T arm) with a reported AE of weight gain were reported to have received systemic corticosteroids, which was changed to three patients in the LGG cohort only upon update. For three of these patients (changed to two in the cleaned data set), the corticosteroid treatment started after the reported weight gain and hence no causality is demonstrated in these cases. For the one remaining patient the corticosteroid treatment started prior to the reported weight increased, but both doses and types of steroids varied. This is not considered sufficient to establish causality. According to the applicant, previous reports in paediatric patients with LGG have suggested an association of weight gain with tumour location in the hypothalamic pituitary region, but no such association was noted in the current study. Hence, the underlying cause of the 'weight gain' ADR in the current population is not known. Apart from weight increased, both the reported AEs and the differences between the D+T and C+V arms respectively are in line with what is expected for these treatments.

AEs by age: The age cohorts in the individual studies and the combination therapy pool were relatively small and did not allow detailed safety analyses by age. Safety analyses were performed for AEs by age subgroups in the combination therapy pool. Due to the limited number of patients in each age subgroup (especially <6 years of age), no firm conclusions can be drawn from the minor differences in AEs between patients <6 years vs. ≥ 6 years of age respectively. Overall, AE data, including grade ≥ 3 AEs, in the age subgroup <6 years (n=43) was consistent with the age subgroup ≥ 6 years of age (n=128) in the combination therapy pool and was also consistent with the known safety profile of D+T in adults. There were no specific safety concerns for children <2 years of age, although this age population was limited, and data should be interpreted with caution. The long-term follow-up study CDRB36G2401 (study G2401) will capture long-term data on paediatric patients treated with D+T combination therapy, including effects on growth and development, potential delayed cardiac effects, or new primary malignancies and is included as a category 3 study in the RMP. All participants in study G2201 will be offered participation in study G2401. Information that data on growth and skeletal maturation are currently lacking has been included in section 4.8 of the SmPC.

Treatment related AEs:

Overall, the listed treatment related AEs in the pivotal study and in the combination therapy pool are in line with what is expected, both for BRAF/MEK inhibitor treatment and for chemotherapy.

Severity of adverse events: In the LGG cohort D+T arm, grade ≥ 3 AEs were reported less frequently than in the C+V arm (46.6% vs. 93.9%). However, pyrexia (8.2%) and weight increased (6.8%) were more frequent grade ≥ 3 AEs in the D+T than in the C+V arm (3.0% vs. 0% respectively), while there was an increased risk of grade ≥ 3 haematological toxicities in the C+V arm (30.3% neutropenia and 15.2% white blood cell count decreased compared to 9.6% and 0% in the LGG cohort respectively).

In the HGG cohort, headache (9.8%) was the most commonly reported grade ≥ 3 AE (1.4% in the LGG cohort D+T arm and 3.0% in the C+V arm respectively).

SAEs: Overall, the incidences of SAEs and suspected study treatment related SAEs were comparable between the D+T and C+V arms in the LGG cohort. Grade ≥ 3 SAEs were reported in 27.4% of the patients in the D+T arm and 21.1% of the patients in the C+V arm respectively. SAEs were relatively more common in the HGG cohort, and grade ≥ 3 SAEs occurred in 53.7% of the patients. The most

frequently reported SAE in all treatment arms was pyrexia. Three cases of SAEs were fatal but considered not treatment related.

Deaths: In total, six on-treatment deaths occurred for patients treated with D+T combination therapy in study G2201, of which four were due to disease progression (one in the LGG cross-over cohort and three in the HGG cohort). Two deaths in the HGG cohort, reported due to other causes, occurred on-treatment but were not considered treatment related. Both could be related to the underlying disease.

Laboratory findings and vital signs: As expected haematological toxicity was less frequent and less severe in the D+T arm compared to the C+V arm. The haematologic toxicity in the HGG cohort was generally consistent with that in the LGG cohort D+T arm.

Overall, no clinically meaningful changes in liver enzymes were noted in the paediatric population. However, hepatic laboratory abnormalities, including increases in ALT and AST, were observed in clinical studies in adults with trametinib monotherapy and D+T combination therapy. As addressed in the proposed SmPC section 4.4, it is therefore recommended that patients receiving treatment with D+T have liver function monitored every four weeks for 6 months after treatment initiation with trametinib.

Hypertension has previously been reported in association with trametinib monotherapy and D+T combination therapy, and safety measures regarding blood pressure during trametinib treatment are noted in the SmPC sections 4.4. and 4.8. Overall, no clinically meaningful changes in left ventricular ejection fraction (LVEF) were noted in the paediatric population, but as addressed in the SmPC section 4.8, D+T combination therapy should be used with caution in patients with conditions that could impair left ventricular function. The information regarding LVEF reduction is adequately reported in sections 4.2 and 4.4 of the SmPC for Spexotras. Only minor QT changes have been reported in association with dabrafenib monotherapy.

MEK inhibitor monotherapy or in combination with BRAF inhibitors have the potential to induce transient retinopathy with time-dependent recurrence and usually mild visual symptoms. Vascular injuries can be observed, and their management is essential in clinical practice. Ocular assessments were performed in the pivotal and supporting monotherapy studies. Ocular AESIs were reported in the LGG cohort D+T arm and in the HGG cohort (9.6% and 14.6% respectively). Overall, the ocular AESIs were varying and relatively few. None were of grade ≥ 3 . Recommendation for management of new visual disturbances is addressed in section 4.4 of the SmPC.

More than 30% in all treatment arms received one or more systemic corticosteroids due to clinical reasons while on study treatment, with dexamethasone the most commonly used (13.7% and 21.2% in the LGG cohort D+T and C+V arms respectively and 34.1% in the HGG cohort).

The use of systemic corticosteroids was relatively higher in the HGG cohort (overall 48.4% in the HGG cohort vs. 30.1% in the LGG cohort D+T arm), which probably reflects the severity of disease in this cohort. Systemic corticosteroids were more commonly used in the C+V arm than in the LGG cohort D+T arm and comparable to the use in the HGG cohort.

Discontinuation due to AEs: The proportion of treatment discontinuation due to AEs was lower in the LGG cohort D+T arm (4.1%) as compared to the LGG cohort C+V arm (18.2%). Corresponding proportion for the HGG cohort was 4.9%. Overall, the low discontinuation rate due to AEs is indicative of a manageable toxicity profile.

ADR

The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy. If haemorrhage occurs, patients should be treated as clinically indicated.

Trametinib in combination with dabrafenib should be used with caution in patients with conditions that could impair left ventricular function.

It is recommended that patients receiving treatment with trametinib have liver function monitored every four weeks for 6 months. Liver monitoring may be continued thereafter as clinically indicated.

Blood pressure should be measured at baseline and monitored during treatment, with control of hypertension by standard therapy as appropriate.

Patients treated with trametinib may develop ILD or pneumonitis. Trametinib should be withheld in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion or infiltrates, pending clinical investigations. For patients diagnosed with treatment-related ILD or pneumonitis, trametinib should be permanently discontinued.

Signs or symptoms of rhabdomyolysis should warrant an appropriate clinical evaluation and treatment as indicated.

Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when restarting treatment after an episode of pancreatitis.

GCP inspection

In a routine inspection at the sponsor site, critical findings such as, 1) relevant safety data were changed in the live eCRF after database lock without adequate justification, 2) there were clear indications that complete AE datasets were removed from or replaced in the database without being traceable, and 3) the completeness of the submitted SAE data and the management of any outstanding issues could not be verified, were identified. In response, the applicant provided a cleaned safety data set along with an explanation of the changes made to the AE records. The changes in the safety data were considered minor by the CHMP and without impact on the overall safety profile or benefit/risk balance.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The distribution and proportions of AEs and SAEs are generally consistent in the LGG cohort D+T arm and the HGG cohort, and the incidences of grade ≥ 3 AEs and SAEs in the respective D+T arms are low. Overall, the AEs and SAEs are in line with what is previously reported in adult patients treated with D+T combination therapy, including pyrexia, skin disorders and gastrointestinal symptoms. As expected, AEs in general as well as grade ≥ 3 AEs were more frequent in the LGG cohort C+V arm. The proportion of AEs leading to dose adjustment and/or interruption in the D+T arms is high, however, the proportion of AEs leading to discontinuation (<5% in the respective D+T arms) is low. Weight increased is considered a new ADR in the paediatric population.

Overall, the safety profile of D+T is considered manageable.

The CHMP considers the following measures necessary to address issues related to safety:

- the MAH should submit the final data delivery from pivotal study G2201, LGG and HGG cohorts.
- as well as from the expansion study CDRB436G2401 (a category 3 study in the RMP).

2.7. Risk Management Plan (version 19.2)

2.7.1. Safety concerns

Table 45. Summary of safety concerns

Important identified risks for trametinib	• Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachment), • Pneumonitis/Interstitial lung disease, • Hepatic events (e.g., AST, ALT increased, and hepatic failure), • Gastrointestinal disorders (diarrhea, colitis, and GI perforation).
Important potential risks for trametinib	• Impaired female fertility, • Developmental toxicity, • Long-term safety in patients < 18 years old (including potential adverse effects on skeletal maturation and sexual maturation) • Pregnancy and risks in breast-feeding.
Important potential risk related to trametinib+dabrafenib combination therapy only	• Pulmonary embolism, deep vein thrombosis.
Missing information for trametinib	• Use in patients with reduced cardiac function or symptomatic Class II, III, or IV heart failure (NYHA functional classification system), • Safety in patients with severe renal impairment, • Safety in patients with recent (within 6 months) acute coronary syndrome including unstable angina, coronary angioplasty, stenting or cardiac arrhythmias (except sinus arrhythmia) and treatment refractory hypertension (blood pressure of systolic > 140 mmHg and/or diastolic > 90 mmHg which cannot be controlled by anti-hypertensive therapy).

2.7.2. Pharmacovigilance plan

Table 46. Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
CDRB436G2401	The primary objective: - To assess the long-term safety of treatment with dabrafenib, trametinib or the combination. The secondary objectives: - To assess the long-term effect of treatment with dabrafenib, trametinib or the combination on general health, growth and development. - To assess efficacy as determined by institutional standard of care procedures.	Long-term safety in patients <18 years old (including potential adverse effects on skeletal maturation and sexual maturation)	Final CSR	May-2027 (Planned)

2.7.3. Risk minimisation measures

Table 47. Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks for trametinib		
Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachment)	Routine risk minimization measures SmPC section 4.8. Additional risk minimization measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Pneumonitis/Interstitial lung disease	Routine risk minimization measures SmPC section 4.8. Additional risk minimization measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Hepatic events (e.g., AST, ALT increased, and hepatic failure)	Routine risk minimization measures SmPC section 4.8. Additional risk minimization measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Gastrointestinal disorders (diarrhoea, colitis, and GI perforation)	Routine risk minimization measures SmPC section 4.4, section 4.8, and section 5.3. Additional risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	None	
Important potential risks for trametinib		
Impaired female fertility	Routine risk minimization measures SmPC section 4.6. Additional risk minimization measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Developmental toxicity	Routine risk minimization measures SmPC section 5.3. Additional risk minimization measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Long-term safety in patients <18 years old (including potential adverse effects on skeletal maturation and sexual maturation)	Routine risk minimization measures SmPC section 4.2. Additional risk minimization measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: CDRB436G2401 (EudraCT number 2018-004459-19).
Pregnancy and risks in breast-feeding	Routine risk communication SmPC Section 4.6. Additional risk minimization measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important potential risks related to trametinib + dabrafenib combination therapy only		
Pulmonary embolism, deep vein thrombosis	Routine risk minimization measures SmPC section 4.4. Additional risk minimization measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Missing information for trametinib		
Use in patients with reduced cardiac function or symptomatic Class II, III, or IV heart failure (NYHA functional classification system)	Routine risk minimization measures SmPC section 4.4. Additional risk minimization measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Safety in patients with severe renal impairment	Routine risk minimization measures SmPC section 4.2. Additional risk minimization measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Safety in patients with recent (within 6 months) acute coronary syndrome including unstable angina, coronary angioplasty, stenting or cardiac arrhythmias (except sinus arrhythmia) and	Routine risk minimization measures SmPC section 4.4. Additional risk minimization measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimization measures	Pharmacovigilance activities
treatment refractory hypertension (blood pressure of systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by anti-hypertensive therapy		

2.7.4. Conclusion

The CHMP considers that the risk management plan version 19.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Low-grade glioma

Spexotras in combination with dabrafenib is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

High-grade glioma

Spexotras in combination with dabrafenib is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment.

3.1.2. Available therapies and unmet medical need

3.1.2.1. LGG

Treatment goals for patients with LGG are generally to prolong overall and progression free survival while minimizing morbidity of treatment. The ten-year OS for molecularly unselected paediatric patients with LGG, is 85–96% (Ostrom et al 2015).

Surgical removal, when practical, is often the treatment of choice. Most patients will eventually experience progression of their disease and require post-surgical therapy. Because of the potential risk for long term neurocognitive effects of radiotherapy in paediatric LGG patients, the post-surgical therapy often includes chemotherapy with carboplatin and vincristine, which has been employed in the systemic treatment of paediatric patients with LGG for decades and served as the standard of care treatment in several large studies (Ater 2012, Gnekow 2017).

In paediatric LGG patients harbouring the BRAF V600E mutation, retrospective data suggests that chemotherapy results in unfavourable PFS and OS outcomes (Lassaletta et al 2017, Ryall et al 2020). Reports from Lassaletta et al 2017 and Nobre et al 2020 suggest a lower ORR of 10% for these patients when treated with chemotherapy.

Thus, paediatric patients with LGG harbouring a BRAF V600 mutation have a worse prognosis than those without this mutation.

3.1.2.2. HGG

Current therapies for children with HGGs are limited. The present standard of care for newly diagnosed children with HGG is gross total surgical resection, followed by focal irradiation to the tumour bed plus additional chemotherapy (MacDonald 2011). Among younger patients (<3 years of age), radiotherapy is generally not used due to its substantial neurocognitive toxicity. These patients are often treated with radiation sparing approaches such as chemotherapy alone (Broniscer 2004).

Temozolomide is most often used in the recurrent disease setting. However, in 5 trials evaluating temozolomide monotherapy or temozolomide-based combinations, the response rate in recurrent or

refractory, paediatric HGG ranged from 0-12% (Lashford 2002; Nicholson 2007; Ruggiero 2006; Warren 2012; Hummel 2013). A variety of targeted agents have also been evaluated in this patient population and response rates have been noted to be less than 10%, as reported by the applicant, and no targeted agents have been approved for patients with paediatric HGG.

Currently, temozolomide is the only authorised anticancer substance in EU for paediatric HGG (for use in relapsed or progressive disease), although mostly based on adult efficacy data.

Long-term outcomes for patients with paediatric HGGs are poor despite aggressive multimodality therapy with neurosurgery, radiotherapy, and chemotherapy. From the time of diagnosis, the median duration of survival for HGG is approximately 9-15 months in children (Mackay et al 2017), and 5-year survival ranges from 10 to 35% (Broniscer 2004; Finlay 2005; Broniscer 2006; Cohen 2011; Wolff 2010).

For paediatric HGG, the BRAF V600E mutation is more frequently found in favourable prognosis subgroups of this disease, and is not found in some of the worst prognostic subgroups, such as those arising from the brainstem (Mackay et al 2017). Thus, the BRAF V600E mutation in newly diagnosed paediatric patients with HGG is associated with an improved OS versus those patients with tumours that are wildtype at BRAF V600. However, according to the applicant, there are no supportive data available on expected outcomes for patients who have failed initial treatment attempts and present with relapsed or refractory BRAFV600 mutant HGG.

3.1.2.3. LGG and HGG

There is an unmet medical need in paediatric patients with BRAF V600E mutation-positive glioma due to the limitations of available therapies.

3.1.3. Main clinical studies

Data to support the sought indications are derived from the multi-centre, open-label, phase II study G2201, conducted in 58 centres across 20 countries. This was an umbrella study comprised of two cohorts, to evaluate the effect of dabrafenib in combination with trametinib in paediatric gliomas.

The two cohorts, which represent two independent experiments, consisted of patients with BRAF V600 mutation positive gliomas, with either low-grade glioma (LGG cohort), or high-grade glioma (HGG cohort).

- The LGG cohort was a 2:1 randomised comparison of dabrafenib with trametinib (D+T) versus chemotherapy carboplatin and vincristine (C+V) in chemotherapy naïve LGG patients. Cross-over to the test treatment was allowed at progression.
- The HGG cohort was a single arm trial that evaluated the effect of dabrafenib with trametinib (D+T) in relapsed or refractory HGG patients who had received at least one prior line of systemic therapy.

There was no attempt to disentangle the effects of MEK and BRAF inhibition (isolate the efficacy of each component). It is notable that the add-on efficacy has been shown in the treatment of melanoma. Moreover, the addition of a MEK inhibitor (the less active component of the treatment) includes overall tolerability of the regimen, particularly with respect to dermatological adverse effects. This effect is considered independent of the treatment indication, and due to the interaction of signalling pathways. Therefore, the lack of study of each component is acceptable.

Dabrafenib and trametinib (D+T) were administered daily and were dosed based on age and weight. Depending on age and weight, patients could be administered either the liquid formulations of dabrafenib and trametinib, or the solid formulations of the products that are currently approved for the treatment of adult patients with BRAFV600 mutant tumours.

The safety analysis is focused on data from the pivotal study G2201 (in total n=147; 106 LGG patients randomised 2:1 to D+T combination therapy [n=73] and C+V standard chemotherapy [n=33], and 41 HGG patients receiving D+T combination therapy). For support regarding safety issues a combination therapy pool (safety analysis set) was constructed, including D+T treated patients from the pivotal study (n=123, including nine who crossed over to D+T in the LGG cohort) and supporting study X2101 (n=48). The combination therapy pool consisted of in total 171 patients, with the following age distribution: n=4 children aged <2 years, n=39 aged 2 to <6 years, n=54 aged 6 to <12 years, and n=74 aged 12 to <18 years.

3.2. Favourable effects

LGG

ORR per Independent review (primary endpoint) was ORR 46.6% in the investigational D+T arm compared to 10.8% in the chemotherapy C+V arm, with an odds ratio of 7.19 (95% CI: 2.3, 22.4) and 1-sided p-value <0.001.

CR were reported in 2 patients (2.7%) in the D+T arm and 1 patient (2.7%) in the C+V arm.

ORR per investigator was consistent with the ORR observed per Independent review.

ORR analysis by Independent review using only the radiographic data (but not including clinical status and steroid use data that may introduce bias) was consistent with the primary ORR analysis using full RANO criteria.

Median PFS was 20.1 months in the D+T arm versus 7.4 months in the C+V arm, with HR 0.31 (95% CI: 0.17, 0.55) per Independent review.

With a median follow-up of 18.9 months (range: 7.9-35.4) in the LGG cohort, OS data are immature with no deaths in the D+T arm and 1 death in the chemotherapy C+V arm at DCO.

HGG

ORR per Independent review (primary endpoint) was met 56.1%, (95% CI: 39.7, 71.5,). The lower bound of the 95% CI for D+T treatment ORR exceeded the 20% rate prespecified in the study protocol based on the historical rates of ORR for patients with molecularly unselected relapsed refractory HGG (5-12%) treated with standard available therapy.

ORR analysis by Independent review using only the radiographic data (but not including clinical status and steroid use data that may introduce bias) is consistent with the primary ORR analysis using full RANO criteria.

Median DOR was 22.2 months (95% CI: 7.6, NE).

3.3. Uncertainties and limitations about favourable effects

LGG

The size of the RCT, and particularly the control arm is limited. This results in the possibility of impact of prognostic factors on outcomes, as well as relatively wide confidence limits for effects.

DoR and PFS data are immature. In addition, OS data are very immature, and the impact of treatment on OS is unclear. The applicant has committed to deliver as recommendation the final analysis of study G2201, which will include the final analysis of LGG cohort, including analyses of DoR, PFS and OS (minimum 2-year OS data).

HGG

The relevant cohort is small and lacks a randomised comparator arm. The impact of treatment on PFS and OS cannot be isolated.

The DoR data are immature, the applicant has committed to deliver as recommendation the final analysis of study G2201, which will include the final analysis of the HGG cohort, including analyses of DoR, PFS and OS.

3.4. Unfavourable effects

AEs

AEs occurring in $\geq 20\%$ of the patients in the LGG cohort D+T arm included pyrexia (68.5% vs. 18.2% in the C+V arm), headache (46.6% vs. 27.3%), vomiting (34.2% vs. 48.5%), diarrhoea (28.8% vs. 18.2%), and dry skin (26.0% vs. 3.0%).

Well-known side effects of D+T combination treatment such as rash (19.2% vs. 9.1%), rash maculopapular (12.3% vs. 3.0%), dermatitis acneiform (12.3% vs. 0%), and eczema (12.3% vs. 0%) occurred at lower frequencies. Most of these events were grade 1-2 severity.

Weight increased was observed in 15.1% in the D+T arm (zero patients in the C+V arm) and is considered a new ADR in the paediatric population.

AEs occurring in $\geq 20\%$ of the HGG patients included pyrexia (51.2%), headache (34.1%), dry skin (31.7%), vomiting (29.3%), diarrhoea (24.4%), and rash (22.0%). The new ADR weight increased was reported in 12.2% of the patients.

Apart from weight increased, the frequency and distribution of AEs are generally in line with what is expected with BRAF and MEK inhibitor treatment.

AEs by severity

Grade ≥ 3 AEs occurred in 46.6% of the patients in LGG cohort D+T arm vs. 93.9% in the C+V arm. Pyrexia (8.2%) and weight increased (6.8%) were the most reported grade ≥ 3 AEs in the D+T arm (3.0% and 0% respectively in the C+V arm).

In the HGG cohort grade ≥ 3 AEs occurred in 68.3% of the patients, with headache (9.8%) being the most reported grade ≥ 3 AE.

SAEs

The incidence of SAEs was overall comparable between the D+T and the C+V arms (39.7% vs. 39.4% respectively) in the LGG cohort. Pyrexia was the most frequently (incidence $\geq 5\%$) reported SAE in both arms (13.7% vs. 18.2% respectively). Grade ≥ 3 SAEs were reported in 27.4% of the patients in the D+T arm and 21.1% of the patients in the C+V arm respectively.

SAEs were reported in 61.0% of the HGG patients, and grade ≥ 3 SAEs were reported in 53.7%. Three SAEs were fatal (not treatment related). The most frequently reported SAEs (occurring in $\geq 5\%$ of patients) were headache and pyrexia (7.3% each).

Deaths: Fifteen patients treated with D+T combination therapy in study G2201 died during the study period (14 patients from the HGG cohort, one patient in the LGG cohort randomised to C+V treatment who crossed over to the D+T treatment arm). Six of these were on treatment deaths; four died due to the underlying disease and two died secondary to other causes.

Discontinuations due to AEs

The discontinuation rate due to AEs is considered low in the context of an oncology setting (LGG cohort D+T arm 4.1%, HGG cohort 4.9%) and indicates a favourable tolerability of D+T combination treatment. Dose interruptions due to AEs occurred in 70.8% of the patients, mainly driven by pyrexia (49.7%) and vomiting (9.4%).

3.5. Uncertainties and limitations about unfavourable effects

The overall paediatric safety population is of limited size, especially for children 1-2 years of age. This imposes uncertainties regarding conclusions on the safety profile for this age group. However, the general safety profile identified is in line with the safety profile described in adults.

Long-term safety (including data on growth and development) in the paediatric population is currently missing, but long-term follow-up data from the pivotal study G2201 (REC) and long-term study G2401 (category 3 study in the RMP) will be provided once available post-approval.

No causal relationship between use of systemic corticosteroids and weight gain has been established. So far, the underlying cause of the 'weight gain' ADR in the current population is unknown.

Most of the studied children from 6 years of age were administered the solid trametinib formulation (52/111 in G2201), which is not part of this MAA. The trametinib liquid formulation has a higher C_{max} than the solid formulation after a single dose, however the increase in C_{max} for the liquid formulation at steady state was shown to be less pronounced, which is considered acceptable from a safety point of view.

The proposed formulation of trametinib (Spexotras powder for oral solution) contains cyclodextrin as an excipient (sulfobutylbetadex sodium). Renal toxicity (juvenile animals) and hearing disorders have been reported in pre-clinical data following administration of cyclodextrin by IV route. Available clinical data on children administered the trametinib oral solution have, so far, not indicated any increased risks of renal toxicity or ototoxicity. The applicant monitor cases of renal impairment and hearing loss post-marketing through routine PhV activities. Relevant warning on such aspects is also included in section 4.4 of the SmPC.

3.6. Effects Table

Table 48. Effects table for LGG cohort study G2201 (data cut-off: 23 August 2021)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Study is currently ongoing.						
			Dabrafenib + Trametinib N=73	Carboplatin + Vincristine N=33	Open-label, limited sample size.	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Overall response rate (ORR) (primary endpoint)	Proportion of patients with a best overall confirmed CR or PR by blinded independent review per RANO criteria.	% (n) (95% CI)	46.6% (34) (34.8, 58.6)	10.8% (4) (3.0, 25.4)	Odds ratio 7.19 (95% CI: 2.3, 2.4) 1-sided p <0.001.	
Progression-free survival (PFS) (secondary endpoint)	Median 95% CI	months	20.1 (12.8, NE)	7.4 (3.6, 11.8)	HR 0.31 (95% CI: 0.17, 0.55), 1-sided p <0.001.	
Overall survival (OS) (secondary endpoint)	The time from date of randomization to death due to any cause.	months	NE	NE	OS data are very immature with no deaths in the targeted therapy (D+T) arm and 1 death in the chemotherapy (C+V) arm.	
Unfavourable Effects						
			Dabrafenib + Trametinib N=73	Carboplatin + Vincristine N=33		
AE ≥10% of patients	Any Pyrexia Headache Vomiting Fatigue Diarrhoea Dry skin Nausea Epistaxis Rash Weight incr.	%	100.0 68.5 46.6 34.2 31.5 28.8 26.0 24.7 20.5 19.2 15.1	100.0 18.2 27.3 48.5 30.3 18.2 3.0 45.5 3.0 9.1 0		
Treatment related AEs	Any Grade ≥3	%	91.8 26.0	97.0 87.9		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Grade ≥ 3	Any Pyrexia Headache Vomiting Diarrhoea Rash Weight incr. Peripheral motor neuropathy Peripheral sensory neuropathy	%	46.6 8.2 1.4 1.4 0 1.4 6.8 0 0	93.9 3.0 3.0 3.0 6.1 3.0 0 3.0 3.0		
SAE (≥ 2 patients by PT)	Any Pyrexia Vomiting Apnoea Hydrocephalus Seizure	%	39.7 13.7 4.1 2.7 2.7 2.7	39.4 18.2 0 0 0 0		
AEs leading to discont.	Any Grade ≥ 3	%	4.1 2.7	18.2 9.1		
Deaths due to AEs	Any	%	0	3.0		

Abbreviations: PT=Preferred Term

Notes: The AE numbers presented in table above are from the initial application, not from the cleaned data set

Table 49. Effects Table for HGG cohort study G2201 (data cut-off: 23 August 2021)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Study is currently ongoing.						
			Dabrafenib + Trametinib N=41	None	Single-arm trial, limited sample size.	
Overall response rate (ORR) (primary endpoint)	The proportion of patients with a best overall confirmed CR or PR by independent assessment per RANO criteria.	% (n) (95 % CI)	56.1% (23) (39.7, 71.5)	NA		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Median duration of response (mDOR) (secondary endpoint)	Median 95% CI	Months	22.2 (7.6, NE)	NA		
Unfavourable Effects						
			Dabrafenib + Trametinib N=41	None		
AE $\geq 10\%$ of patients	Any Pyrexia Headache Dry skin Vomiting Diarrhoea Rash Nausea	%	100 51.2 34.1 31.7 29.3 24.4 22.0 19.5	NA		
Treatment related AEs	Any Grade ≥ 3	%	82.9 26.8	NA		
Grade ≥ 3	Any Pyrexia Headache Vomiting Diarrhoea Rash	%	68.3 2.4 9.8 4.9 2.4 2.4	NA		
SAE (≥ 2 patients by PT)	Any Headache Pyrexia General physical health deterioration Intracranial pressure incr.	%	61.0 7.3 7.3 4.9 4.9	NA		
AE leading to discontinuation	Any Grade ≥ 3	%	4.9 0	NA		
Deaths due to AEs	Any	%	34.1	NA		

Abbreviations: PT=Preferred Term

Notes: The AE numbers presented in table above are from the initial application, not from the cleaned data set

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

For both HGG and LGG, current treatment options are not satisfactory, and there exists an unmet medical need.

In the first line systemic treatment of BRAF V600 mutated LGG, a clinically relevant increase in ORR and PFS, compared to standard chemotherapy was demonstrated.

In subjects with relapsed or refractory BRAF V600 mutated HGG, the demonstration of efficacy and safety is based on a single arm trial. In contrast to PFS and OS, the ORR observed in a SAT can to a great extent be ascribed to the experimental agent since spontaneous regression is not anticipated. Consequently, ORR must form the basis for the inference of a potential clinical benefit from the presented SAT. Due to the limitations of ORR, the results should be outstanding in relation to what can be achieved with existing therapeutic options.

Considering the poor prognosis of paediatric patients with glioma and the poor outcome with current available treatment, the ORR at 46.6% and 56.1% after dabrafenib and trametinib combination treatment in the LGG and HGG cohort, respectively, can be considered outstanding. Thus, the activity in terms of ORR, along with the DoR, is anticipated to translate into an important clinical benefit. The lack of a randomised controlled arm in HGG by which to isolate effects on PFS and OS is acceptable given the level of activity seen and the lack of satisfactory treatment options.

Data on DoR in both settings are immature and the applicant has agreed to deliver the final analysis of study G2201 as a post approval recommendation.

Limited data are available for the youngest (1-2 years) and/or low weight children, especially in the HGG cohort. Even though similar efficacy is reasonable to assume, available data indicate a slightly lower dabrafenib exposure in younger/low weight patients compared to older/heavier patients with the proposed dose regimen. However, simulations of exposure vs body weight support that the PK exposures are reasonable across the whole body weight range.

The safety data base is considered limited, in particular for the sub-group of patients <2 years of age (n=4). For both the LGG cohort D+T arm and the HGG cohort the distribution and proportions of AEs and SAEs are generally consistent. Frequencies of reported AEs and SAEs are high, however, judged by the low rate of treatment discontinuations due to AEs which indicates a favourable tolerability, the toxicity appears manageable.

The overall safety profile of dabrafenib + trametinib is generally comparable to that seen in adults and does not raise any major concerns. However, weight increased is considered a new ADR in the paediatric population.

Most of the studied children from 6 years of age were administered the solid trametinib formulation, which is not part of this MAA. The trametinib liquid formulation has a higher C_{max} than the solid formulation after a single dose, however the increase in C_{max} for the liquid formulation at steady state was shown to be less pronounced. This is unlikely to translate to a clinically relevant elevated risk of safety.

3.7.2. Balance of benefits and risks

The demonstrated benefits in the sought indications outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit /risk balance of Spexotras in combination with dabrafenib dispersible tablets solution is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Spexotras is not similar to Finlee within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Spexotras is favourable in the following indication(s):

Low-grade glioma

Spexotras in combination with dabrafenib is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

High-grade glioma

Spexotras in combination with dabrafenib is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or

as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0423/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.