14 September 2023
EMA/443504/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Finlee

International non-proprietary name: dabrafenib

Procedure No. EMEA/H/C/005885/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

BOR best overall response

BRAF B-Raf proto-oncogene, serine/threonine kinase

CBR clinical benefit rate

CCNU lomustine

CI confidence interval

C+V carboplatin plus vincristine

CR complete response

CRC colorectal cancer

cuSCC cutaneous squamous cell carcinoma

DOR duration of response

D+T dabrafenib plus trametinib

DT dispersible tablet

EC European Commission

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

HDPE High Density Polyethylene

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

KRAS Kirsten rat sarcoma virus

KF Karl Fischer titration

LCH Langerhans cell histiocytosis

LDPE Low density polyethylene

LGG	low grade glioma
LPLV	last patient last visit
LS	least squares
MAP	managed access program
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
PDGFRβ	platelet-derived growth factor receptor β
p-ERK	phosphorylated extracellular signal-regulated kinase
PFS	progression free survival
Ph. Eur.	European Pharmacopoeia
pHGG	pediatric high-grade glioma
pLGG	pediatric low-grade glioma
PK	pharmacokinetics
PR	partial response
RANO	Response Assessment in Neuro Oncology
RAPNO	Response Assessment in Pediatric Neuro-oncology
RAS	rat sarcoma virus
RH	Relative Humidity
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
XRD	X-Ray 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 Finlee, 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.

Finlee was designated as an orphan medicinal product EU/3/20/2372 on 09 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 Finlee 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: www.ema.europa.eu/en/human/EPAR/Finlee

The applicant applied for the following indication.

Low-grade glioma (LGG)

Finlee in combination with trametinib powder for oral solution 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)

Finlee in combination with trametinib powder for oral solution 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 P/0423/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP 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 not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific Advice

The applicant received Scientific Advice on the development relevant for the indication subject to the present application:

The Scientific Advice pertained to the following *clinical aspects:*

- The need to develop further therapeutic options in paediatric patients with high grade glioma
- The initiation of a phase 2 trial in recurrent, refractory or progressed BRAF V600 mutant high grade glioma, taking into account the available data from study BRF-PEDS-01;
- The overall design of study BRF-PEDS-02 as well as particular elements of said study including population, dose, endpoints, sample size, statistical analysis, safety monitoring.
- The potential of study BRF-PEDS-02 to support registration of dabrafenib in paediatric patients with recurrent or refractory BRAF V600E-mutant High Grade Glioma.
- The relevance of the size of the planned clinical safety database to support registration.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Eva Skovlund

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	3 January 2023
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 routine GCP inspection were requested 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 The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	12 May 2023 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 Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 August 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 Finlee on	14 September 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)

Finlee in combination with trametinib powder for oral solution 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)

Finlee in combination with trametinib powder for oral solution 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 categorizes 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 pediatric 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, tumor 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 practical, 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 utilized are the COGA9952 protocol (Ater 2012) and the SIOP-LGG-2004 protocol (Gnekow 2017). There have been no randomized 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 harboring 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 authorized 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

Dabrafenib is an orally available inhibitor of RAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway. The most commonly observed BRAF mutation is V600E, which has been identified in 17% of paediatric LGG and approximately 6% of paediatric HGG.

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

Table 1. Dosing regimen by body weight

Body weight*	Recommended dose (mg dabrafenib) twice daily	Recommended dose (number of 10 mg tablets) twice daily
8 to 9 kg	20 mg	2
10 to 13 kg	30 mg	3
14 to 17 kg	40 mg	4
18 to 21 kg	50 mg	5
22 to 25 kg	60 mg	6
26 to 29 kg	70 mg	7
30 to 33 kg	80 mg	8
34 to 37 kg	90 mg	9
38 to 41 kg	100 mg	10
42 to 45 kg	110 mg	11
46 to 50 kg	130 mg	13
≥51 kg	150 mg	15

*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 trametinib powder for oral solution SmPC, "Posology" and "Method of administration", for dosing instructions for treatment with trametinib when used in combination with Finlee.

In the sought indication for treatment of LGG and HGG in patients aged 1 year and older harbouring a BRAF V600E mutation dabrafenib is administered in combination with trametinib. Trametinib is an

orally available reversible, allosteric inhibitor of MEK1 and MEK2 activation and kinase activity. The combination of dabrafenib with trametinib results in the inhibition of two sequential kinases in the mitogen-activated protein kinase (MAPK) pathway, 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 paediatric patients 1 year of age and older. 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, and 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 program 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 minimize 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 dispersible tablet containing dabrafenib mesilate as the active substance equivalent to 10 mg of dabrafenib.

Other ingredients are: mannitol (E 421), microcrystalline cellulose (E 460), crospovidone (E 1202), hypromellose (E 464), acesulfame potassium (E 950), magnesium stearate (E 470b), artificial berry flavour (maltodextrin, propylene glycol [E 1520], artificial flavours, triethyl citrate [E 1505], benzyl alcohol [E 1519]), silica, colloidal anhydrous (E 551).

The product is available in an opaque white HDPE bottle with a polypropylene screw cap and a silica gel desiccant as described in section 6.5 of the SmPC. Two dosing cups with 5 ml increments are provided with each pack presentation.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of dabrafenib is N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, corresponding to the molecular formula $C_{23}H_{20}F_3N_5O_2S_2$. It has a relative molecular mass of 519.57 g/mol for the free base and 615.68 g/mol for the salt. The active substance has the following structure:

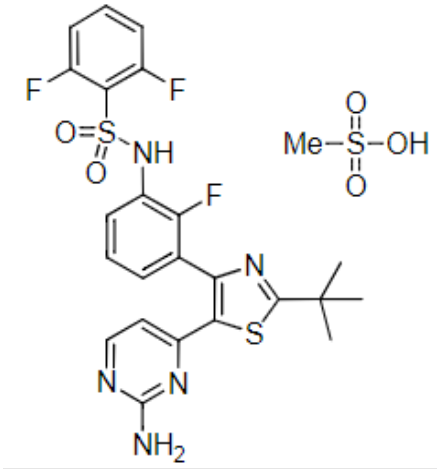


Figure 1: active substance structure

The active substance from the same applicant has been approved in a previous centralised procedure for the product Tafinlar, EMEA/H/C/2604. The chemical structure of dabrafenib was elucidated by a combination of IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. The solid state properties of the active substance were measured by XRD.

The active substance is a non-micronised powder and it is non hygroscopic. In aqueous media the solubility of dabrafenib mesilate is limited and decreases with increasing pH values, it is very slightly soluble at pH 1 and practically insoluble at pH 4-8. The active substance shows high permeability and during development the non-micronised form showed improved relative bioavailability as compared to the micronised form.

Dabrafenib has no chiral centers and does not exhibit stereoisomerism. Polymorphism has been observed for dabrafenib mesilate, various crystalline forms were identified using high throughput solvent screening. An amorphous form and three solvates were also identified, however the solvents in question are not used in the synthesis. Various hydrated forms were identified, however, the hydrated forms are less stable than the selected crystalline form 1. The manufacturing process has been designed to generate the required polymorphic form 1, and the solid state form is considered stable.

2.4.2.2. Manufacture, characterisation and process controls

The active substance has been manufactured by two manufacturing sites.

Full details of the active substance are included in the application. Two sources of the non-micronised active substance are described both using the same synthetic route. Dabrafenib mesilate is synthesised in four main steps using well defined starting materials with acceptable specifications. The potential to reprocess the active substance or intermediates by repeating part or all of the process is acceptably described. Reworking is also described in certain instances in line with the approach already

approved for the dabrafenib mesilate capsule containing formulations from the applicant. In contrast to the process for the previously approved capsule formulations, no micronisation process takes place as the non-micronised form is used in the dispersible tablet formulation.

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 commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

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 (visual), particle size (laser light diffraction), identity (IR), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), and residue on ignition (Ph. Eur.).

The proposed limit for one impurity, is above the ICH qualification limit of 0.15%.This impurity is considered qualified by toxicological data and clinical studies and appropriate specifications have been set. The limits for other impurities are set below the qualification threshold of ICH Q3A.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from batches from each proposed site for the non-micronised dabrafenib mesilate are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from batches of active substance from proposed manufacturers stored in a container closure system representative of that intended for the market for up to 36 months under long term conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. These results are considered representative.

The following parameters were tested: appearance, particle size (laser light diffraction), assay (HPLC), 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, no significant change has been observed in any of the parameters studied during accelerated, long term conditions, or after ICH Q1B photo-stability testing.

Long term stability studies are ongoing, including those from the other proposed active substance manufacturing site. In line with ICH guidance relevant commitments to continue ongoing stability studies are provided. With respect to ongoing studies, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. The active substance is photo-stable.

Results on stress conditions under aqueous acidic and alkaline stress conditions at increased temperature for several days were provided. Solid state stress testing conditions for several days were also provided. In the solid state no substantial degradation occurred.

A significant amount of data was also provided related to stability of the micronised active substance produced using the same synthetic route as the non-micronised proposal. Stability testing of micronised batches were provided, using the same long term and accelerated testing conditions as the non-micronised active substance. For the micronised batches up to 48 months of long term data is available. The additional stability data currently available for the micronised active substance also supports setting the same storage condition and retest period for the non-micronised form.

The stability results indicate that the non-micronised active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period with the applicants proposed storage condition in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is an immediate release dosage form for oral administration after suspension with water. The tablets are white to slightly-yellow, round biconvex 6 mm tablet with "D" debossed on one side and "NVR" on the other.

A dabrafenib capsule formulation is marketed as Tafinlar® 50 mg and 75 mg hard capsules by the same applicant for the treatment of adults. To expand use to the paediatric population and for patients unable to swallow capsules, a dabrafenib 10 mg dispersible tablet has been developed.

The excipients used are standard pharmacopoeial excipients commonly used in pharmaceutical formulations with the exception of the non-compendial artificial berry flavour. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The artificial flavour contains benzyl alcohol which is an excipient of known effect and is therefore declared in the product information. The choice and ratio of the excipients was based on experimental studies to achieve a stable dosage form with quality attributes pertinent for a dispersible tablet e.g. disintegration time within 3 minutes. Excipient compatibility for a number of the excipients was previously known based on the capsule dosage form, for additional excipients these were evaluated by studies of compositional blends. The active substance was found to be stable in the presence of all excipients and the final compatibility was confirmed through the stability studies. The choice of the excipients was suitably justified for the intended age group in line with the Guideline on pharmaceutical development of medicines for paediatric use, EMA/CHMP/QWP/805880/2012.

The target patient population for the paediatric trials ranged from 1 to 17 years of age, and it was anticipated that patients < 6 years would require an oral liquid formulation. Based on the poor aqueous solubility of dabrafenib mesilate, the liquid formulation was anticipated to be a suspension. For paediatric Phase 1 studies, lower strength capsules (10 mg and 25 mg) were developed with the same qualitative composition as the 50 mg and 75 mg capsules, along with a powder in stickpacks for oral suspension (150 mg PfOS) for patients that are unable to swallow capsules.

The 10 mg dispersible tablet for oral suspension was established for use during the pivotal paediatric Phase 2 study and as the proposed commercial dosage form. A relative bioavailability study was performed to bridge between the capsule and the dispersible tablet formulations and to select the final composition of the dispersible tablet. The dispersible tablet composition has not changed since the introduction of the tablet formulation to the clinical program.

The development of the dissolution method used for quality control has been described, this development was based on the method used for the adult capsule formulation. Several parameters have been adjusted to achieve a discriminative method. The method has been found to have a sufficient level of discriminating capability for dispersible tablet formulation made with different compositions as well as for storage conditions where a slow-down of dissolution rate was observed with the increase of water content.

During manufacturing development batch sizes from laboratory scale, through pilot scale and further scale up were studied. The manufacturing process has been the same in terms of unit operations and their sequence throughout development with a few minor process improvements. These minor adaptations include lower room humidity during tableting and packaging. The data gathered was used to inform the parameters selected for commercial scale manufacture.

The primary packaging is an opaque white HDPE container with a polypropylene screw cap. A silica desiccant is also present. Compliance with relevant EC regulations and directives are provided for the materials. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site. The manufacturing process consists of four main steps. The process is considered to be a standard manufacturing process.

In addition to initial verification studies a formal process validation is intended and a scheme is presented for this. The in-process controls and limits have been described and are considered justified and acceptable.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (visual), mean tablet mass, disintegration time (Ph. Eur.), fineness of dispersion (Ph. Eur.), identification (HPLC & UV), water (Ph. Eur.), dissolution (HPLC), assay (HPLC), content uniformity (Ph. Eur.), degradation products (HPLC), and microbiological quality (Ph. Eur).

The proposed specifications are suitably justified. The specification for fineness of dispersion ensures complete disintegration into an appropriately fine suspension, which can be easily administered. Degradation products are controlled in line with ICH Q3B and are below the relevant qualification threshold. The limits proposed for dissolution and disintegration have been justified and are considered acceptable.

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.

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). Testing results confirmed the absence of nitrosamine impurities. Based on the information provided, it is accepted that

there is no risk of nitrosamine impurities in the active substance or the finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and 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 results are provided 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 12 months under long term conditions (25ºC / 60% RH & 30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches were packed in the primary packaging proposed for marketing and are representative.

Samples were tested for appearance, assay (HPLC), fineness of dispersion, degradation products (HPLC), dissolution (HPLC), water content (Ph. Eur.), disintegration time (Ph. Eur.) and microbiological quality (Ph. Eur). The analytical procedures used are stability indicating. No significant change was observed in any of the parameters during the studies.

In addition, product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No photo-instability was observed, and therefore the absence of an instruction to protect from light is acceptable.

For ongoing stability studies, in accordance with EU GMP guidelines (*6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union)* any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The in-use stability results provided were acceptable, and in consideration of the intended use and absence of significant changes it was considered that a formal in-use shelf life for the opened HDPE containers was not required. The tablet dispersion should be used within 30 minutes following preparation.

Based on available stability data, the proposed shelf-life of 24 months and conditions to store in the original container in order to protect from 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.

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

N/A

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 Tafinlar® (dabrafenib). All prior non-clinical data for dabrafenib have been reviewed in procedures related to Tafinlar® 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 EPARs of Tafinlar is presented below.

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

2.5.2. Pharmacology

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

Dabrafenib inhibited human wildtype BRAF and CRAF enzymes with IC_{50} values of 3.2 and 5.0 nM, respectively, as well as the mutant forms $BRAF^{V600E}$, $BRAF^{V600K}$ and $BRAF^{V600D}$, having IC_{50} values of 0.65, 0.5 and 1.84 nM, respectively. Other analyses showed that dabrafenib is a time-dependent, reversible inhibitor of WT BRAF and $BRAF^{V600E}$ enzymes, and is an ATP competitive inhibitor of WT BRAF and CRAF and $BRAF^{V600E}$. Three active dabrafenib metabolites have been identified, with two metabolites (desmethyl-dabrafenib and hydroxy-dabrafenib) demonstrating potent inhibition of WT BRAF and CRAF and mutant BRAF kinases, and one metabolite (carboxy-dabrafenib) showing reduced activity against these enzymes (13- to 47-fold). The dabrafenib metabolites also showed similar activities against rat, dog and monkey WT BRAF compared to their respective values on the human orthologue.
MEK and ERK are downstream substrates of RAF kinases, and inhibition of BRAF activity in cells containing mutant $BRAF^{V600E}$ is shown to result in decreased phosphorylation of MEK and ERK in cell line models, but not in cell lines containing WT BRAF or mutated RAS proteins, using in-cell Western, Western blot assays or ELISA assays. The 3 metabolites (hydroxy-dabrafenib (M7), desmethyl-dabrafenib (M8), and carboxy-dabrafenib (M4) were also examined. Whereas hydroxy-dabrafenib and desmethyl-dabrafenib had similar potency as dabrafenib, carboxy-dabrafenib was 17-fold less potent in inhibition of ERK phosphorylation, and 37-fold less potent in inhibition of cell proliferation.

The duration and reversibility of pERK inhibition in SK-MEL-28 cells were investigated after compound removal following treatment with dabrafenib (300 nM, 33-fold the pERK IC50) for 2 hours. The inhibition of pERK formation persisted for 4 hours with complete recovery by 6 hours post-compound

removal. The cells showed noticeable regrowth after 3 and 4 days. In SK-MEL-28 and A375PF11s human melanoma cell lines containing the $BRAF^{V600E}$ mutation, dabrafenib treatment was able to induce a concentration-dependent G0/G1 cell cycle arrest and some apoptosis. In contrast, HN5, a head and neck squamous carcinoma cell line containing wildtype BRAF and RAS, as well as normal human fibroblast cells, were not susceptible to either significant G0/G1 arrest or the induction of apoptosis, reflecting the observed lack of sensitivity of these cells to dabrafenib in the cell growth assays.

The ability of dabrafenib to inhibit proliferation of >110 human tumour cell lines, each with confirmed BRAF mutational status, was evaluated in a 3 day growth assay. Sensitivity to dabrafenib significantly correlated with the presence of $BRAF^{V600E}$ with 16 out of 18 cell lines with IC_{50s}.

Secondary pharmacodynamic studies

A study was conducted to investigate potential off-target activity of dabrafenib against a broad panel of proteins including fourteen 7-transmembrane receptors, two enzymes, seven ion channels, four kinases and three transporter molecules. Dabrafenib had no inhibiting or activating effect on the majority of proteins tested in these assays (XC_{50} >5 µM). Dabrafenib showed moderate potency (0.3-3.2 µM) against the α2C-adrenergic receptor (EC_{50} >0.3 µM) and inhibition of LCK (IC_{50} >0.6 µM), GSK3β (IC_{50} >0.8 µM) and Aurora B kinases (IC_{50} >3.2 µM). All activities against these proteins were at least 100-fold less potent than against BRAF enzymes.

Safety pharmacology programme

No adverse effects on neurobehavioral function or affect body temperature in the male rat following a single oral administration of dabrafenib.
No adverse effect on respiratory function or body temperature in the male rat.
In vitro, dabrafenib, hydroxy-dabrafenib and desmethyl-dabrafenib did not inhibit the capacity of labelled dofetilide (hERG inhibitor) to bind hERG (pIC_{50} <4.3).
Dabrafenib and the hydroxy-, carboxyland desmethyl- metabolites when investigated in vitro up to their limits of solubility did not inhibit hERG (IC_{50} values of 48, >30, >150 and 56 µM, respectively).
Concentration-dependent inhibition of hERG tail current recorded in HEK293 cells. The IC_{25} value was estimated to be 11.7 µM (6.1 µg/mL). Insufficient inhibition occurred to allow reliable estimation of IC_{50} or IC_{75} values.
in Rabbit, QT interval shortening (29.7% at 30 µM), a 47.1% reduction in transmural dispersion of repolarization ($T_{p\text{-}e}$) at 30 µM and no torsadogenic potential, as evidenced by a negative T_{dP} score of -2 (scores >3 indicate torsadogenic potential). A concentration-dependent decrease in contractile force was observed (maximum 64% at 30 µM).
In rats (Sprague Dawley), dose-dependent, mild to moderate increase in heart rate (up to 48 beats/ minute or 18%) has been observed. The increased heart rate was evident between 2 and 7 hours post dose at 5 mg/kg. A sustained increase in heart rate was noted between 2 and 24 hours post dose for doses ≥20 mg/kg. There was no effect on arterial blood pressures or body temperature.
in dogs (beagle), at 50 mg/kg, a mild, reversible increase in heart rate (up to 18 beats/minute or 28%) and a mild, reversible decrease in PR interval duration (up to 7 msec or 7%) have been observed. No electrocardiographic waveform abnormalities, arrhythmias or effects on body temperature at any dabrafenib dose.

2.5.3. Pharmacokinetics

In previous applications PK, distribution, metabolism and elimination of dabrafenib have been investigated in oral studies in mouse, rat, dog, pig and monkey. In addition, in vitro studies were also performed. The *in vivo* studies showed that dabrafenib had a wide organ distribution with no evidence

of penetration into the brain with an intact blood brain barrier. In vitro, dabrafenib and its pharmacologically active metabolites were highly bound to plasma proteins. Main metabolites were similar in nonclinical species and humans (carboxy-dabrafenib, hydroxyl-dabrafenib and desmethyl-dabrafenib) but there were quantitative differences. Faecal elimination was the major (≥90%) route of excretion of drug-related material in both rats and dogs following single oral administration of 14C-dabrafenib.

2.5.4. Toxicology

An oral dose juvenile toxicity study with a 6 week off-drug period in rats to support the paediatric clinical development was conducted concerning the non-orphan Tafinlar (dabrafenib). The toxicity of dabrafenib was tested in dog, rat and mouse by oral gavage. Tolerability and toxicokinetics were characterized in oral dose ranging studies in rats and in dogs following single oral dosing and/or twice daily dosing. Safety pharmacology studies were carried out *in vivo* in rat, rabbits and dog. Repeat dose toxicity was assessed in mice, rats and dogs. A standard battery of genotoxicity studies was conducted and reproduction and embryofoetal toxicity studies were performed in rats. Phototoxicity was assessed in an in vitro mouse fibroblast. These studies are summarised below.

2.5.4.1. Single dose toxicity

2.5.4.2. Repeat dose toxicity

The toxicity of repeated oral gavage doses of dabrafenib has been assessed in rats (at doses up to 200 mg/kg/day for up to 13 weeks), dogs (doses up to 50 mg/kg/day for 4 weeks; doses up to 20 mg/kg/day for 13 weeks) and in mice (doses up to 1000 mg/kg/day for 2 weeks).

Major findings in mice were minimal spermatid retention in the seminiferous tubules in majority of males at all doses. Increased incidence of prominent residual bodies in the seminiferous tubules of males at ≥300 mg/kg. Lower thymus weight in males, most prominent at 300 mg/kg with lower lymphocyte count. Higher total white blood cells in females at 100 mg/kg.

In a rat the major findings were detected in male reproductive organs, body weight loss and reduced food consumption in HD rats, minimal to mild focal epithelial (keratinocyte) degeneration in the keratin overlaying the junctional ridge of the stomach at all doses (reversed after recovery) and slight dose-related increase in incidence of minimal cardiomyopathy in males at ≥20 mg/kg.

In repeat-studies in dogs, major findings were observed in animals that exhibited thin body condition, inappetence, body weight loss, dehydration, red gums/gingivitis, liquid faeces and emesis. In addition, effects on male reproductive organs were also observed.

In repeat dose studies, mild to marked reversible decreases in reticulocyte counts and decreased red cell mass was noted in dogs. In rats, decreased red cell mass were observed in female rats without corresponding microscopic findings in the bone marrow. Minimal to marked lymphoid depletion with reduced thymus weights were observed in dogs.

Cardiovascular effects, including coronary arterial degeneration/necrosis and/or haemorrhage, cardiac atrioventricular valve hypertrophy/haemorrhage and atrial fibrovascular proliferation were seen in dogs (≥2 times human clinical exposure based on AUC). Focal arterial/perivascular inflammation in various tissues was observed in mice and an increased incidence of hepatic arterial degeneration and spontaneous cardiomyocyte degeneration with inflammation (spontaneous cardiomyopathy) was observed in rats (≥0.5 and 0.6 times human clinical exposure for rats and mice, respectively). Hepatic

effects, including hepatocellular necrosis and inflammation, were observed in mice (≥0.6 times human clinical exposure). Bronchoalveolar inflammation of the lungs was observed in several dogs at ≥20 mg/kg/day (≥9 times human clinical exposure based on AUC) and was associated with shallow and/or laboured breathing.

Juvenile toxicity study

In the oral-repeat study in juvenile rats some findings were not observed in adult animals, mainly those related to bone growth and kidney. Effects on absolute long bone growth were observed at all doses on both males and female rats. Effects on long bone growth were still evident after the 6-week off-drug period in males at 10/20 mg/kg/day, indicating that the effect on growth did not fully recover in this study.

Microscopic findings were observed in kidneys at all doses, in both females and males. Some findings were reversible, or partially reversible such as (cortical cysts, tubular basophilia, tubular deposits with secondary tubular dilatation, interstitial fibrosis/inflammation, pelvic dilatation and/or localized pelvic transitional cell hyperplasia). Severity of the findings were more pronounced in younger (dosed at PND7) animals compared to older (dosed at PND 21).

2.5.4.3. Genotoxicity

The mutagenic potential of dabrafenib has been assessed in the standard Ames test and in mammalian cells in the mouse lymphoma assay. The *in vivo* clastogenic potential of orally administered dabrafenib has been assessed in rats using the micronucleus test. In all studies, dabrafenib was not mutagenic in either in vitro or *in vivo* test systems.

2.5.4.4. Carcinogenicity

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

2.5.4.5. Reproductive and developmental toxicity

In combined female fertility, early embryonic and embryofoetal development studies in rats numbers of ovarian corpora lutea were reduced in pregnant females at 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC), but there were no effects on oestrous cycle, mating or fertility indices. Developmental toxicity including embryo-lethality and ventricular septal defects were seen at 300 mg/kg/day and delayed skeletal development and reduced foetal body weight at ≥ 20 mg/kg/day (≥ 0.5 times human clinical exposure based on AUC). Male fertility studies with dabrafenib have not been conducted. However, in repeat dose studies, testicular degeneration/depletion was seen in rats and dogs (≥ 0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period.

A repeat-dose study in juvenile rats was performed where the main findings were detected on bone length growth, renal effects and effects on male reproductive organ. Severity of the findings were more pronounced in younger (dosed at PND7) animals compared to older (dosed at PND 21).

2.5.4.6. Other toxicity studies

Phototoxicity

In a neutral red uptake phototoxicity test in Balb/c 3T3 mouse fibroblasts, the photo irritation factor (PIF) value for dabrafenib was >83, indicating a phototoxic effect.

Combination with trametinib

In a study in dogs in which dabrafenib and trametinib 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.

2.5.5. Ecotoxicity/environmental risk assessment

The data submitted in this MAA reflects the previous data provided for dabrafenib for the non-orphan parent brand Tafinlar (dabrafenib). The applicant has refined the Fpen based on the addition of the paediatric glioma indication. The overall PEC of 0,10766 µg/L exceeds the trigger value of 0.01 µg/L and the assessment therefore proceeds to Phase II – Tier A. In Phase II – Tier A a refined PECsurfacewater is calculated based on marketing forecast figures. A tier B risk evaluation is also performed. Based on the current ERA, dabrafenib is not expected to pose a risk to the environment.

Table 2. Summary of main study results

Substance (INN/Invented Name): Dabrafenib/Tafinlar			
CAS-number (if available): 1195768-06-9			
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	0.168-3.384 3.229 at pH=5 3.384 at pH=7 0.168 at pH=9	Potential PBT: N
	BCF	4.38 L/kg_{ww}	not B
Persistence	DT50 (at 12°C)	$DT50_{totalsystem}$: 344 d, 652 d	vP
Toxicity	NOEC	58.3 µg/L	not T
PBT-statement:	Dabrafenib is considered to be not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, Default Fpen=0,66	0,10776 µg/L (overall PEC $_{surfacewater}$, calculated based on previously approved indications for NSCLC and melanoma	µg/L	> 0.01 threshold: Yes
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption GLP	OOPTS 835.1110, using one type of sludge at concentrations in the range 1-12 g/L.	K_{oc} =2460	Low binding to sludge.

Inherent ultimate biodegradability test GLP	OECD301B/302C	Not readily or inherently biodegradable. Ultimate biodegradation (DOC)=0% at day 28 Primary degradation= 63% on day 14 and 81% at day 28.			Results suggest primary degradation of parent compound in the STP's, but low ultimate biodegradation.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems GLP	OECD 308 Two water-sediment systems over a period of 100 days.	DT50, water =16-28 days DT50, sediment = No detectable decline over the study period (100 days) DT50, whole system= 162-307 days (extrapolated) % shifting to sediment =96-100% % CO_2 = 0.2 % at test end % NER = 17.1-31.1 % at test end Transformation products >10%= YES, Single compound: C23H18O2N5F3S2 Sediment and Total System, Swiss Lake: day 59: 10.4 %/14.0 %			DT50 at 20°C. Results show dissipation from water surface into sediment where dabrafenib appears to be persistent. This triggers a sediment toxicity test. Formation of metabolites was detected in both water and sediment portions.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ Pseudokirchneriella subcapitata GLP	OECD 201	NOEC	0,22	mg/L	72 hours
Daphnia sp. Reproduction Test/ Daphnia magna GLP	OECD 211	NOEC	0.105	mg/L	21 days
Fish, Early Life Stage Toxicity Test/Pimephales promelas GLP	OECD 210	NOEC	1.47(length) 2.61 (wet weight) 3.65 (hatching success and post-hatch survival	mg/L	21 days
Activated Sludge, Respiration Inhibition Test	OECD 209	Total respiration EC50 NOEC	>1000 312.5	mg/L	

GLP					
Phase IIb Studies					
Bioaccumulation Onchorhynchus mykiss GLP	OECD 305	BCF	**0.01mg/L** BCFss=3.98 Depuration DT50=0.71 days DT95=3.06 days **0.1 mg/L** BCFss=4.38 Depuration DT50=0.71 days DT95=3.06 days	L/kg	28 days exposure 13 days depuration Due to low uptake of radioactive residues, lipid values were not used in BCF calculation. BCF < 5 suggest low potential for bioaccumulation. TGD B criterion: BCF > 2000
Sediment dwelling organism Chironomus riparius GLP	OECD 218 Nominal test concentrations up to 1000 mg/kg	NOEC	Emergence success: 64 Development rate:160 Sex ratio: 160	mg/kg as free base	Toxicity on the sediment-dwelling non-biting midge, Chironomus riparius was detected at concentrations >64 mg/kg.

2.5.6. Discussion on non-clinical aspects

The applicant has included the non-clinical study reports previously submitted for the approved non-orphan product Tafinlar (dabrafenib). All prior non-clinical data for dabrafenib have been reviewed in previous procedures related to Tafinlar and a summary of previously known pharmacology information is provided above. No other concerns have been raised on this aspect for this procedure. A special attention has been given to the studies in juvenile animals and in general the relevant non clinical aspects have been reflected in the SmPC.

Dabrafenib 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 for this application and previous data provided in the context of the authorised dabrafenib product, Tafinlar are considered sufficient to characterize the non-clinical profile of finlee.

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 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.

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.

Table 3. 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 **Study Status**: complete **Report date**: 07-Mar-2019	A randomized, open-label, three-period cross-over study to investigate the relative bioavailability of two new oral suspension formulations of dabrafenib (10 x 10 mg 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	**Total**: 26 **Age**: 20-75 (47.9) years **Groups**: 6 A/B/C: 5 B/C/A: 4 C/A/B: 4 A/C/B: 4 B/A/C: 4 C/B/A: 5	**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 **Doses**: **Treatment A**: single oral dose of dabrafenib 100 mg given as 10 × 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 × 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 × 50 mg HPMC capsules

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage
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, Randomized, Crossover Study to Assess the Relative Bioavailability of GSK1120212 Tablet Formulation and the GSK1120212 Pediatric Oral Solution Formulation Following Single-Dose Administration to Adult Subjects with Solid Tumors	**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 tumors	**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 GSK2118436, and the Repeat Dose Pharmacokinetics of GSK2118436 in Subjects with BRAF Mutant Solid Tumors	**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 Part C (gemfibrozil): 17 Part D (repeat dose dabrafenib): 13	**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 **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

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage
			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 tumors	**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 tumors	**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, Randomized, Crossover Study to Evaluate the Effect of Food on the Single Dose Pharmacokinetics of the MEK Inhibitor, GSK1120212, in Subjects with Solid Tumors	**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 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,	Phase I/IIa, 2-part, Multicenter, Single-Arm, Open-Label Study to Determine the Safety, Tolerability, and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Patients with Advanced BRAF	**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

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage
United Kingdom, United States **Study Status**: complete **Report date**: 20-Apr-2021	V600- Mutation Positive Solid Tumors		or withdrawal from the study for any reason) **Doses**: Doses PO. Weight-based per available regulatory guidance. Part 1 dose escalation; part 2 tumor 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 tumor: 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 ● Langerhans Cell Histiocytosis: 10	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.
CDRB436G2201 Start: 28-Dec-2017 Data cut-off date: 23-Aug-2021 Countries:	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	Total: LGG: 110 HGG: 41 Age (years): LGG: 1-17 (9.1) HGG: 2-17 (12.12) Groups: 2 LGG Cohort: 2	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

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage
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	Grade Glioma (LGG) or relapsed or refractory High Grade Glioma (HGG)	dabrafenib and trametinib: 73 cisplatin and vincristine: 37 HGG Cohort: 1 dabrafenib and trametinib: 41	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/m2 IV weekly infusion vincristine: 1.5 mg/m2 IV weekly infusion

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The paediatric development program 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)

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", also called BRF116013) which investigated dabrafenib monotherapy
- study CTMT212X2101 ("Study X2101", also called MEK116540) which investigated trametinib monotherapy and D+T combination therapy.

Several formulations were used in the paediatric development programme for each substance, as detailed in Table 4 and in Table 5 and Table 6 by age group in the paediatric studies for dabrafenib, and trametinib, respectively.

Table 4: Overview of drug product formulations used in the liquid formulation development program

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 5: 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 6: 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.

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 three clinical studies in paediatric patients (CDRB436A2102 [BRF116013], CTMT212X2101 [MEK116540] and CDRB436G2201) including a total of 2154 PK observations from 243 patients. The population pharmacokinetic analysis included 61 patients aged 1 to <6 years, 77 patients aged 6 to <12 years and 105 patients aged 12 to <18 years. Both liquid and solid formulations of dabrafenib and trametinib were used for model development. Observations below the lower limit of quantification (2.81% of concentrations in X2101, and 1.53% of concentrations in G2201, and 0.57% in A2102 across all age ranges) 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. The final paediatric model was a two-compartment model with a delayed first-order absorption model with two separate depot compartments and an inducible dose- and time-dependent clearance (CLind/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 clearance (CL), inter-compartmental clearance (Q) and central volume of distribution (VC). In addition, combination treatment was included on the extent of inducible clearance, sex was included on CL and the effect of powder in in stick-packs formulation was included on relative bioavailability. The parameters of the final model are shown in Table 7. The final model evaluation included prediction-corrected visual predictive checks (pcVPCs) shown in Figure 2 (stratified on formulation), Figure 3 (stratified on weight) and Figure 4 (stratified on occasion).

Table 7. Final model parameters

Parameter name (unit)	Mean	95% Conf. Int.
Vp/F (L)	5.25	NA – fixed parameter
Clbase/F (L/h)	16.446	14.415 – 18.677
Vc/F (L)	59.294	52.33 – 66.539
Q/F (L/h)	4.343	3.2 – 5.6
Ka1 (1/h)	1.126	0.919 – 1.368
Ka2 (1/h)	2.94	2.19 – 3.99
Absorption lag 2nd depot (h)	0.714	0.65 – 0.768
Fraction into 1st depot	0.079	0.046 – 0.119

Powder in stick-packs formulation on relative F	0.936	0.811 – 1.072
Clindmax (L/h)	8.96	7.788 – 10.279
Alpha (-)	1.019	0.999 – 1.039
T50 (h)	113.695	75.351 – 152.267
WT_CL (-)	0.786	0.711 – 0.865
WT_Q (-)	1.089	0.84 – 1.32
WT_Vc (-)	0.997	0.872 – 1.121
Sex_CL (-)	0.935	0.883 – 0.993
Combination treatment on Clind	0.895	0.805 – 0.994
Variance of Clbase/F	0.403	0.3 – 0.527
Covariance of Clbase/F and Vc/F	0.211	0.151 – 0.285
Variance of Vc/F	0.151	0.105 – 0.21
Variance of Q/F	0.657	0.433 – 0.917
Variance of Ka1	5.49	1.962 – 10.695
Variance of Ka2	1.188	0.686 – 1.825
Variance of Absorption lag 2nd depot	0.318	0.205 – 0.468
Variance of Fraction into 1st depot (additive on the logit scale)	2.282	1.286 – 3.661
Proportional residual error (variance)	0.213	0.195 – 0.232

Statistics summarized (using the coda package) from pooled Bayesian posterior samples from 3 chains with 15000 samples per chain. 95% CI, 2.5th – 97.5th percentiles of the posterior samples

Parameter name	Mean	95% Conf. Int.
VP (L)	5.25	NA
Form1_F (-)	0	NA
CLbase (L/h)	16.446	(14.415 - 18.677)
VC (L)	59.294	(52.33 - 66.539)
Q (L/h)	4.343	(3.2 - 5.6)
KA (1/h)	1.126	(0.919 - 1.368)
ALAG2 (h)	0.714	(0.65 - 0.786)
CLindmax (L/h)	8.96	(7.788 - 10.279)
Alpha (-)	1.019	(0.999 - 1.039)
T50 (h)	113.695	(75.351 - 152.267)
WT_CL (-)	0.786	(0.711 - 0.865)
WT_Q (-)	1.089	(0.84 - 1.32)
WT_VC (-)	0.997	(0.872 - 1.121)
SEX_CL (-)	-0.067	(-0.124 - -0.007)
Combo_CLind (-)	0.895	(0.805 - 0.994)
Form2_F (-)	0.936	(0.811 - 1.072) #
F_Depot1 (-)	0.079	(0.046 - 0.119)
KA2 (1/h)	2.94	(2.19 - 3.99)
SIGMA.1.1.	0.213	(0.195 - 0.232)
OMEGA.1.1.	0.403	(0.3 - 0.527)
OMEGA.2.1.	0.211	(0.151 - 0.285)
OMEGA.2.2.	0.151	(0.105 - 0.21)
OMEGA.3.3.	0.657	(0.433 - 0.917)
OMEGA.4.4.	5.49	(1.962 - 10.695)
OMEGA.5.5.	1.188	(0.686 - 1.825)
OMEGA.6.6.	0.318	(0.205 - 0.468)
OMEGA.7.7.	2.282	(1.286 - 3.661)
SIGMA.1.1.	0.213	(0.195 - 0.232)
MCMCOBJ	24379.37	(24130.95 - 24627.033)

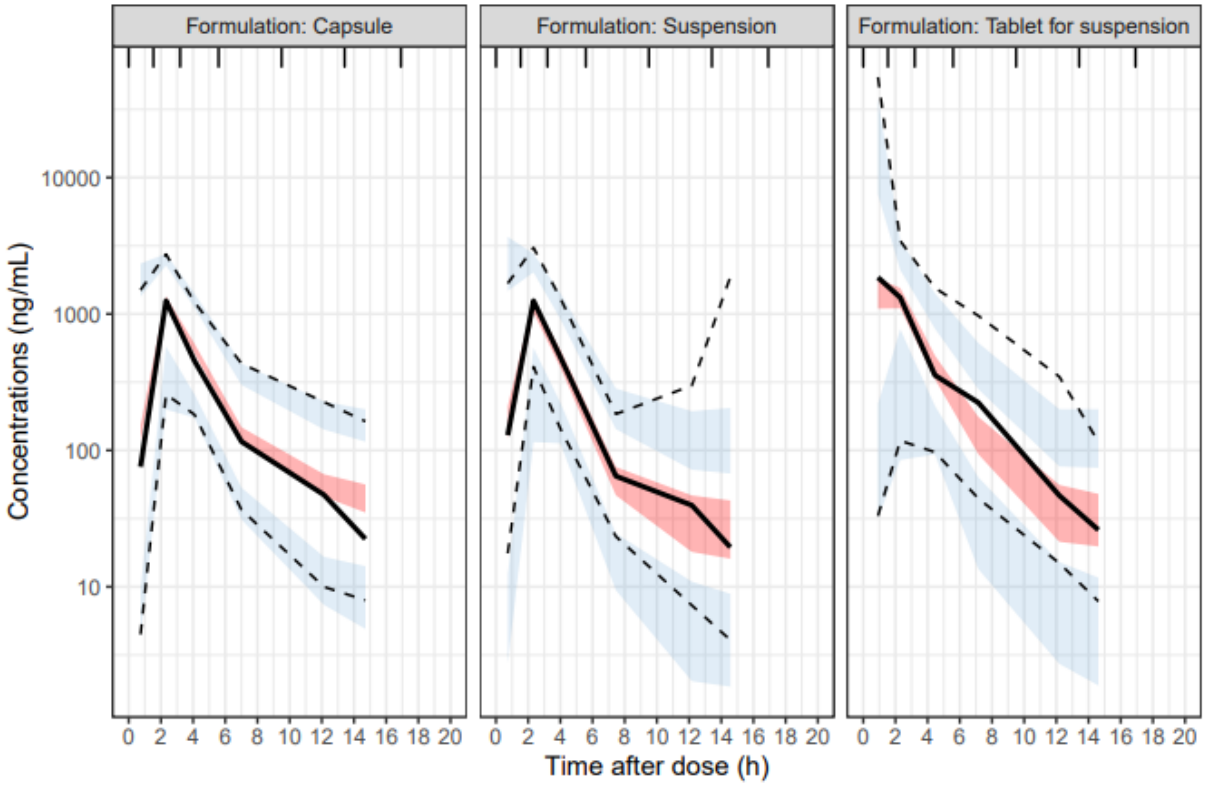


Figure 2. Prediction-corrected VPC for dabrafenib final PopPK model stratified by formulation.

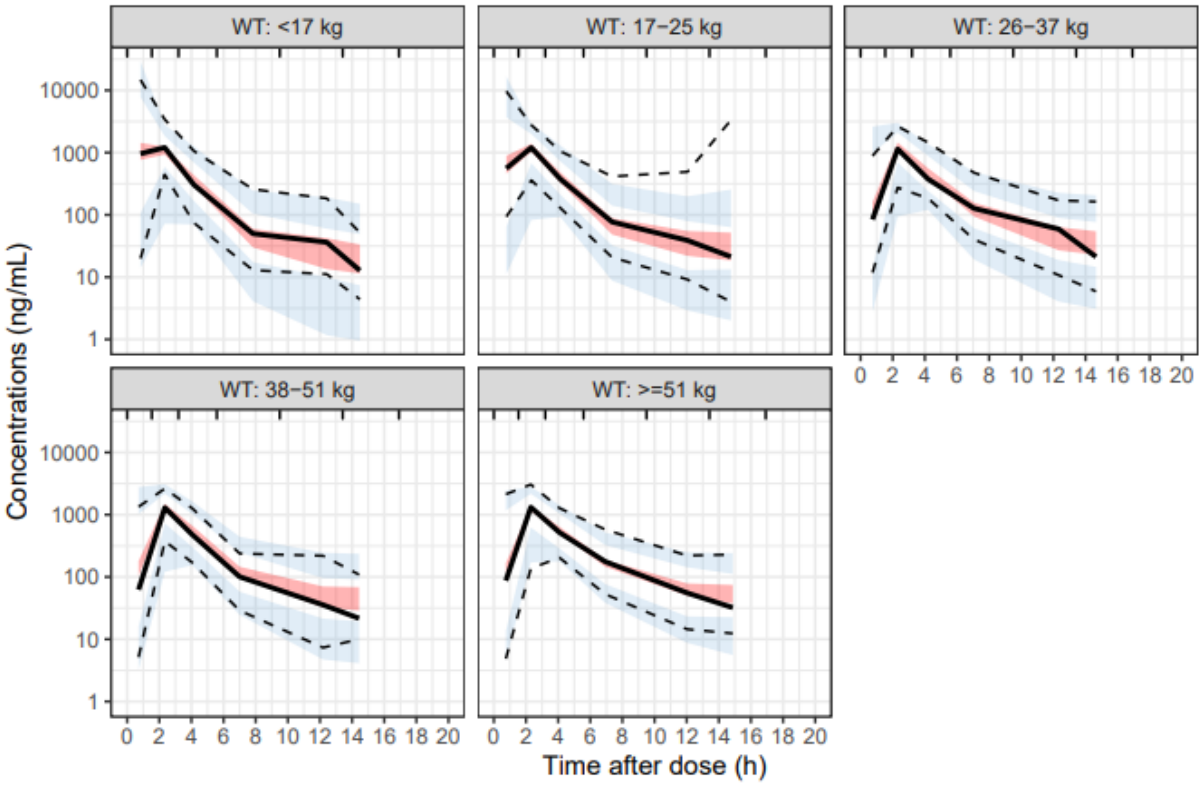


Figure 3. Prediction-corrected VPC for dabrafenib final PopPK model stratified by weight.

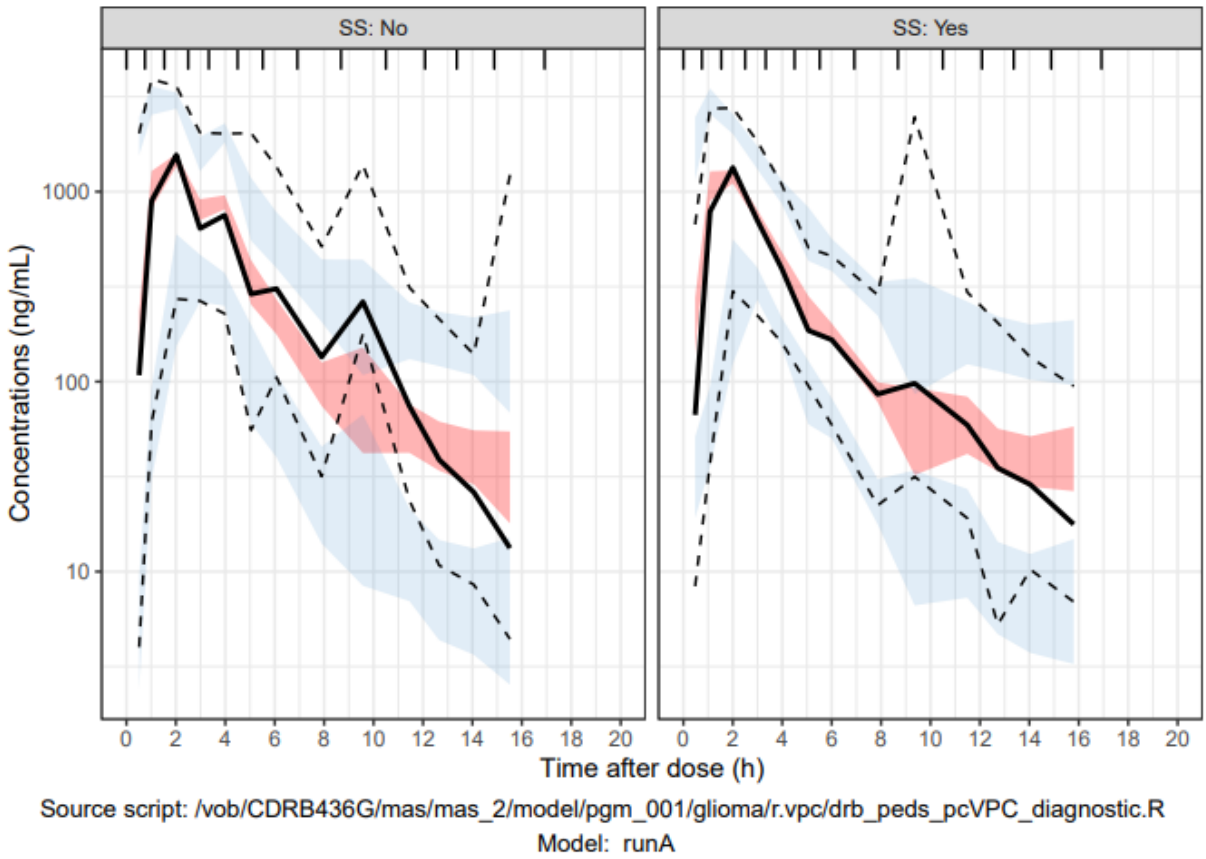


Figure 4. Prediction-corrected VPC for dabrafenib final PopPK model stratified by occasion.

The final model was used to perform simulations of PK exposure at steady state to support a simplified posology, shown in figure 5. In general, the simplified dabrafenib posology was developed with the goals of achieving an efficacy target of dabrafenib steady state average concentration (Cavg) of about 300 ng/mL.

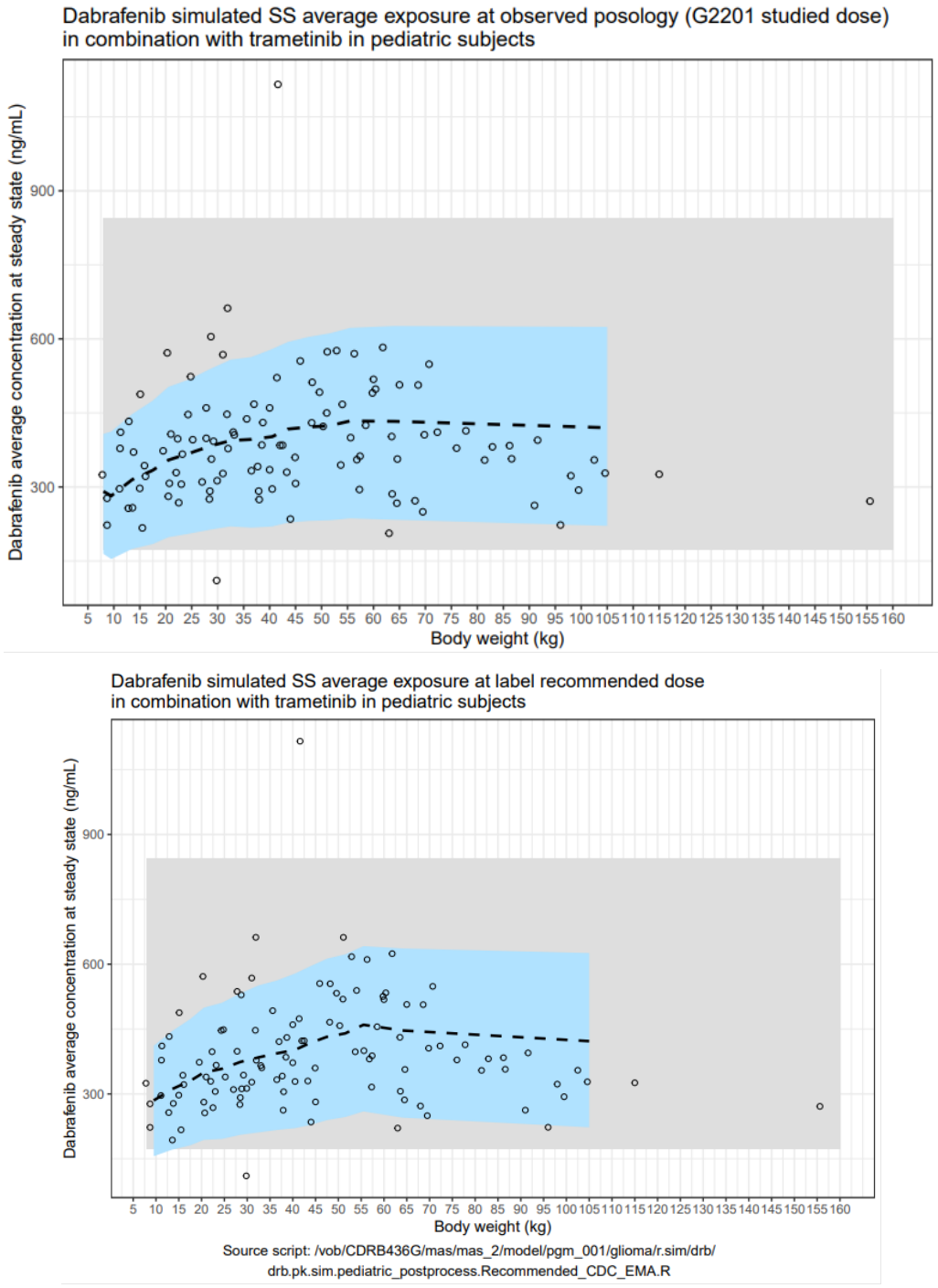


Figure 5. Dabrafenib simulated steady-state exposure at dabrafenib dosing using the liquid formulation according to the G2201 protocol (top panel, included for reference) and for the recommended dosing (lower panel) in combination with trametinib in paediatric patients.

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 represent the 5th to the 95th percentiles of the observed non-compartmental-based Cavg in patients from G2201 study. Black circles represent individual predicted Cavg at respective doses for patients in G2201 using EBEs

Absorption

Dabrafenib, and metabolites hydroxy- and desmethyl-dabrafenib, but not carboxy-dabrafenib were substrates of PgP and BCRP.

Dabrafenib has low solubility and high permeability (BCS class II). Despite its pH-dependent solubility, administration of the pH elevating agent rabeprazole 40 mg once daily, with a solid formulation of dabrafenib 150 mg BID, resulted in a 3% increase in dabrafenib AUC(0-T) and a 12% decrease in dabrafenib Cmax relative to administration of dabrafenib 150 mg BID alone (study A2103). Systemic exposure to the metabolites hydroxy-dabrafenib and carboxy-dabrafenib, as measured by AUC(0-T), Cmax and Ct, were similar in presence or absence of rabeprazole.

The absolute bioavailability (BA) previously established for the solid formulation of dabrafenib was 94.5% (Denton CL et al 2013).

In the pivotal paediatric trial G2201, dabrafenib steady state geometric mean (%CV) Cmax and AUC(0-tau) were 1330 ng/ml (93.5%) and 4910 ng*hr/ml (54.0%) in the LGG cohort and 1520 ng/ml (65.9%) and 4300 ng*hr/ml (44.7%) in the HGG cohort.

In Study G2101 it was shown that dabrafenib exposures (AUCinf, AUClast and Cmax) were reduced by 20%, 21% and 48.5%, respectively, following treatment with Variant B dispersible tablets [the intended commercial formulation] in suspension relative to administration of HPMC dabrafenib capsules. Rapid absorption was observed with median Tmax of 1.4 h and 1.5 h for solid and liquid formulations, respectively. A longer t½ was observed for the dispersible tablet (11.5 hours) compared to the capsule (4.8 hours).

For the metabolites, the decreases in magnitude of AUC and Cmax for the dispersible tablet were similar to that of the parent. The AUC ratios of metabolite versus parent for hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib for the dispersible tablet were similar as compared to dabrafenib capsules.

In all trials, dabrafenib was recommended to be administered under fasting conditions, either one hour before or two hours after a meal, with approximately 12 hr between each dose. The impact of food on the pharmacokinetics of the dispersible tablets suspension has not been investigated. Administration of dabrafenib (capsule formulation) with food reduced the bioavailability (Cmax and AUC decreased by 51% and 31% respectively) and delayed the absorption of dabrafenib when compared to the fasted state in an adult healthy volunteer study.

Distribution

The human plasma protein binding was determined to be 99.7%, 99.5% and 99.9% for dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib respectively and 96.3% for hydroxy-dabrafenib. There was no evidence of concentration dependent protein binding.

Blood-plasma ratios for dabrafenib and its metabolites was low, ranging from about 0.45 to 0.71 across species. Thus, dabrafenib and its metabolites are not preferentially distributed to blood cells.

Dabrafenib volume of distribution was estimated in the absolute bioavailability study, with an IV microdose of 50 µg [14C]-dabrafenib administered together with a single oral 150 mg dose of un-labelled dabrafenib. Dabrafenib had a Vdss of 45.5 L, consistent with total body water. Vdss of the active metabolites was not determined.

Biotransformnation and Elimination

Oxidation of dabrafenib was catalysed by CYP3A4 and 2C8 and occurred primarily at the t-butyl group to initially form the mono-oxygenated product hydroxy-dabrafenib (Figure 6). Hydroxy-dabrafenib underwent further oxidation via CYP3A4 to the carboxylic acid derivative carboxy-dabrafenib, which decarboxylates non-enzymatically to form desmethyl-dabrafenib. Both hydroxy- and desmethyl-dabrafenib have relevant pharmacodynamic activity, while carboxy-dabrafenib had a lower potency. Finally, desmethyl-dabrafenib is metabolised mainly by CYP3A4 to minor oxidative metabolites, detected at low concentrations in human plasma (M26, M28, M29, M30 and M31). Some direct glucuronidation of dabrafenib was observed in vitro but this appears to be a minor pathway *in vivo*. Metabolism was similar in human and non-clinical species.

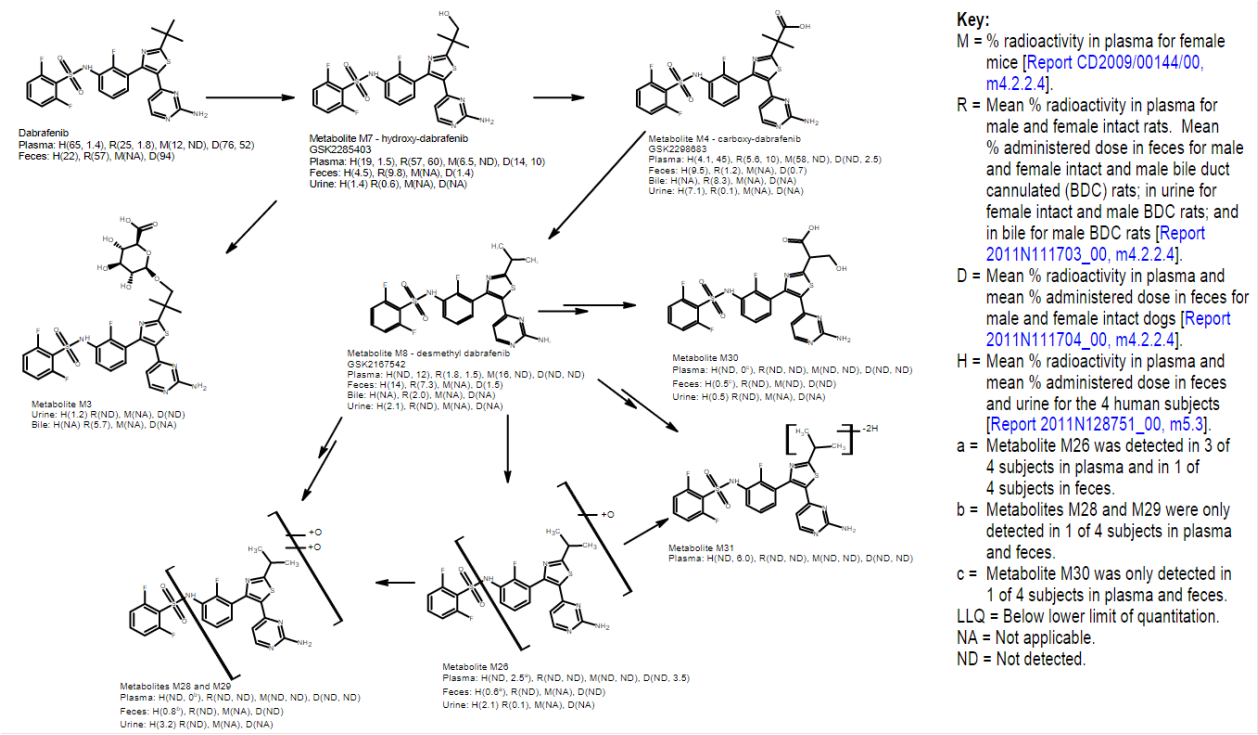


Figure 6. Metabolic pathways of dabrafenib in human and non-clinical species

The geometric mean IV plasma clearance (CL) of dabrafenib was 12.0 L/hr (Denton CL et al 2013). After single oral dosing of the solid formulation, CL/F was 14.0 L/hr, consistent with the high absolute bioavailability at a single dose of 94.5%. Terminal half-life following an intravenous single microdose is 2.6 hours. Dabrafenib terminal half-life after oral administration is longer (4.8h) due to flip-flop PK.

Dabrafenib showed a time dependent increase in apparent clearance (CL/F) following multiple doses, which was likely due to induction of its own metabolism through CYP3A4 (see study BRF113771).

The elimination of dabrafenib and its major metabolites has been characterised in a single dose mass-balance study and in several *in vitro* metabolism studies using human liver microsomes (HLM) and recombinant CYP enzymes. The main elimination route of dabrafenib was the oxidative metabolism via CYP3A4/2C8 and biliary excretion. The elimination route by CYP3A4 and 2C8 have been confirmed in interaction studies.

Mean total recovery in the mass-balance study was 94%, with 71% and 23% of the dose recovered in faeces and urine respectively, with structural identification of a total of 70% of the dose excreted. About 22% were unchanged drug in faeces, while carboxy-dabrafenib dominated (7%) in urine, where

no parent drug was detected. Carboxy-dabrafenib is excreted in bile and urine. Desmethyl-dabrafenib may also be formed in the gut and reabsorbed. Overall, about 80% of the dose was metabolised. The parent drug and its hydroxy-, carboxy- and desmethyl- metabolites accounted for 11, 8, 54 and 3% of the plasma radioactivity, respectively (study BRF113463 and Puszkiel et al 2019).

Hydroxy dabrafenib terminal half-life parallels that of parent with a half-life of 10 hrs while the carboxy- and desmethyl metabolites exhibited longer half-lives (21-22 hours). Mean metabolite to parent AUC ratios following repeat dose administration of the capsule formulation (in adults) were 0.9, 11 and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. The MR in the paediatric population are summarised in Table 8.

Table 8. Steady state dabrafenib AUC and metabolic ratio in paediatric patients from studies X2101, A2102 and G2201

		SS Metabolic Ratio (MR)			
Age Group	Statistics	Dabrafenib SS AUC* (h.ng/mL)	Hydroxy-Dabrafenib	Desmethyl-Dabrafenib	Carboxy-Dabrafenib
<2 y	Geomean (CV%)	2473.07 (56.3)	0.81 (18.9)	0.27 (57.7)	26.19 (105.7)
	Min to Max (n)	1191.47 to 4367.30 (6)	0.63 to 1.08 (6)	0.11 to 0.56 (6)	11.51 to 106.56 (5)
2 to 17 y	Geomean (CV%)	4361.22 (44.4)	0.64 (27.9)	0.69 (61.5)	15.62 (48.5)
	Min to Max (n)	1041.54 to 15183.41 (200)	0.16 to 1.45 (195)	0.10 to 4.31 (178)	4.33 to 51.13 (182)

*AUCtau was used for Studies X2101 and G2201. Due to no AUCtau determined in the legacy Study A2102, AUClast was used because majority of the Clast of A2102 patients was equal to the Ctau.

Source: [Table HA2-Q1.F16.1]

Dose proportionality and time dependencies

Based on popPK analysis, dabrafenib exposure increased in dose proportional manner between 12 and 300 mg following single-dose administration, but the increase was less than dose-proportional after repeat twice daily dosing.

Study BRF113771 Part D was an open-label cohort to characterise the repeat dose pharmacokinetics of dabrafenib in 13 subjects using HPMC capsules. PK parameters on day 1 and 18 are summarised in Table 9 for dabrafenib. There was no accumulation of dabrafenib after BID administration and the time invariance ratio was less than one, indicating that dabrafenib induced its own metabolism upon repeated dose administration. The extent of this auto-induction process was dependent on the dose in adults, resulting in a dabrafenib systemic exposure at steady state that increased less than dose proportionally over the dose range of 75-300 mg twice daily.

Table 9. Dabrafenib plasma PK parameters on day 1 and 18 after oral administration of dabrafenib 150 mg bid study BRF113771 part D

Parameter	Day 1 (n=13)	Day 18 (n=11)
Cmax[a] (ng/mL)	2521 (1849, 3435) (55)	2458 (1583, 3818) (73)
tmax[b] (h)	2.0 (0.5 – 3.1)	1.5 (1.0 – 2.1)
AUC(0-τ)[a] (ng*hr/mL)	9359 (7115, 12311) (48)	6545 (4383, 9771) (61)[c]
AUC(0-24)[a] (ng*hr /mL)	10274 (7610, 13871) (53)	NA
AUC(0-∞)[a,c] (ng*hr /mL)	9626 (7342, 12622) (45)[c]	NA
t½[a] (h)	4.15 (3.07, 5.61) (53)	2.13 (1.61, 2.81) (43)
Cτ [b](ng/mL)	103.2 (40.2 – 1036.2)	31.1 (12.9 – 120.5)[d]
Ro[e]	NA	0.73 (0.62, 0.86)
Rt[e]	NA	0.68 (0.57, 0.80)
Rcmax[e]	NA	1.00 (0.80, 1.24)

NA – not applicable; Ro – observed AUC(0-τ) accumulation ratio; Rt – time invariance ratio
Rcmax – observed Cmax accumulation ratio
a. Data presented as geometric mean (95% CI) and (CVb %)
b. Median (range)
c. n = 12
d. n=10
e. Reported as geometric least squares mean ratio (90% CI)

Median tmax of hydroxy-dabrafenib was delayed by at least one hour relative to that of parent with a median tmax of 3.8 hours after a single dose. The t½ of hydroxy-dabrafenib and dabrafenib was approximately 4 hours after a single dose of dabrafenib. The mean hydroxy-dabrafenib t½ also was similar to that of parent (2.1 hours and 2.6 hours for dabrafenib and hydroxy-dabrafenib, respectively) after repeated dose administration of dabrafenib. Similar to parent, there was no accumulation of hydroxy-dabrafenib with BID administration of dabrafenib. Systemic exposure to carboxy-dabrafenib was greater than parent after single- and repeated-dose administration of dabrafenib. Repeated BID administration of 150 mg dabrafenib resulted in accumulation in the plasma of both carboxy-dabrafenib and desmethyl-dabrafenib. Geometric mean metabolite to parent AUC ratios on Day 18 were 0.580, 10.7 and 0.759 for hydroxy-dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib, respectively.

Target population

For all studies in the target population, several formulations were used for each substance, as detailed in Table 4 and in Table 5 and Table 6. 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 A2102 was a 2-part, Phase I/IIa, open-label study to determine the safety, tolerability, and PK of oral dabrafenib (solid and liquid formulations) administered in children and adolescents aged ≥12 months to <18 years with BRAF V600 mutation-positive advanced solid tumours. The primary objective of the study was to determine a safe and tolerable dabrafenib dose in paediatric patients that would achieve a similar exposure as in adults with BRAF V600 mutation positive tumours. PK was a secondary objective. Part 1 (n=27) was a dose escalation to determine the recommended dose. The dose escalation Part 1 included dose levels of dabrafenib 3, 3.75, 4.5, 5.25, and 6.0 mg/kg/day that were divided into two equal doses per day (i.e. twice daily). No patients received the highest dose of 6 mg/kg/day. Part 2 (n=58) was an expansion to further evaluate safety, tolerability, PK, and clinical activity of dabrafenib in four tumour-specific paediatric populations (BRAFV600 mutant HGG, LGG, LCH, Other). Based on preliminary PK from Part 1, two recommended expansion dose levels of 5.25

mg/kg/day in children (1 to 11 years old) and 4.5 mg/kg/day in adolescents (12 to 17 years old) were further explored to understand the PK and safety in paediatric patients. In all study parts, the total daily dose administered in this study did not exceed 300 mg (150 mg twice daily).

Part 1: On Day 1, the geo-mean Cmax of dabrafenib 3.0 mg/kg, 3.75 mg/kg, 4.5 mg/kg and 5 mg/kg was 1820 ng/mL, 1250 ng/mL, 1250 ng/mL, and 1900 ng/mL, respectively. Cmax was comparable on Day 15 to the concentrations of Day 1. The geo-mean exposure of dabrafenib (AUClast and AUCtau) was comparable across all the dose groups (3 mg/kg: 3350 hr*ng/mL; 3.75 mg/kg: 3710 hr*ng/mL; 4.5 mg/kg: 4690 hr*ng/mL and 5.25 mg/kg: 4510 hr*ng/mL). The median terminal half-life was lowest for the 5.25 mg/kg dose group compared to the other dose groups (1.77 hours for 3 mg/kg dose group, 2.14 hours for 3.75 mg/kg, 2.44 hours for 4.5 mg/kg dose group, and 1.57 hours for 5.25 mg/kg dose group). Dabrafenib day 15 Ctrough at 3mg/kg, 3.75 mg/kg, 4.5 mg/kg and 5.25 mg/kg was 11.8 ng/mL, 23.6 ng/mL, 58.4 ng/mL, and 13.1 ng/mL, respectively.

Part 2: There was no major difference in the plasma concentration of dabrafenib across dose or disease cohort. Tmax of dabrafenib was at 2 hr post-dosing on Day 1 and Day 15. In the 4.5 mg/kg dose group, Cmax was comparable on Day 1 (1340 ng/mL) and Day 15 (1450 ng/mL); AUC was 4400 hr*ng/mL; the median terminal half-life was 2.22 hours; and the geo-mean Ctrough was 42.7 ng/mL. In the 5.25 mg/kg dose group, Cmax was comparable on Day 1 (1550 ng/mL) and Day 15 (1310 ng/mL); AUC was 3940 hr*ng/mL, the median terminal half-life was 1.82 hours, and the geo-mean Ctrough was 22.8 ng/mL. The MTD of dabrafenib was not established in paediatric patients, similar to the previous dose finding efforts in adult patients. The exposures achieved at RP2D in paediatric subjects were considered similar to the adult approved dose of 150 mg BID (Cavg:372 ng/mL and AUCtau: 4463.2 hr*ng/ml, respectively).

Across dose levels (age pooled), metabolite-to-dabrafenib AUC geo-mean ratios (MR) at Day 15 were contained within the adult range for hydroxy-dabrafenib 0.64-0.79 in paediatric patients and 0.58-0.91 in adults (studies BRF113771 - DDI study with ketoconazole and BRF 113683 phase III study). For desmethyl-dabrafenib, the ratios range was 0.41-0.70 in study A2101, while it was 0.73 to 0.76 in adults. For carboxy-dabrafenib, the ratios range was 14-20.9 in study A2101, while it was 10.7 in adults. No clear dose dependency was noted upon increasing the dabrafenib dose, except for carboxy-dabrafenib, which increased MR with dose. Ratios stratified by age in part 2 are presented in Table 10.

Table 10. Plasma PK parameters at Week 3 Day 15 (Study A2102 - Part 2; PK population)

Parameter	Statistics	Part 2: 5.25 mg/kg/day <2 years	Part 2: 5.25 mg/kg/day 2 - <6 years	Part 2: 5.25 mg/kg/day 6-11 years	Part 2: 4.5 mg/kg/day 12-17 years
Dabrafenib					
Cmax (ng/mL)	N	2	11	16	26
	Geometric mean	900	1450	1280	1450
	CV% geo. Mean	60.9	40.5	54.2	57.8
AUCtau (hr*ng/mL)	N	2	11	16	26
	Geometric mean	2620	3700	4330	4400
	CV% geo. Mean	82.6	31.4	41.6	31.6
Cavg (ng/mL)	Calculated geo. Mean	218	308	361	367
Tmax (hr)	Median	1.50	2.0	2.0	2.0
Metabolite to parent AUC ratio - Geo mean (geo CV%)					
Hydroxy-Dabrafenib		0.99 (12.5%)	0.69 (24.9%)	0.61 (25.0%)	0.64 (37.2%)
Desmethyl-Dabrafenib		0.28 (16.7%)	0.61 (89.9%)	0.62 (43.1%)	0.63 (40.7%)
Carboxy-Dabrafenib		39.3 (251.5%)	16.7 (41.3%)	16.3 (58.9%)	16.3 (36.8%)

Parameter	Statistics	Part 2: 5.25 mg/kg/day <2 years	Part 2: 5.25 mg/kg/day 2 - <6 years	Part 2: 5.25 mg/kg/day 6-11 years	Part 2: 4.5 mg/kg/day 12-17 years
Dabrafenib					

n: number of patients with corresponding evaluable PK parameters. Metabolite to parent ratio for AUC is adjusted for differences in molecular weight between parent and metabolite. Cavg = (AUCtau / 12)

Study X2101 was a 4-part, Phase I/IIa, multicenter, 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 characterisation and pop PK was a secondary objective. This study had four 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 Cavg (Table 11) 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 11. 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 (Table 8 and Table). PK parameters on day 15 (week 3 day 1) for dabrafenib and trametinib in the LGG and HGG cohort are presented in Table 12 and Table 13.

Table 12. 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	23.5	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 calculation. Assumed steady state Ctrough is similar to steady state pre-dose concentration. Cavg = (AUCtau / Tau).
Source: Table 14.2-4.1L

Table 13. 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	3860
	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.

PK parameters of dabrafenib's major metabolites are summarised in Table 14.

Table 24. Dabrafenib metabolites AUC and Cmax at day 15 (geomean; %CV)

	Hydroxy-dabrafenib	Carboxy-dabrafenib	Desmethyl-dabrafenib
HGG cohort, n=33			
AUCtau [hr*ng/ml]	2840 (35.7%)	71200 (34%)	3360 (57.7%)
Cmax [ng/mL]	801 (58.8%)	9050 (31.4%)	388 (67.2%)
LGG cohort, n = 54			
AUCtau [hr*ng/ml]	2960 (47.4%)	60700 (45.7%)	3660 (66.9%)
Cmax [ng/mL]	687 (82.6%)	7210 (51.6%)	377 (67.2%)

On day 15 in the LGG cohort, the geometric mean (% CV) dabrafenib metabolite to parent AUC0-τ ratios were 0.62 (26.6%), 13.1 (51.6%), and 0.73 (63.6%) for hydroxy-, carboxy-, and desmethyl-dabrafenib respectively.

On day 15 in the HGG cohort, the geometric mean (% CV) dabrafenib metabolite to parent AUC0-τ ratios were 0.67 (27.7%), 17.1 (53.3%), and 0.74 (63.6%) for hydroxy-, carboxy-, and desmethyl-dabrafenib respectively.

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 2011N113667_00 (and reviewed by Puszkiel et al 2019), unless noted otherwise.

The impact of renal impairment on the pharmacokinetics of dabrafenib was evaluated using a population approach in 233 (39.2%) adult patients with mild and 30 (5.0%) patients with moderate renal impairment. Mild and moderate renal impairment did not have any significant impact on the pharmacokinetics of dabrafenib and its metabolites. No data are available in patients with severe renal impairment.

In the PopPK analysis (595 adult patients), only three subjects (0.5%) presented moderate hepatic impairment (according to the National Cancer Institute classification). Therefore, pharmacokinetic data from these patients were pooled with data of 65 patients (10.9%) with mild hepatic impairment for the means of covariate analysis. Mild hepatic impairment did not impact plasma concentrations of dabrafenib and its metabolites. No data from patients with severe hepatic impairment were available in that study.

In the PopPK analysis in adults, evaluation of sex as a covariate showed that dabrafenib Cmax, AUC τ and Ctrough values were, respectively, 3, 9 and 26% higher in female patients than in male patients, which was not considered clinically relevant. Sex did not have any influence on plasma exposure of active metabolites of dabrafenib. Differences in BW may explain the difference in plasma exposure between female and male patients.

Sex was explored as a covariate during the paediatric PopPK analysis. Sex was identified as a significant predictor for clearance. The final PopPK model predicted a decrease in clearance of 6.5% for females compared to males.

Only few subjects were not Caucasian, therefore race and ethnicity covariates was not explored in the popPK. In a phase I dose-escalation study conducted in 12 Japanese patients, 150 mg dabrafenib bid showed a similar pharmacokinetic profile to that of Caucasian patients (Yamazaki et al 2018).

Body weight (BW) was identified as a significant covariate on dabrafenib CL/F, Vc/F and apparent inter-compartmental clearance (Q/F) in the PopPK analysis in adults.

Weight was included as a covariate in the paediatric PopPK analysis and identified as an influential covariate on clearance and volume terms. Body weight was included using allometric scaling with estimated coefficients. Clearance and volume terms increased significantly with increased weight.

Pharmacokinetic interaction studies

Study BRF113771

Administration of ketoconazole (a CYP3A4 inhibitor) 400 mg once daily, with dabrafenib 75 mg twice daily, resulted in a 71 % increase in dabrafenib AUC and a 33 % increase in dabrafenib Cmax relative to administration of dabrafenib 75 mg twice daily alone. Co-administration resulted in increases in hydroxy- and desmethyl-dabrafenib AUC (increases of 82 % and 68 %, respectively). A decrease of 16 % in AUC was noted for carboxy-dabrafenib.

Administration of gemfibrozil (a CYP2C8 inhibitor) 600 mg twice daily, with dabrafenib 75 mg twice daily, resulted in a 47 % increase in dabrafenib AUC bur did not alter dabrafenib Cmax relative to administration of dabrafenib 75 mg twice daily alone. Gemfibrozil had no clinically relevant effect on the systemic exposure to dabrafenib metabolites (≤ 13 %).

Administration of dabrafenib 150 mg twice daily and single dose warfarin (a CYP2C9 substrate) resulted in a decrease in AUC of S- and R- warfarin and of 37 % and 33 % compared to administration of warfarin alone. Cmax of S- and R- warfarin increased 18 % and 19 %.

Study A2103

Administration of rifampin resulted in a decrease in the systemic exposure of dabrafenib (AUC(0 -tau)) on average of 34%, and maximum concentration (Cmax) of 27% relative to administration of dabrafenib alone. The AUC ratios of metabolite versus parent for hydroxy-, carboxy- and desmethyl-dabrafenib in presence of rifampin were 1.05, 40.3 and 0.61, respectively, compared to 0.67, 13.8 and 0.57, respectively, in absence of rifampin.

Administration of the pH elevating agent, rabeprazole 40 mg once daily, with dabrafenib 150 mg BID, resulted in a 3% increase in dabrafenib AUC(0-T) and a 12% decrease in dabrafenib Cmax relative to administration of dabrafenib 150 mg BID alone.

Study A2104

Dabrafenib increased Cmax of rosuvastatin (OATP1B1, 1B3 and BCRP substrate), both after single (94%) and multiple (2.56-fold) administration. Total exposure (AUC) was only marginally affected (22% and 7% increase, respectively). The increased Cmax of rosuvastatin is unlikely to have clinical relevance.

A single dose of dabrafenib did not affect midazolam (CYP3A4 substrate) PK parameters. After repeat dosing of dabrafenib, administration of dabrafenib at steady state with a single dose of midazolam resulted in a 65% decrease in midazolam AUC(0-∞) and a 47% decrease in midazolam Cmax relative to administration of midazolam alone. The midazolam data indicates that dabrafenib is a moderate inducer of CYP3A4. No direct CYP3A4 inhibition is thus evident.

Table 15 provide a summary of interaction potential of dabrafenib and its metabolites:

Table 35. DDI summary for dabrafenib & metabolites: in vitro & *in vivo* (in vitro not described if *in vivo* available)

Enzyme/ transporter	Perpetrator	Victim	Consequence
CYP1A2	No inhibition, no induction	No	-
CYP2A6	No inhibition	-	-
CYP2B6	No inhibition, induction in vitro	No	Caution for sensitive substrates (induction)
CYP2C8	No inhibition Induction likely	Substrate (dabrafenib only) Dabrafenib AUCR 1.47 with gemfibrozil	Caution with strong inhibitors, Caution for sensitive substrates (induction)
CYP2C9	No inhibition Induction Warfarin AUCR 0.63	No	Caution for sensitive substrates (induction)
CYP2C19	No inhibition Induction likely	No	Caution for sensitive substrates (induction)
CYP2D6	No inhibition	No	-
CYP3A4	No inhibition (*in vivo*) Moderate induction Midazolam AUCR 0.35	Substrate (all except carboxy-dabrafenib) Auto-induction Dabrafenib AUCR 1.71 with ketoconazole Dabrafenib AUCR 0.66 with rifampicin	Caution with strong inhibitors, strong inducers contraindicated Caution for sensitive substrates (induction)
PgP	No systemic inhibition, inconclusive in intestine Induction likely	Dabrafenib, hydroxy- and desmethyl-dabrafenib are substrates, not carboxy-dabrafenib Dabrafenib AUCR 1.71 with ketoconazole	Substrate: discussion on clinical relevance required Caution for sensitive substrates (induction)
BCRP	Weak inhibition Rosuvastatin AUCR* up to 1.22 (d1), CmaxR up to 2.56 (d14)	Dabrafenib, hydroxy- and desmethyl-dabrafenib are substrates, not carboxy-dabrafenib	Inhibition not considered clinically relevant Substrate: discussion on clinical relevance required

OATP1B1	Weak inhibition Rosuvastatin AUCR* up to 1.22 (d1), CmaxR up to 2.56 (d14)	Not a substrate, except carboxy-dabrafenib	Inhibition not considered clinically relevant Substrate: no clinical relevance expected
OATP1B3	Weak inhibition Rosuvastatin AUCR* up to 1.22 (d1), CmaxR up to 2.56 (d14)	Not a substrate, except carboxy-dabrafenib	Inhibition not considered clinically relevant
OATP1A2	NA	Not a substrate, except carboxy-dabrafenib	-
OAT1	No inhibition	-	-
OAT3	No inhibition	-	-
OCT2	No inhibition	Not a substrate, except carboxy-dabrafenib	-
pH		Rabeprazole AUCR 1.03	None

* Inhibition of rosuvastatin *in vivo*, however inhibition of BCRP and OATP1B3 was over the cutoff in vitro, and close to the cutoff for OATP1B1.

Pharmacokinetics using human biomaterials

Concentrations relevant for addressing the relevance of in vitro studies:

Unbound Cmax

Dabrafenib 0.028 uM (50 x Cmaxu = 1.4 uM)

M7 hydroxy-dabrafenib 0.070 uM (50 x Cmaxu = 3.5 uM)

M4 carboxy-dabrafenib 0.112 uM (50 x Cmaxu = 5.6 uM)

M8 desmethyl-dabrafenib 0.0007 uM (50 x Cmaxu = 0.04 uM)

Gastrointestinal cutoff 0.1* dose /250 (115 µM)

The results for CYP inhibition by dabrafenib and its metabolites is summarised in Table 16. Dabrafenib was also shown to induce human CYP3A4 and CYP2B6 in hepatocytes.

Table 16. Direct and Metabolism-Dependent Cytochrome P450 Inhibition Using Dabrafenib and Metabolites

	CYP Inhibition (µM)											
	Direct										CYP3A4 Metabolism-Dependent	
	1A2	2A6	2B6	2C8	2C9	2C19	2D6	3A4[a]	3A4[b]	3A4[c]	Fold Change	MDI

Dabrafenib	87	>100	>100	8.2	7.2	22	>100	16	>100	32	1.5[a]; >4[b]; 2.1[c]	K_{inact}/K_I= 0.001
Hydroxy-dabrafenib	83	ND	>100	>100	28.6	ND	>100	>100	47	>100	Not observed	NA
Carboxy-dabrafenib	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	Not observed	NA
Desmethyl-dabrafenib	>100	>100	78	49.3	6.3	35.9	>100	19.6	16.7	27.5	2.1[b]; 2.3[c]	ND

Key:
a = Atorvastatin. b = Midazolam. c = Nifedipine.
NA = Not applicable. ND = Not determined.

Dabrafenib, hydroxy- and desmethyl-dabrafenib, but not carboxy-dabrafenib were substrates of PgP and BCRP. Dabrafenib is not a substrate of OATP1B1, OATP1B3 or OATP2B1 transporters.

None of dabrafenib or its 3 active metabolites inhibited Pgp in vitro up to 30 µM.

Dabrafenib, hydroxy- and desmethyl-dabrafenib, but not carboxy-dabrafenib inhibited BCRP in vitro. Only the inhibition by dabrafenib was at clinically relevant concentrations for the intestine.

Dabrafenib and its desmethyl metabolite inhibited OCT2 in vitro with IC50 9.31 µM and 27.9 µM, respectively. Clinically relevant inhibition could be excluded based on the respective cutoffs. Hydroxy and carboxy-dabrafenib did not inhibit human OCT2 in vitro.

Dabrafenib inhibited OATP1B1 and 1B3 with IC50 values of 1.4 µM and 4.7 µM, respectively. Hydroxy-dabrafenib inhibited OATP1B1 and 1B3 with IC50 values of 4.3 µM and 23 µM, respectively. Carboxy-dabrafenib inhibited OATP1B1 and 1B3 with IC50 values of 18 µM and 20 µM, respectively. Desmethyl-dabrafenib inhibited OATP1B1 and 1B3 with IC50 values of 0.83 µM and 4.3 µM, respectively.

Dabrafenib, hydroxy- and desmethyl-dabrafenib inhibited OAT1 with IC50 values of 6.9 µM, 29 µM and 10 µM, respectively. Dabrafenib hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib inhibited OAT3 with IC50 values of 3.4 µM, 7.3 µM, 9.0 µM and 3.4 µM, respectively.

Exposure relevant for safety evaluation

Based on day 15 data from study G2201 pooled across doses, ages and formulations, geomean (CV%) steady state exposure of dabrafenib was AUCtau 4300 (44.7%) and 4910 (54%) hr*ng/ml in the HGG and LGG cohorts, respectively, with Cmax of 1520 (65.9%) and 1330 (93.5%) ng/mL. Exposure of dabrafenib major metabolites is summarised in Table 14.

Similarly, trametinib AUCtau was 307 (22.8%) and 339 (22.2%) hr*ng/ml in the HGG and LGG cohorts, respectively, with Cmax of 21.3 (36.3%) and 22.7 (41.1%) ng/mL.

2.6.2.2. Pharmacodynamics

Mechanism of action

Dabrafenib is an inhibitor of RAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway. The most commonly observed BRAF mutation is V600E, which has been identified in 19% of paediatric LGG and approximately 5% of paediatric HGG.

Preclinical data generated in biochemical assays demonstrated that dabrafenib inhibits BRAF kinases with activating codon 600 mutations (Table 17).

- **Table 17 Kinase inhibitory activity of dabrafenib against RAF kinases**

Kinase	Inhibitory concentration 50 (nM)

BRAF V600E	0.65
BRAF WT	3.2
CRAF WT	5.0

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. 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 dabrafenib with trametinib 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 dabrafenib flat dose of 150 mg twice daily (corresponding to ≤5.9 mg/kg/day doses) in patients weighing ≥51 kg, and a dabrafenib dose of 2.5 mg/kg twice daily in patients weighing <51 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

Dabrafenib and its three active metabolites were generally inactive against a panel of >270 protein and lipid kinases, and dabrafenib generally had no inhibiting or activating effect (XC50 >5 μM) against a panel of 14 seven-transmembrane receptors, 2 enzymes, 7 ion channels, 4 kinases and 3 transporter molecules Dabrafenib showed moderate potency against the α2C-adrenergic receptor (XC50 >0.3 μM) and inhibition of LCK (XC50 >0.6 μM), GSK3β (XC50 >0.8 μM) and Aurora B kinases (XC50 >3.2 μM); however, all activities against these proteins were at least 100-fold less potent than against BRAF enzymes.

2.6.3. Discussion on clinical pharmacology

Overall, the clinical developmental program is acceptable.

Bioanalytics

During the routine GCP inspection of investigator sites of study G2201, it was observed that no documentation was available on the handling and preparation of PK samples (eg 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. As study G2201 provides the reference therapeutic exposure for both formulations and supports the posology, the integrity of the PK data must be warranted. In the applicant's response to the critical findings, the analytical reports confirming the

stability of dabrafenib and its metabolites in whole blood (at room temperature and cooled) were provided. It is agreed that prolonged storage at room temperature or on ice prior to centrifugation is unlikely to have an impact for dabrafenib and its metabolites. Thus, the GCP inspection finding has no consequence on the validity of PK data for dabrafenib and its metabolites.

Population pharmacokinetic analysis

Pharmacokinetics of dabrafenib was evaluated in the target population consisting of paediatric glioma patients, including analysis using a population pharmacokinetic (PopPK) approach.

The objectives of the 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 three 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 dabrafenib formulation.

A Bayesian approach was used for estimating model parameters. The reason why this was chosen over more conventional estimation methods (such as FOCE) was to allow utilisation of information obtained from the corresponding PopPK analyses of the adult data. However, the paediatric dataset is probably informative enough (both in terms of number of subjects and number of PK samples) to allow for a more standard estimation approach (such as FOCE). Bearing this in mind, a Bayesian approach could be considered acceptable as long as the model can be deemed fit-for-purpose.

Overall, relevant covariates were explored during covariate model development. Weight was implemented using estimated allometric exponents in the PopPK model. The Applicant also explored standard fixed allometric exponents (0.75 for clearances and 1 for volumes). Based on various goodness-of-fit plots and changes the OFV, it is deemed acceptable to rely on estimated coefficients.

The implementation of dose-dependent on dabrafenib autoinduction was implemented in the paediatric PopPK model. A body-weight-normalised dose (i.e. the dose expressed as mg/kg) was used to drive the dose-dependency in autoinduction instead of actual dose in mg. Importantly, a mg/kg dose to drive this relationship gave a better description of the data based on the OFV and had a large impact on the estimate of the allometric exponent for body weight on CL.

$$\frac{CL_{ind}}{F} = CL_{ind,SS} \times \left(\frac{DOSE \times F_1}{150}\right)^{\alpha} \times (1 - e^{-\frac{ln2}{T_{50}} \times t})$$

The liquid trametinib formulation contains Captisol (i.e. sulfobutylbetadex sodium). Co-administration of the liquid trametinib formulation was tested in the PopPK analysis as a covariate on the dabrafenib absorption parameters and was shown to not be a significant covariate. This could indicate that there is no clinically relevant DDI between sulfobutylbetadex sodium and dabrafenib.

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). The pcVPCs show that the final model gives acceptable description of the data (Figure 2).

In the final model, the inter-compartmental clearance 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.

Absorption

The in vitro studies were adequately performed. Dabrafenib is a BCS class II (low solubility, high permeability) compound. The high permeability is also confirmed by the high bioavailability of the solid formulation.

Dabrafenib and its metabolites were PgP and BCRP substrates, except for carboxy-dabrafenib. Based on the high permeability and dose-proportionality, it is unlikely that PgP and/or BCRP inhibition would result in a clinically relevant interaction.

Regarding the pH-dependent solubility of dabrafenib and the use with antacids, an interaction study has been conducted with rabeprazole. Additionally, data from a two-stage dissolution experiment with the dispersible tablets indicated that dabrafenib was dissolved in gastric fluid at pH 1.6 and it remained in solution in intestinal fluid at pH 6.5. As this covers the gastric pH range after use of rabeprazole or other PPIs, it is considered to support that the results of the study with rabeprazole and the solid formulation are also valid for the liquid formulation.

The study design of the relative bioavailability study G2101 is considered acceptable. Dabrafenib 10 mg dispersible tablet variant B was selected for use in clinical studies (Study A2102 and Study X2101) and the pivotal study (Study G2201).

In Study G2101 it was shown that dabrafenib exposures (AUCinf, AUClast and Cmax) were reduced by 20%, 21% and 48.5%, respectively, following treatment with Variant B dispersible tablets in suspension relative to administration of HPMC dabrafenib capsules. As the solid and to be marketed liquid formulation are not bioequivalent, a clear warning regarding their lack of interchangeability is included in section 4.2, which is considered acceptable.

No formulation bridge has been established for the powder in stick pack formulationwhich was used at the beginning of the paediatric programme. Both the stick pack formulation and the dispersible tablet contained non-micronised dabrafenib mesylate and similar excipients, in addition to both being suspended in water prior to use. Considering this, and that the stick pack was not used in the pivotal study G2201, the issue is not pursued.

No food interaction study was performed for the dabrafenib dispersible tablets and the recommendation in the SmPC is that Finlee should be taken without food, at least one hour prior to or two hours after a meal. The fasting recommendation for Finlee is based on that this was the same recommendation as used in Phase II and the results from the food interaction study with the tablet/capsule (fasting vs high-fat, high-calorie meal). The effect of food on Mekinist and Tafinlar 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 and especially for the dabrafenib which is administered twice daily. 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.

The formulations of the tablet/capsule of Mekinist and Tafinlar are different compared to the applied liquid formulation for Finlee and the conclusion that the food effect of the liquid formulations is expected to be similar to the immediate release solid formulations are not fully agreed. A study is

needed to investigate the food effect for Finlee, and also if similar food effect of high-fat, high-calorie meal is achieved as with the tablet/capsule formulations further food-drug interaction studies are recommended 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 (see Conclusion on Clinical Pharmacology).

Until the food effect study is available, the SmPC text in section 4.2 is agreed, as the text based on study B2102 (low-calorie low-fat meal with the dabrafenib capsule) has been removed.

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. See section 4.2 of the SmPC.

Distribution

The *in vitro* plasma protein binding of dabrafenib and its metabolites in human plasma was high and not concentration dependent. The suggested SmPC text in section 5.2 regarding distribution is considered adequate.

Based on available non-clinical data, minimal penetration to the brain is expected across the intact blood brain barrier.

Elimination

When interpreting the results of the radio-labelled mass-balance study, it should be kept in mind that due to auto-induction, single-dose data may not be fully representative of steady state. However, the major metabolites were also analysed in plasma in the paediatric studies, so in terms of plasma exposure, metabolite exposure at steady state may be considered sufficiently evaluated.

Dabrafenib has three metabolites. Carboxy-dabrafenib is a major metabolite, and hydroxy- and desmethyl-dabrafenib are active metabolites that were attributed less than 10% of the radioactive dose in the single dose mass balance study. Please refer to the target population below for metabolite ratios in the target population.

The SmPC text in section 5.2 regarding elimination and biotransformation is generally considered acceptable.

A study with the CYP2C8 inhibitor gemfibrozil is available, which could correspond to poor metabolisers. Strong inhibitors of CYP2C8 are not recommended but should be used with caution in case of co-administration as per section 4.5 of the SmPC.

There was no clear dose dependency in metabolic ratios for dabrafenib major metabolites, except for carboxy-dabrafenib, which increased MR with dose.

Auto-induction of dabrafenib has been observed, resulting in decreased exposure at steady-state. The proposed SmPC text is acceptable.

Target population

Diverse formulations were used during the paediatric development programme; in addition to the dabrafenib HPMC capsules, two different oral solutions were used in the clinical studies, i.e. dabrafenib 10 mg DT (G2201, X2101 [only one patients received DT in the latter]) and 150 mg powder in stick-

packs (A2102, X2101). Across the clinical studies in the popPK dataset, capsules were primarily used in the oldest patients (94% [99/105] of patients 12-17 years), but also in the age group 6-11 years a relatively larger proportion (57% [44/77]) received capsules instead of the liquid formulations. Liquid formulations were administered as DT and stick packs in ~38% (23/61) and 52% (32/61), respectively, of patients <1-5 years. Overall, across all studies and age groups, 61% (149/243), 21% (51/243) and 18% (43/243) of patients received capsules, stick packs and DT, respectively. In the pivotal study G2201, 22 (22/24, 92%), 16 (16/34, 47%) and 4 (4/53, 8%) patients in age groups 1-5, 6-11, and 12-18 years, respectively, were administered the DT formulation.

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.

Uncertainties were identified regarding the efficacy using the proposed dose and applied DT formulation in paediatric glioma patients. Most of the studied children from 6 years of age were administered the solid dabrafenib formulation. The dabrafenib liquid formulation applied for has a lower Cmax and AUC than the solid formulation, based on the single dose study G2101. This implies that the studied dose in these older/heavier children would result in a lower exposure when using the liquid formulation, putting them at risk of lack of efficacy. The adequacy of the posology using the liquid formulation of dabrafenib has been ensured by requesting additional analyses which entailed a comparison of NCA PK data by formulation and PK bridging using popPK.

The applicant derived a target exposure range based on the observed dabrafenib exposure (Cavg,ss) from study G2201 where efficacy in paediatric patients have been established, which ranged from 174 to 845 ng/mL (representing the corresponding 5^{th} and 95^{th} percentiles of observed data calculated by non-compartmental analysis). The Applicant used popPK model simulations to justify the proposed posology. Importantly, the liquid formulation has lower bioavailability based on single dose data in adults (Study G2101) and it is important to demonstrate that the posology delivers exposure within the target exposure range in the respective bodyweight groups. The current simulations indicate that the proposed posology using the liquid formulation achieves adequate exposure across a relevant body weight range. The simulated exposure, represented by the 90% prediction interval, falls within the target exposure range for patients weighing >17kg. Below ~17 kg, the lower end of the 90% prediction interval of the simulations is below the target exposure range, however, the median of the simulations (black dashed line) is still within the target exposure range. The simulations show that the exposure following the recommended posology is overall reasonable across different body weights.

According to the Applicant, the proposed dose of 2.5 mg/kg BID represents an intermediate of the two clinically tested dose levels (2.25 and 2.625 mg/kg BID for patients ≥12-18y and 1-<12y, respectively, in study G2201). In reality, due to inherent limitations with the 10 mg strength DT to accommodate a weight-based posology, the proposed dose in patients below 12 years nevertheless (nearly) reflect the doses actually used in the pivotal study, which is reassuring. However, PK data from paediatric studies indicate a slightly lower exposure in patients aged 1-2 years, although no conclusion can be drawn due to small subgroups. With the proposed posology and based on current

simulations, it appears that low body weight patients will receive a somewhat lower exposure compared to patients with higher body weight which could be considered overall acceptable.

The applicant provided a comparison of steady state parameters calculated by NCA for the age group 6-11 years, where PK was available from a meaningful number of subjects. In contrast to the single dose study in adults (Study G2101), a similar mean Cmax was observed between formulations and slightly higher mean AUC and Cavg of the liquid formulation compared to the capsules. The variability was however high for all parameters. The observed steady state PK from 6-11 year old patients from study G2201 suggests a greater degree of similarity for the solid and liquid formulation than one might predict based on the findings from single dose relative-bioavailability study in adult healthy volunteers (G2101). Apart from comparisons of observed data, formulation was not identified a clinically relevant covariate based on the PopPK covariate analysis. The autoinduction of dabrafenib is possibly one of the causes of the higher similarity between formulations at steady-state.

Taken together, the popPK covariate analysis, simulations and comparisons of steady-state PK parameters supports that the difference in AUC between the solid and liquid formulations is less pronounced at steady-state than in the single dose study G2101 and that the proposed posology with the liquid formulation of dabrafenib results in exposures within the range of observed exposure in study G2201 where efficacy and safety have been established.

Metabolites are not included in the popPK, thus the assessment must be based on NCA parameters, with the uncertainties named above about pooling of formulations.

The applicant considers metabolite-to-parent AUC ratios to be similar between paediatrics and adults at steady-state. For the active metabolites hydroxy- and desmethyl-dabrafenib, MR for the lowest age range <2 years overlapped with those of patients 2 to 17 years. For the largest metabolite, carboxy-dabrafenib, the MR is not only higher, but also the range for <2y not included in the 2 to 17y range. This is strongly driven by the MR in one of the patients (106.56).

The applicant referred to exposure-response investigations in adult patients with melanoma which determined that the parent drug dabrafenib was an appropriate surrogate for the total exposure of active components. Since the MR for hydroxy- and desmethyl-dabrafenib across the age ranges are similar, it is acceptable that the pivotal popPK analyses regarding the adequacy of the dose for each age/BW range are made with the parent substance.

The less active but predominant metabolite carboxy-dabrafenib had increased AUC ratios compared to studies in adults. This applied to all age ranges and was additionally increasing with dose. The applicant did not consider that the contribution of carboxy-dabrafenib to efficacy should be revisited, based on the 25.5 lower pharmacologic activity. Regarding safety, the applicant referred to the general good tolerability of dabrafenib and in particular the lack of grade 3 AE in the patient with the highest carboxy-dabrafenib MR. Carboxy-dabrafenib is the largest dabrafenib related molecule in plasma, and despite the 1.6 increase in MR, as efficacy and safety have been investigated in the 1-17y age range, data provided do not raise major concerns at this point in time.

Special populations

Renal excretion appears to be a minor route of elimination for the active moiety. Mild to moderate renal impairment is therefore not expected to significantly affect pharmacokinetics of active moiety. Severe renal impairment or end-stage renal disease might also affect metabolism and transport and could therefore have a larger than expected effect on dabrafenib active moiety. The Applicant suggests a warning in the SmPC section 4.2 that no data are available and that dabrafenib should be used in caution in patients with severe renal impairment. This is considered adequate.

A population pharmacokinetic analysis in adult patients indicates that mildly elevated bilirubin and/or AST levels (based on National Cancer Institute [NCI] classification) do not significantly affect dabrafenib oral clearance. In addition, mild hepatic impairment as defined by bilirubin and AST did not have a significant effect on dabrafenib metabolite plasma concentrations. No data are available in patients with moderate to severe hepatic impairment and the potential need for dose adjustment cannot be determined. As hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites, administration of dabrafenib should be undertaken with caution in patients with moderate to severe hepatic impairment.

Exposure changes in special populations are well described. The SmPC claims for special populations are generally agreed.

The covariate analysis of sex as a covariate in paediatric patients appears overall reasonable. The claims in SmPC section 5.2 are agreed.

The posology in children has been adapted to their bodyweight.

Pharmacokinetic interaction studies

Dabrafenib has a potential for drug-drug interactions, both as a victim and as a perpetrator. In this MAA, information on DDI potential obtained for dabrafenib in adult subjects using the solid formulation are extrapolated to the paediatric population and the new formulation. The data used for the cutoffs was taken from the adult program. As concentrations *in vivo* are in a similar range, this is generally acceptable. Carboxy-dabrafenib concentrations are higher in paediatric patients, but as there were no in vitro signals detected at > 100 µM (Table 12), which is much higher than the adult cutoff (0.112 µM) and what the paediatric cutoff would be, there are no new concern relevant to the paediatric population.

The in vitro and *in vivo* studies were adequately designed and performed and their conduct were acceptable.

Study BRF113771 showed that a strong CYP3A4 inhibitor (ketoconazole) inhibits dabrafenib metabolism. The study also showed that a strong CYP2C8 inhibitor (gemfibrozil) inhibits dabrafenib metabolism leading to increased exposure. An inducing effect of dabrafenib on warfarin, a CYP2C9 substrate was shown. This strengthens the picture that dabrafenib is an inducer both via PXR and CAR pathways.

In study A2103, a modest decrease of the steady-state exposure of both dabrafenib and one of its active metabolites was observed when co-administered with the strong inducer rifampicin. The modest net effect despite that dabrafenib is a known substrate of CYP3A4 may be due to the inducing properties of dabrafenib itself. The induction caused by dabrafenib itself does not however appear to maximize CYP activity, as further induction of rifampicin is observed. Given the high variability in exposure (CV in AUC 40-50%), a cautious recommendation to avoid strong inducers is proposed and agreed.

The pH increasing agent rabeprazole appears to have no relevant effect on the bioavailability of dabrafenib solid formulation.

In study A2104, an increase in rosuvastatin Cmax both after single and multiple doses of dabrafenib indicates increased rate of absorption when dabrafenib is added, but limited effect on overall exposure. It can probably also be concluded that the net effect of dabrafenib on both OATPs and BCRP should be inhibition rather than induction, and that the increase in Cmax is unlikely to be clinically relevant.

The midazolam data indicates that dabrafenib is a moderate inducer of CYP3A4, and no direct CYP3A4 inhibition was seen in after a single dose.

The interaction potential of dabrafenib and its metabolites is generally well characterised and adequately reflected in the SmPC.

Table 18. DDI summary for dabrafenib & metabolites: in vitro & *in vivo* (in vitro not described if *in vivo* available)

Enzyme/ transporter	Perpetrator	Victim	Consequence
CYP1A2	No inhibition, no induction	No	-
CYP2A6	No inhibition	-	-
CYP2B6	No inhibition, induction in vitro	No	Caution for sensitive substrates (induction)
CYP2C8	No inhibition Induction likely	Substrate (dabrafenib only) Dabrafenib AUCR 1.47 with gemfibrozil	Caution with strong inhibitors, Caution for sensitive substrates (induction)
CYP2C9	No inhibition Induction Warfarin AUCR 0.63	No	Caution for sensitive substrates (induction)
CYP2C19	No inhibition Induction likely	No	Caution for sensitive substrates (induction)
CYP2D6	No inhibition	No	-
CYP3A4	No inhibition (*in vivo*) Moderate induction Midazolam AUCR 0.35	Substrate (all except carboxy-dabrafenib) Auto-induction Dabrafenib AUCR 1.71 with ketoconazole Dabrafenib AUCR 0.66 with rifampicin	Caution with strong inhibitors, strong inducers contraindicated Caution for sensitive substrates (induction)
PgP	No systemic inhibition, inconclusive in intestine Induction likely	Dabrafenib, hydroxy- and desmethyl-dabrafenib are substrates, not carboxy-dabrafenib Dabrafenib AUCR 1.71 with ketoconazole	Substrate: discussion on clinical relevance required Caution for sensitive substrates (induction)
BCRP	Weak inhibition Rosuvastatin AUCR* up to	Dabrafenib, hydroxy- and desmethyl-dabrafenib are	Inhibition not considered clinically relevant

	1.22 (d1), CmaxR up to 2.56 (d14)	substrates, not carboxy-dabrafenib	Substrate: discussion on clinical relevance required
OATP1B1	Weak inhibition Rosuvastatin AUCR* up to 1.22 (d1), CmaxR up to 2.56 (d14)	Not a substrate, except carboxy-dabrafenib	Inhibition not considered clinically relevant Substrate: no clinical relevance expected
OATP1B3	Weak inhibition Rosuvastatin AUCR* up to 1.22 (d1), CmaxR up to 2.56 (d14)	Not a substrate, except carboxy-dabrafenib	Inhibition not considered clinically relevant
OATP1A2	NA	Not a substrate, except carboxy-dabrafenib	-
OAT1	No inhibition	-	-
OAT3	No inhibition	-	-
OCT2	No inhibition	Not a substrate, except carboxy-dabrafenib	-
pH		Rabeprazole AUCR 1.03	None

* Inhibition of rosuvastatin *in vivo*, however inhibition of BCRP and OATP1B3 was over the cutoff in vitro, and close to the cutoff for OATP1B1.

The liquid formulation of trametinib contains Captisol as a solubilising agent and therefore has theoretical potential for interactions with other drugs, including dabrafenib. 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 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. However, 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 profile of dabrafenib is generally well-described and it is considered acceptable.

As recommendation post approval the CHMP considers the request of the following measures 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 pediatric 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 Tumors

Methods

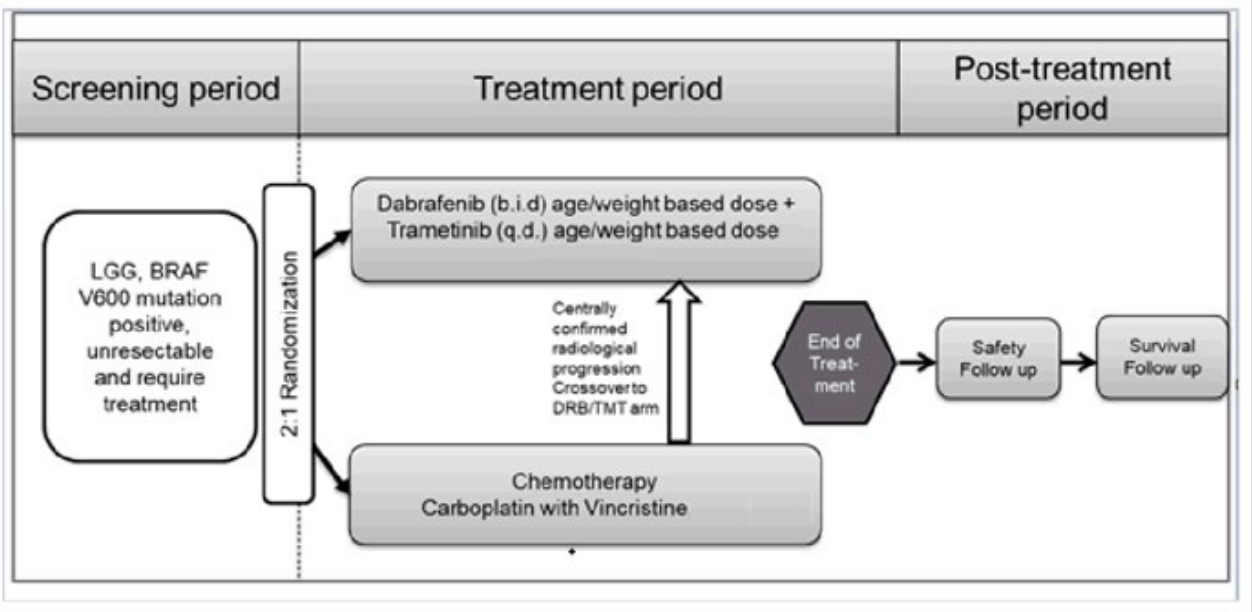
The pivotal study CDRB436G2201 (hereafter referred to as study G2201) combined two paediatric glioma cohorts into a single multi-centre, open-label, phase II study. Patients were enrolled at 58 centers across 20 countries.

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).

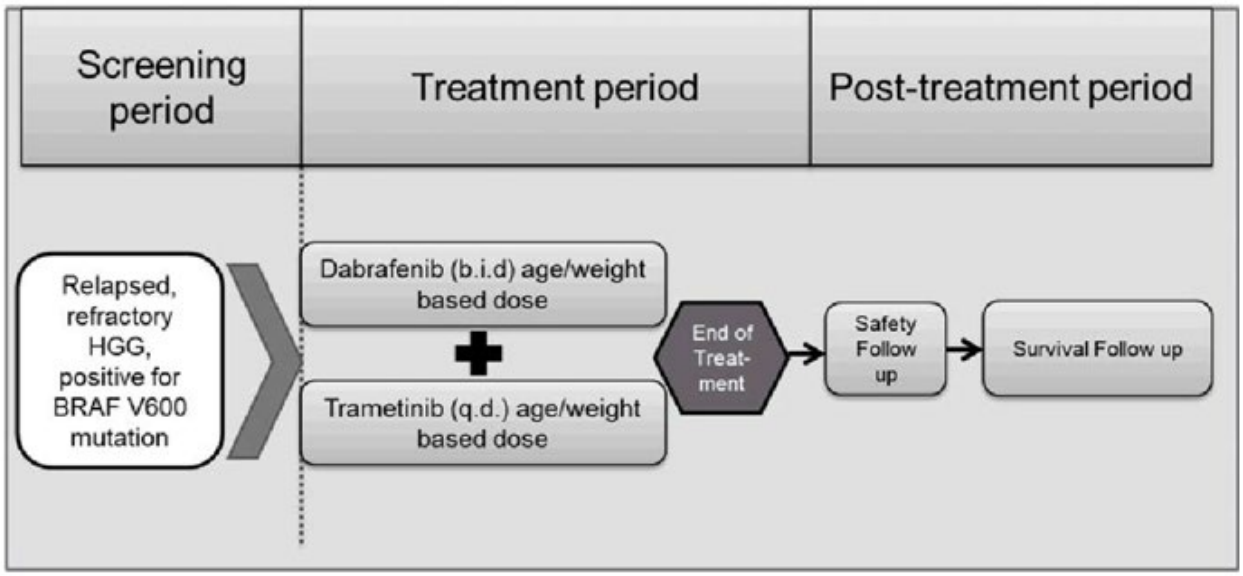
- The LGG cohort was a 2:1 randomized comparison of dabrafenib with trametinib (D+T) versus chemotherapy carboplatin and vincristine (C+V) in chemotherapy naïve LGG patients.
- The HGG cohort had a single arm that evaluated the effect of dabrafenib with trametinib (D+T) in relapsed or refractory HGG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

Figure 7. Study design for a) LGG cohort, and b) HGG cohort.

a) Study design for LGG cohort



b) Study design for 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 enrollment.
- 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 randomized 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 wase 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 randomized 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 randomized 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 alpha 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 randomized 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 randomized to the control arm who did not receive randomized treatment due to patient/guardian or physician decision.

- **Statistical methods**

The data for the HGG and LGG cohorts were analyzed 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 analyzed according to the treatment they had been assigned to during the randomization procedure. This population was the primary population for efficacy analyses.

Safety set (Safety set-L) included all patients who received at least one dose of any component of the study treatment. Patients were analyzed according to the study treatment they actually received,

where treatment received was defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

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

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

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 tumor assessment data. Only tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) was considered in the assessment of BOR.

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 summarized using descriptive statistics (N, %) by treatment arm along with two-sided exact binomial 95% CIs (Clopper and Pearson 1934). The odds ratio (dabrafenib + trametinib vs carboplatin + vincristine) and its 95% CI were determined by logistic regression.

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 characterized by the following attributes:

- Population: all subjects randomized 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 randomized 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, tumor assessment data collected after discontinuation of study treatment for any reason will be used to derive BOR. This includes subjects who were randomized but not treated.
Start of new anti-neoplastic therapy	Per while on treatment strategy, tumor assessments collected before start of new anti-neoplastic therapy will be used to derive BOR. Tumor 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 tumor 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 tumor 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 tumor 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 19. 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 summarized separately for each of the study treatment components, using the duration of exposure of each of the components. DI and RDI were summarized 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 summarized 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 tumor assessment at baseline, a follow-up tumor assessment at least 8 weeks after starting treatment (unless disease progression was observed before that time) or had discontinued for any reason. An adequate tumor assessment at baseline refers to baseline measurable disease assessed by the investigator and confirmed by central independent reviewer per RANO criteria. The Evaluable set was used for sensitivity analyses.

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 tumor assessment data. Only tumor assessments performed before the start of any further antineoplastic therapy (i.e., any additional secondary antineoplastic therapy or surgery) was considered in the assessment of BOR.

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 20. Handling of Intercurrent events of primary estimand for HGG cohort

Intercurrent events	Strategy
Discontinuation of study treatment for any reason	Per treatment policy strategy, tumor 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, tumor assessments collected before start of new anti-neoplastic therapy were used to derive BOR. Tumor 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 tumor assessment, all post-baseline overall lesion responses were expected to be 'Unknown'. If no valid post-baseline tumor 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 ≤ 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. Enrollment continued into the HGG cohort of the study. This futility analysis had no impact on the LGG cohort of this trial, which also continued enrollment. 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 randomized 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 randomized 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 randomized 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 analyzed where both intercurrent events are treated according to treatment policy strategy.

Results

- **Participant flow**

LGG cohort

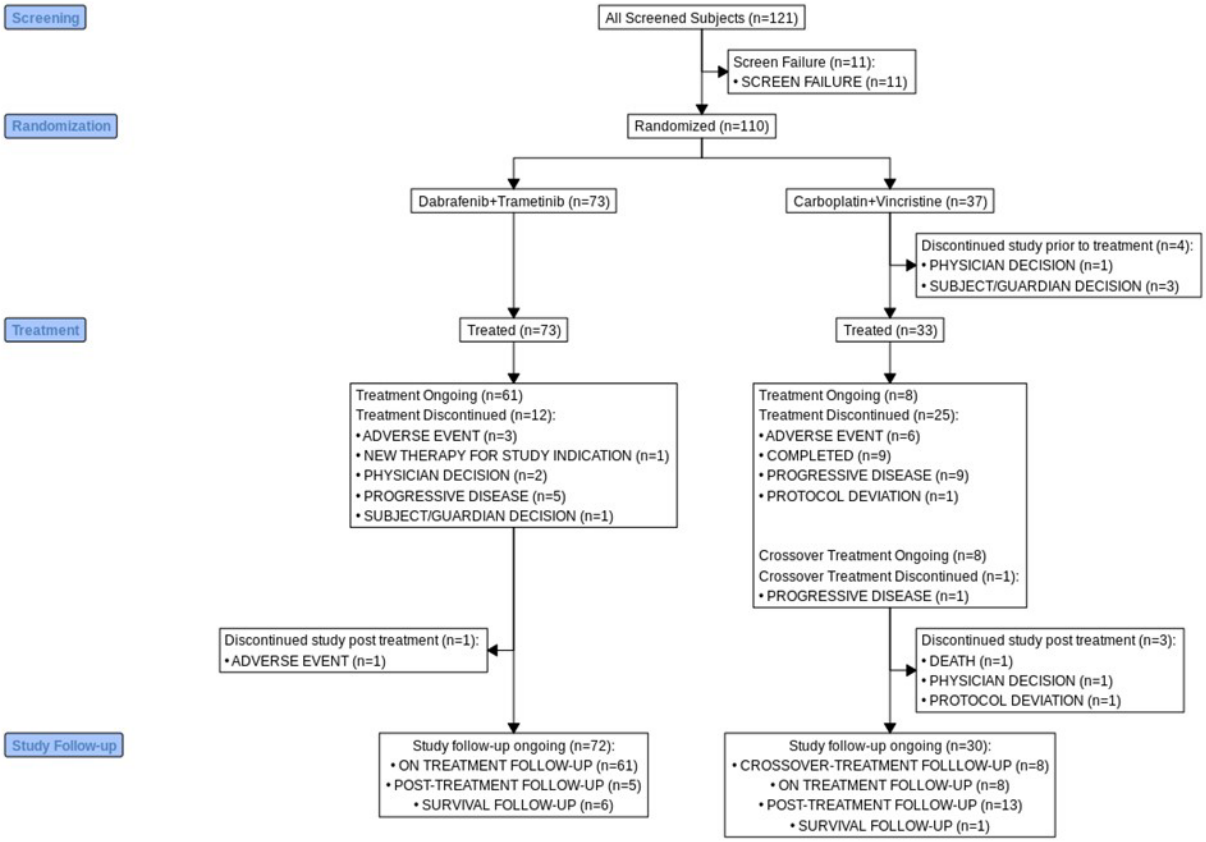
Table 21. Patient disposition in the LGG cohort

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

[1]Ongoing in randomized phase at the time of the DCO date 23-Aug-2021.
[2]Detailed narratives for patients who discontinued due to AEs are provided in Section 14.3.3.
[3]Two patients in the D+T am 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).
[4]One patient in the D+T arm discontinued as the patient had radiotherapy (Listing 16.2.4-4.4L).
[5]One 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.
[6]One 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 8. 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).

HGG cohort

Table 22. Patient disposition in the HGG cohort

	All patients N = 41 n (%)
Patients treated	41 (100)
Treatment ongoing[1]	21 (51.2)
No RANO progressive disease	19 (46.3)
Continuing post progressive disease	2 (4.9)
Discontinued treatment	20 (48.8)
Reason for discontinuation	
Progressive disease	16 (39.0)
Death	2 (4.9)
Adverse event[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)

[1]Ongoing at the time of the 23-Aug-2021 DCO date.
[2] Detailed narratives for patients who discontinue due to AEs are provided in Section 14.3.3.
[3]The 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 tumor assessment) or had discontinued earlier.

Study centers:

The pivotal study G2201 was conducted in 58 centers 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 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 23. 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 24. Disease characteristics in the LGG cohort

Disease history	D + T N=73	C + V N=37	All patients N=110
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 25. 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 26. 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)

[1]Local 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 27. 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+SD[5])	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.
[1]The exact binomial 95% CI (Clopper and Pearson 1934).
[2]Odds ratio (D+T vs C+V) and 95% confidence interval are from a logistic regression with treatment as the only covariate. Odds ratio > 1 favors D+T.
[3]The p-value is computed from chi-square test (Mantel-Haenszel) at a one-sided 2.5% level of significance
[4]SD: Response SD for 16 weeks or longer is recorded at 15 weeks or later (i.e ≥ 105 days) from randomization date.
[5]SD: Response SD for 24 weeks or longer is recorded at 23 weeks or later (i.e ≥ 161 days) from randomization date.

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 randomized 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 28. 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)

[1]The exact binomial 95% CI (Clopper and Pearson 1934).
[2]Odds 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 9. Kaplan-Meier plot of PFS based on independent review and using RANO criteria (FAS-L)

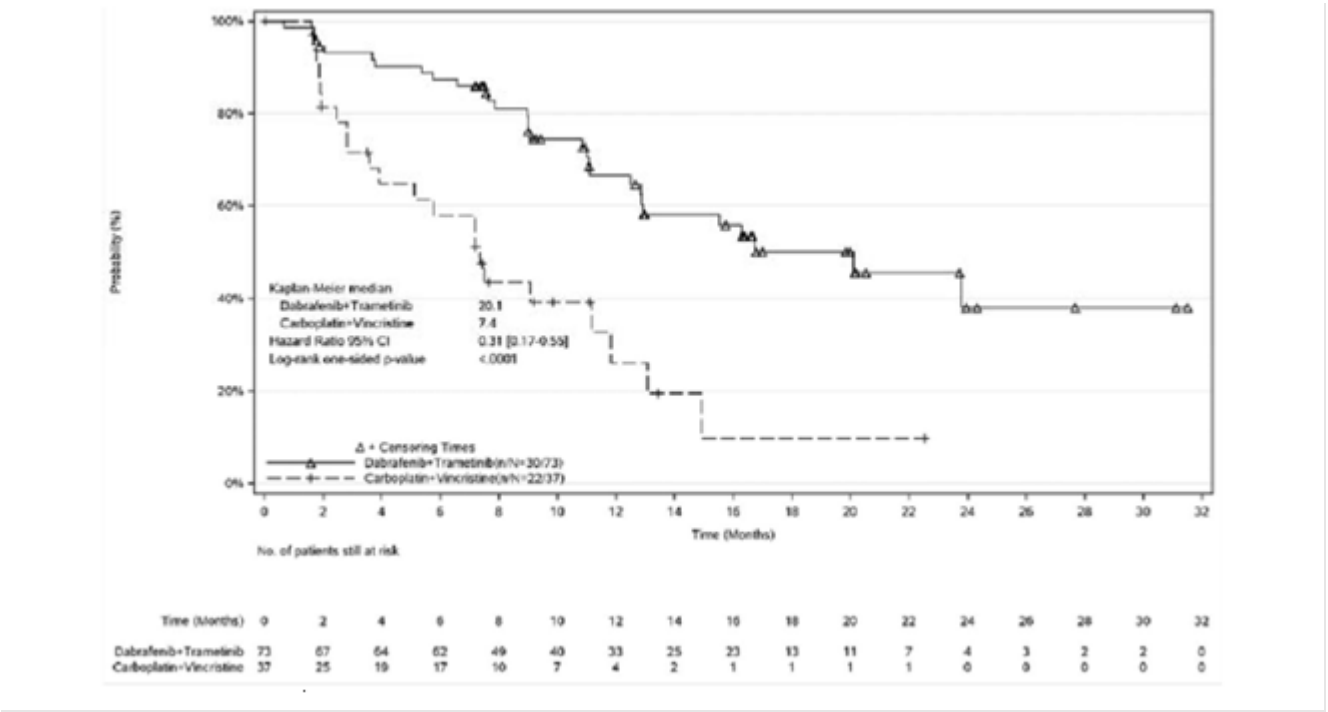


Table32. Reasons for censoring in the PFS analysis based on Independent review

Reason of censoring	Dabrafenib+Trametinib N=73 n (%)	Carboplatin+Vincristine N=37 n (%)
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**

Table33. 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.
[1]SD: Response SD for 16 weeks or longer is recorded at 15 weeks or later (i.e. ≥ 105 days) from treatment start date.
[2]SD: Response SD for 24 weeks or longer is recorded at 23 weeks or later (i.e. ≥ 161 days) from treatment start date.
The exact binomial 95% CI/80% CI (Clopper and Pearson 1934) is presented.

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.

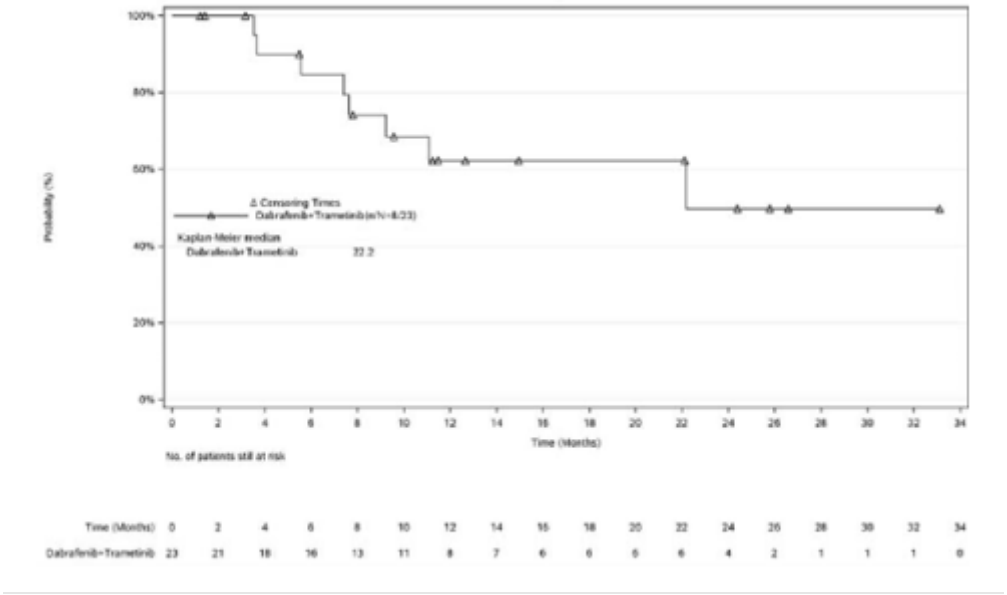
Table 29. Supportive analyses of ORR

	D+T	
	N (%)	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)

[1]The 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 10: KM plot of DOR per Independent review (FAS-H).

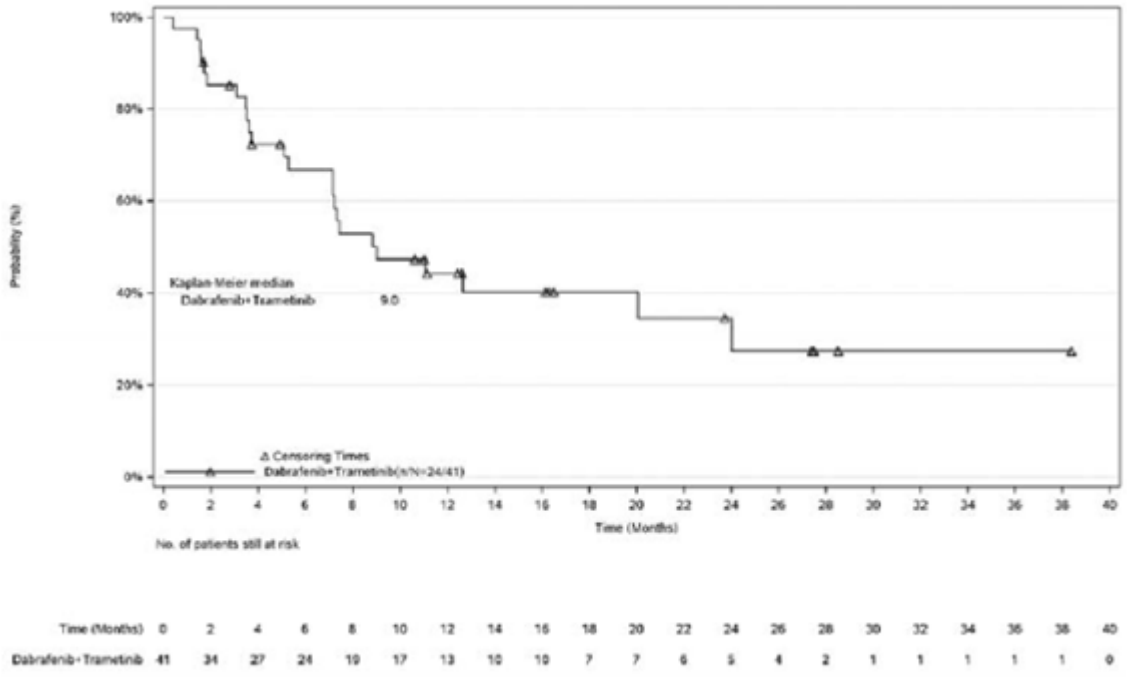


The CBR was 65.9% (95% CI: 49.4, 79.9) per Independent review.

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 11: 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**

Table 30. Summary of efficacy for study G2201, LGG cohort

<table>
<tr><td colspan="3"><u>Title:</u> 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)</td></tr>
<tr><td>Study identifier</td><td colspan="2">CDRB436G2201
EudraCT number 2015-004015-20
www.clinicaltrials.gov NCT02684058</td></tr>
<tr><td rowspan="4">Design</td><td colspan="2">LGG cohort; randomized, open-label, phase II, cross-over, multi-center

First patient first visit 28-Dec-2017, the study is currently ongoing.</td></tr>
<tr><td>Duration of main phase:</td><td>Dabrafenib + trametinib (D+T) arm; administered orally, daily, treatment continued until progression, unacceptable toxicity, or loss of clinical benefit as determined by the Investigator.

Carboplatin + vincristine (C+V) arm; 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.</td></tr>
<tr><td>Duration of Run-in phase:</td><td>NA.</td></tr>
<tr><td>Duration of Extension phase:</td><td>D+T arm; treatment continued indefinitely as appropriate, as outlined above.

C+V arm; the maximum total planned duration of treatment was 60 weeks.</td></tr>
<tr><td>Hypothesis</td><td colspan="2">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 ORRt is the ORR in the D+T arm, and ORRc is the ORR in the C+V arm.</td></tr>
</table>

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	*Effect estimate per comparison*

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) (95% CI)	46.6% (34) (34.8, 58.6)	10.8% (4) (3.0, 25.4)	Odds ratio 7.19 (95% CI: 2.3, 22.4) 1-sided p <0.001
	Median PFS (months) (95% CI)	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
	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 31. 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-center First patient first visit 28-Dec-2017, the study is currently ongoing.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	*Dabrafenib + trametinib (D+T)*; administered orally, daily, treatment continued until progression, unacceptable toxicity, or loss of clinical benefit as determined by the Investigator. NA. *D+T arm;* 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) (95% CI)	56.1% (23) (39.7, 71.5)	-
	Median DOR (months) (95% CI)	22.2 (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 (Navigate BioPharma, a Novartis subsidiary, Carlsbad, CA) 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 32. Overview of supportive studies for LGG and HGG cohort

	Supportive studies	
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 A2102, 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 33. 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 program (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 program, 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 program 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 tumors. 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.

Further, in SmPC section 4.2 it is stated that dose modifications are necessary for only one of the two products in case of a number of AEs that are primarily related to either dabrafenib or trametinib. 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 have 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 utilized 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 randomized 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., tumor 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 analyzed 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 randomized 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 randomized 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 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 shorter 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 start of 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 clarifies 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 tumor assessment in case of following: absence of event, the event occurred after a new anticancer therapy, or the event occurred after two or more missing tumor 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 where events that occurred after a new anticancer therapy, or after two or more missing tumor 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 favor 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 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/Recommended conditions for marketing authorisation and product information in case of a positive opinion.

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 as post approval recommendation, which will include the final analysis of the HGG cohort, including analyses of DoR, PFS and OS. However, PFS and OS are time dependent endpoints that do not isolate drug effects in a single-arm trial, and therefore are not presented in the SmPC section 5.1.

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 fact that 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 randomized 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.

As recommendation post approval the CHMP expects the final data delivery from pivotal study G2201, LGG and HGG cohorts. Due to early data cut-off the applicant is requested to provide updated survival data.

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 34. 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 35. 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 program 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 program 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

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.

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.

2.6.8.2.1. LGG cohort

Table 36. 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 37. Adverse events by system organ class – LGG cohort (Study No. CDRB436G2201)

	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33		Dabrafenib+Trametinib vs Carboplatin+Vincristine Risk Difference (95% CI)	
Primary system organ class	**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.

2.6.8.2.2. HGG cohort

Table 38. 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 39. 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.

2.6.8.2.3. 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 (≥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.

AEs by PT

2.6.8.2.4. LGG cohort

Table 40. abbreviated by the rapporteur. Adverse events (>10% in any treatment arm) by preferred term - LGG cohort

	D +T N=73		C + V N=33		D +T vs. C + V Risk difference	
Preferred term	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]

2.6.8.2.5. HGG cohort

Table 41. Adverse events (>10%) by preferred term - HGG cohort

	All patients N=41	
	All grades	Grade ≥ 3
Preferred term	n (%)	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.

2.6.8.2.6. 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.

2.6.8.2.7. AEs 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 SOCs). 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 mucolo-papular 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 AEs

2.6.8.2.8. 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 ≥20% in the D+T arm compared to the C+V arm (12.1%).

2.6.8.2.9. 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 ≥3AEs. The most frequently reported AEs (≥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.

2.6.8.2.10. 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 AEs

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.

AEs leading to dose modification and dose interruption

2.6.8.2.11. 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 ≥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 $\geq$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.

2.6.8.2.12. 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 ≥ 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.

2.6.8.2.13. 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.

AESI

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 program 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.

2.6.8.2.14. LGG cohort

Table 42. Overview of AESIs - LGG cohort

	D+T N=73		C+V N=33	
Safety topics	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).

2.6.8.2.15. HGG cohort

Table 43. Overview of AESIs - HGG cohort

	All patients N=41	
Safety topic	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.

2.6.8.2.16. 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

2.6.8.2.17. 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.

2.6.8.2.18. 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.

2.6.8.2.19. 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

2.6.8.3.1. LGG cohort

Table 44. abbreviated by the rapporteur. Serious adverse events by preferred term – LGG cohort (Study No. CDRB436G2201)

	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33		Dabrafenib+Trametinib vs Carboplatin+Vincristine Risk Difference (95% CI)	
Preferred term	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.

2.6.8.3.2. HGG cohort

Table 45. abbreviated by the rapporteur. Serious adverse events by preferred term - HGG cohort (Study No. CDRB436G2201)

	All subjects N=41	
Preferred term	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 ≥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.

2.6.8.3.3. 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 grad 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 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 hade treatment related AESIs. None were considered grade $\geq$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. Non were grade $\geq$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

2.6.8.7.1. LGG cohort

Table 46. Adverse events leading to discontinuation of study treatment by preferred term - LGG cohort (Study No. CDRB436G2201)

	D +T N=73		C + V N=33		D +T vs C + V Risk difference	
Preferred term	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.

2.6.8.7.2. HGG cohort

Table 47. Adverse events leading to discontinuation of study treatment by preferred term - HGG cohort (Study No. CDRB436G2201)

	All patients N=41	
Preferred term	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.

2.6.8.7.3. 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.

2.6.8.8.1. 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 48. 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**

2.6.8.8.2. 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 49. 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. ADR summary as included in the SmPC

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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥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 50. Adverse reactions reported in the integrated paediatric safety population of dabrafenib in combination with trametinib (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 erythrodysaesthesia 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 dabrafenib in combination with trametinib 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, have occurred in adult patients taking dabrafenib in combination with trametinib.

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.

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.

Patients with LVEF lower than the institutional lower limit of normal were not included in clinical studies with dabrafenib. Dabrafenib in combination with trametinib should be used with caution in patients with conditions that could impair left ventricular function.

Pyrexia

Fever has been reported in clinical studies with dabrafenib in combination with trametinib (see section 4.4). Pyrexia was reported in 65% of paediatric patients, with Grade 3 events occurring in 8.8% of patients. Approximately half of the first occurrences of pyrexia in adult patients happened within the first month of therapy and approximately one-third of the patients had 3 or more events. In 1% of patients receiving dabrafenib as monotherapy in the integrated adult safety population, serious non-infectious febrile events were identified as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency of pre-renal origin in patients with normal baseline renal function. The onset of these serious non-infectious febrile events was typically within the first month of therapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care.

Hepatic events

Hepatic adverse reactions have been reported in adult and paediatric clinical studies with dabrafenib in combination with trametinib. In the paediatric safety population, increased ALT and AST were very common, reported in 12.3% and 15.2% of patients, respectively. Please refer to the trametinib powder for oral solution SmPC for additional information.

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.

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

Arthralgia

Arthralgia was reported very commonly in the integrated adult and paediatric safety populations of dabrafenib in combination with trametinib. In the paediatric safety population, arthralgia was reported in 12.3% of patients, with <1% of patients with Grade 3 severity. Arthralgia was reported in 25% of adult patients, although these were mainly Grade 1 and 2 in severity with Grade 3 occurring uncommonly (<1%).

Hypophosphataemia

Hypophosphataemia has been reported commonly in the integrated adult and paediatric safety populations of dabrafenib in combination with trametinib in 4% and 5.8% of patients, respectively. It should be noted that Grade 3 events occurred in 1% of adult patients. In paediatric patients, hypophosphataemia occurred only with Grade 1 and 2 severity.

Pancreatitis

Pancreatitis was reported in 1.2% of paediatric patients, with <1% of patients with Grade 3 severity. In clinical studies in adult patients, one pancreatitis event occurred on the first day of dabrafenib dosing of a metastatic melanoma patient and recurred following rechallenge at a reduced dose. 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 (see section 4.4).

Cutaneous malignancies

In the integrated adult safety population for dabrafenib in combination with trametinib, 2% of patients developed cuSCC with a median time to onset of 18 to 31 weeks. The median time to diagnosis of the first occurrence of cuSCC was 223 days (range 56 to 510 days). All adult patients who developed cuSCC or new primary melanoma continued on treatment without dose modification.

Non-cutaneous malignancies

Activation of MAP kinase signalling in BRAF wild-type cells which are exposed to BRAF inhibitors may lead to increased risk of non-cutaneous malignancies, including those with RAS mutations. Non-cutaneous malignancies were reported in <1% of patients in the integrated adult safety population of dabrafenib in combination with trametinib. Cases of RAS-driven malignancies have been seen with dabrafenib in combination with trametinib. Patients should be monitored as clinically appropriate.

Renal failure

Renal failure due to pyrexia-associated pre-renal azotaemia or granulomatous nephritis was uncommon in adult patients; however, dabrafenib has not been studied in patients with renal insufficiency (defined as creatinine >1.5 x ULN). Caution should be used in this setting.

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 characterize 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 characterize 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.

Final data from the pivotal study as well as from the expansion study CDRB436G2401 will be submitted once available and the applicant is requested to submit these data in the post approval setting.

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 SmPC section 4.8 for Finlee. 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 (≥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 (reflected in section 4.4 in 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 ≥38°C. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics 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 SmPCs section 4.4. and 4.8. Overall, no clinically meaningfully 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 Finlee. 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 $\geq$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.

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.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 51. Summary of safety concerns.

Important identified risks for dabrafenib (including combination therapy)	• Pre-renal and Intrinsic Renal failure • Uveitis • Severe Photosensitivity
Important potential risks for dabrafenib (including combination therapy)	• Non-specific cardiac toxicity • Testicular Toxicity • Developmental toxicity • Pregnancy and risks in breast feeding • Safety in patients <18 years of age (including potential adverse effects on skeletal maturation and sexual maturation)
Important potential risks related to dabrafenib+ trametinib combination therapy only	• Pulmonary embolism, deep vein thrombosis
Missing Information for dabrafenib	• None

2.7.2. Pharmacovigilance plan

Table 52. On-going 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				
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 53. Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified dabrafenib risks (also applicable to combination therapy)		
Pre-Renal and Intrinsic Renal Failure	**Routine risk minimization measures** Dose modifications in Section 4.2 of the SmPC Undesirable effects in Section 4.8 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Targeted follow-up checklist **Additional pharmacovigilance activities:** None
Uveitis	**Routine risk minimization measures** Dose modifications in Section 4.2 of the SmPC Undesirable effects in Section 4.8 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Severe Photosensitivity	**Routine risk minimization measures** Undesirable effects in Section 4.8 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Important potential dabrafenib risks (also applicable to combination therapy)		
Non-specific Cardiac Toxicity	**Routine risk minimization measures** None **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Testicular toxicity	**Routine risk minimization measures** Preclinical safety data in Section 5.3 of the SmPC **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** Preclinical safety data in Section 5.3 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Pregnancy and risks in breast feeding	**Routine risk minimization measures** Fertility, pregnancy and lactation in Section 4.6 of the SmPC **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 dabrafenib and trametinib combination therapy only		
Long-term safety in patients <18 year 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)
Pulmonary embolism, Deep vein thrombosis	**Routine risk minimization measures** Dose modifications in Section 4.2 of the SmPC Special warnings and precautions in Section 4.4 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Missing dabrafenib monotherapy information		
None		

2.7.4. Conclusion

The CHMP and PRAC considers that the risk management plan version 11.1 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

Based on a new population (paediatric), limited safety-database, new formulation and posology (weight-based), the CHMP is of the opinion that the already existing entry in the EURD list for dabrafenib needs to be amended as follows: the PSUR cycle for the medicinal product should follow a yearly cycle (now 3-year cycle). The data lock point should be aligned with that of trametinib (currently on a 1-year interval with previous DLP 2022-May-29 according to the EURD list).

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

Finlee in combination with trametinib 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

Finlee in combination with trametinib 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 pediatric 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 authorized 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, 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 a 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 randomized 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.

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.

Limited data is available for the youngest children in the HGG cohort, as only five patients (12.2%) were between 12 months and 6 years, and only two of these patients were aged 1-2 years.

General

According to the popPK dataset, in the pivotal study G2201, 42/111 patients received the final liquid formulation for dabrafenib, 69 received the solid formulation, predominantly patients 6-18 years, and 52/111 patients received the final liquid formulation for trametinib, 59 received the solid formulation. Most of the studied children from 6 years of age were administered the solid formulations. The dabrafenib and trametinib liquid formulations (dispersible tablets and powder for oral solution) which is the subject of the current procedure was therefore not studied extensively in the target population. The dabrafenib liquid formulation has a lower Cmax and AUC than the solid formulation according to a single dose study in adults. This implies that the studied dose in these older/higher weight children could result in a lower exposure when using the liquid formulation, putting them at risk of lack of efficacy. In addition, limited efficacy data are available for the age group 1-2 years. Nevertheless, the adequacy of the posology using the liquid formulation of dabrafenib has been ensured by additional analyses which entailed a comparison of NCA PK data by formulation and PK bridging using popPK. Taken together, the popPK covariate analyses, simulations and comparisons of steady-state PK parameters support that the difference in AUC is smaller at steady-state than in the single dose study G2101, and that the proposed posology with the liquid formulation of dabrafenib results in exposures within the range of observed exposure in study G2201 where efficacy and safety have been established.

3.4. Unfavourable effects

AEs

AEs occurring in ≥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 maculo-papular (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 weight increased is considered a new ADR in the paediatric population.

AEs occurring in ≥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 ≥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 ≥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.

The safety profile according to different formulations and different doses throughout the study is missing.

The exposure/response relation for adverse effects is unclear.

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 (requested as recommendation post approval) and long-term study G2401 (category 3 study in the RMP) will be provided once available.

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.

3.6. Effects Table

Table 54. 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.	
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 46 are from the initial application, not from the cleaned data set

Table 55. 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 ≥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 discont.	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 47 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, 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 randomized 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 post approval recommendation.

Limited data is 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.

3.7.2. Balance of benefits and risks

The demonstrated benefits in the final indications outweighs the risks.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of Finlee in combination with trametinib powder for oral solution is positive subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Finlee is favourable in the following indication(s):

Low-grade glioma

Finlee in combination with trametinib 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

Finlee in combination with trametinib 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 (PSURs)**

The requirements for submission of PSURs 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/0424/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.