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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Mekinist

trametinib

Procedure no: EMEA/H/C/002643/P46/014

Note

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

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List of abbreviations and definition of terms

AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BOR	Best overall response
BRAF/*BRAF*	B-Raf serine/threonine-protein kinase/proto-oncogene encoding B-Raf
CAP	CT of chest, abdomen and pelvis
Cavg	Average steady-state plasma concentration
CBR	Clinical benefit rate
CI	Confidence interval
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed concentration
CNS	Central nervous system
COVID-19	Severe acute respiratory syndrome coronavirus 2
CR	Complete response
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed tomography
C_T	(trough) concentration
CTC	Common terminology criteria
CTCAE	Common terminology criteria for adverse events
DI	Dose intensity
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DRB	Dabrafenib
ECG(s)	Electrocardiogram(s)
ECHO	Echocardiogram
eCRF	Electronic case report form
ERK	Extracellular signal-regulated kinase
GCP	Good clinical practice

GSK	GlaxoSmithKline
H&E	Hematoxylin and Eosin
HIV	Human Immunodeficiency Virus
HLGT	High level group term
HLT	High level term
HVA/VMA	Homovanillic Acid / Vanillylmandelic Acid
IA	Interim analysis
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International normalized ratio
IP	Investigational product
ka	Absorption rate constant
LCH	Langerhans Cell Histiocytosis
LGG	Low Grade Glioma
LVEF	Left Ventricular Ejection Fraction
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	MAPK/ERK kinase
MIBG	Meta-iodobenzylguanidine
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MTIME	Time when absorption rate changes
MUGA	Multiple-gated acquisition scan
NCI	National Cancer Institute
NF-1	Neurofibromatosis Type-1
NF-1 with PN	Neurofibromatosis Type-1 associated plexiform neurofibromas
NMQ	Novartis MedDRA queries
NR	Not reachable
ORR	Objective response rate
PD	Progressive disease
PK	Pharmacokinetics
PN	Plexiform neurofibroma
popPK	Population pharmacokinetic

PP	Polypropylene
PR	Partial response
PT	Preferred term
Q/F	Apparent intercompartmental clearance
RANO	Response Assessment in Neuro-Oncology
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAE	Serious adverse event
SD	Standard deviations
SMQ	Standardized MedDRA queries
SOC	System organ class
TBL	Total bilirubin
Tmax	Time of occurrence of Cmax
TMT	Trametinib
ULN	Upper limit of normal
Vc/F	Central volume of distribution
V/F	Volume of distribution

1. Introduction

On 15 June 2021, the MAH submitted a completed paediatric study for trametinib, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Study CTMT212X2101 is part of a paediatric clinical development program, and is a clinical measure in the trametinib PIP EMEA-001177-PIP01. The study completion data (LPLV) was 29-Dec-2020. No changes are proposed to the paediatric information of the current Mekinist Summary of Product Characteristics (SmPC).

2.2. Information on the pharmaceutical formulation used in the study

The study used both solid and liquid oral formulations. In addition, both monotherapy trametinib and the combination trametinib and dabrafenib were evaluated. The oral solid dose forms used were the approved adult formulations, dabrafenib 50 mg and 75 mg capsules and trametinib 0.5 mg and 2 mg tablets, for children who were able to swallow tablets/capsules. The oral liquid formulations used were dabrafenib 10 mg dispersible tablets for oral suspension, dabrafenib powder for oral suspension (150 mg) that was reconstituted with a specified volume of water at the time of use to form an oral suspension of 10 mg/mL dabrafenib, and trametinib powder for oral solution (0.05 mg/mL).

Throughout the study, starting dose was assigned based on patient weight. The dose levels selected for study were guided by adult dosing recommendations of 300 mg per day for dabrafenib and 2 mg per day for trametinib, considering the average adult weight as 80 kg.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study CTMT212X2101, hereafter referred to as Study X2101, a 4-part, Phase I/IIa, multicenter, open-label study in paediatric subjects with refractory or recurrent solid tumours likely to have mitogen-activated protein kinase (MAPK) pathway activation.

The Applicant has provided a CSR for Study X2101, below a summary of the most important methods and results of Study X2101 is provided.

2.3.2. Clinical study

Study X2101

Description

Study X2101 is a 4-part, Phase I/IIa, multicenter, open-label study in paediatric subjects with refractory or recurrent solid tumours likely to have MAPK pathway activation.

Methods

Objective(s)

The primary objective is shown in Table 1 and the secondary objectives are shown in Table 2.

Table 1 Primary objective and endpoints

Objective	Endpoint
To determine the safe and tolerable trametinib dose(s) for chronic dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures (C_T) to the recommended adult dose	Adverse events (AEs); ECG; ECHO; changes in laboratory values and vital signs. Steady state C_T of trametinib

Source: Appendix 16.1.1-Protocol Amendment 9-Table 2-1

Table 2 Secondary objectives and endpoints

Objective	Endpoint
To characterize the pharmacokinetics of trametinib	C_T (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F) Cmax, tmax and Cavg, as appropriate
To characterize the safety and tolerability of trametinib	AEs; ECG; changes in laboratory values and vital signs
To assess any preliminary anti-tumor activity of trametinib	Tumor response to trametinib as defined in Appendix 16.1.1-Protocol Amendment 9-Appendix 3-Appendix 7 assessed by investigator assessment.
To determine the effect of covariates such as age and weight on the pharmacokinetics of trametinib using a population pharmacokinetics approach	CL/F, volume of distribution (V/F), absorption rate (ka), and coefficients for significant covariates
To characterize the pharmacokinetics of trametinib and dabrafenib when administered in combination	C_T (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F) Cmax, tmax and Cavg of trametinib and dabrafenib when administered in combination, if the data permit
To characterize the safety and tolerability of trametinib and dabrafenib when administered in combination	Adverse events (AEs); ECG; ECHO; changes in laboratory values and vital signs.
To determine the safe and tolerable dabrafenib dose(s) when administered in combination with the recommended trametinib dose for chronic continuous daily dosing in pediatric subjects (infants, children and adolescents) that achieves similar exposures to the recommended adult dose	Adverse events (AEs); ECG; ECHO; changes in laboratory values and vital signs. Steady state C_T of trametinib; steady state AUC(0-12) of dabrafenib
To assess any preliminary anti-tumor activity of trametinib and dabrafenib when administered in combination	Tumor response to dabrafenib and trametinib combination as defined in Appendix 16.1.1-Protocol Amendment 9-Appendix 3–Appendix 7 by investigator assessment.
To determine the acceptability and palatability of trametinib and dabrafenib in pediatric subjects	Palatability questionnaire data

Study design

This study was a 4-part, Phase I/IIa, multi-center, open-label clinical study in paediatric subjects with refractory or recurrent solid tumours. Approximately 142 subjects were planned to be enrolled in the study (approximately 48 subjects in Part A, at least 40 subjects in Part B, approximately 24 subjects in Part C and at least 30 subjects in Part D).

- **Part A** was a repeat dose, dose escalation and expansion phase to evaluate safety, tolerability, and pharmacokinetics (PK) in three age ranges (1 month to < 2 years, 2 to ≤ 12 years, and > 12 years of age). The primary goal of Part A was to establish the toxicity profile, PK, and recommended Phase II dose (RP2D) of trametinib in each age cohort. All enrolled patients were to have a solid tumour with presumed MAPK pathway activation.
- **Part B** was an monotherapy disease cohort expansion phase to further evaluate the safety, tolerability, and preliminary clinical activity of trametinib in tumour-specific paediatric populations. Disease cohorts were selected based on understanding of molecular drivers of paediatric solid tumours and selecting those that were KNOWN to have frequent MAPK pathway activation. It was planned that 10 subjects were enrolled in each of the following 4 disease cohorts:
    - B1: Refractory or relapsed neuroblastoma
    - B2: Recurrent or unresectable low-grade glioma (LGG) with B-Raf serine/threonine-protein kinase (BRAF) tandem duplication with fusion (referred to in this CSR as glioma fusion)
    - B3: Neurofibromatosis Type -1 associated plexiform neurofibromas (NF-1 with PN) that are unresectable and medically significant
    - B4: BRAF V600 mutant tumours
- **Part C** was a limited dose escalation of the combination of trametinib along with dabrafenib in children and adolescents with recurrent, refractory, or unresectable BRAF V600 mutated tumours. This part of the study was planned to establish the RP2D of trametinib and dabrafenib when given in combination in children and adolescents.
- **Part D** was a tumour cohort expansion to further evaluate the safety, tolerability, and preliminary clinical activity of the combination of trametinib and dabrafenib in BRAF V600 mutant tumour-specific paediatric populations in children and adolescents with recurrent, refractory or unresectable BRAF V600 mutated tumours (LGG and Langerhans cell histiocytosis (LCH)).

Study population /Sample size

The key inclusion criteria were:

1. Written informed consent – a signed informed consent and/or assent (as age appropriate) for study participation including PK sampling was obtained according to institutional guidelines.

2. Male or female between 1 month and < 18 years of age (inclusive) at the time of signing the informed consent form (Part C and Part D between 12 months and < 18 years of age, inclusive; Part A extension between 1 month and < 6 years of age, inclusive; Part C extension between 12 months and < 6 years of age, inclusive).

3. Subjects had a disease that was relapsed/refractory to all potentially curative standard treatment regimens or had a current disease for which there was no known curative therapy, or therapy proven to prolong survival with an acceptable quality of life.

4. Prior therapy: The subject's disease (i.e. cancer, NF-1 with PN, or LCH) must had relapsed after or failed to respond to frontline curative therapy or there must not be other potentially curative treatment options available.

5. Performance score of ≥ 50% according to the Karnofsky/Lansky performance status scale.

There were also specific eligibility criteria per part of the study such as for Part A that patients had a histologically confirmed solid tumour, for Part B that patients had a histologically confirmed solid

tumour for the disease cohorts listed above, for Part C and Part D that tumours were documented to harbour BRAF V600 mutation at diagnosis or relapse and for part D that patients had recurrent or refractory BRAF V600 mutant LGG or LCH tumours.

The key exclusion criteria were:

1. Lactating or pregnant female.

2. History of another malignancy including resected non-melanomatous skin cancer.

3. Subjects with NF-1 associated optic pathway tumours were excluded if they are actively receiving therapy for the optic pathway tumour or did not met criteria for PN or malignant solid tumour

4. Subjects with a history of NF-1 related cerebral vascular anomaly (such as Moyamoya)

5. Subjects with NF-1 who actively received therapy for the optic pathway tumour

6. Subjects with NF-1 and only PN lesions (only applicable to Part B)

7. Part B, C and D: Previous treatment with dabrafenib or any BRAF inhibitor, trametinib or another MEK inhibitor, or an ERK inhibitor. Subjects who had received prior dabrafenib or another BRAF inhibitor enrolled into Part B4. Subjects who had prior dabrafenib or BRAF inhibitor therapy was enrolled in Part C or Part D if they had prior benefit to dabrafenib or BRAF inhibitor monotherapy, as determined by the investigator.

8. For subjects with solid tumours that were not primary CNS tumours or NF-1 associated plexiform neurofibromas, subjects with symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression were excluded.

Treatments

Trametinib was administered orally, once daily under fasted conditions (at least 1 hour before or 2 hours after a meal). Two different formulations of trametinib were in use in the study: tablets (0.125, 0.5, and 2 mg) were available for children who were able to reliably swallow tablets and powder for oral solution (0.05 mg/mL after reconstitution) was available to subjects who were not able to swallow tablets.

Dabrafenib was administered orally, twice daily under fasted conditions. Three different formulations of dabrafenib were in use in the study: capsules (50 mg and 75 mg) that were administered orally with approximately 1 ounce (30 mL) of water for every 10 pounds (4.5 kg) of body weight, powder for oral suspension (150 mg) that was reconstituted with a specified volume of water at the time of use to form an oral suspension of 10 mg/mL dabrafenib and dispersible tablets (10 mg) that were suspended in water and taken in entirety.

Outcomes/endpoints

The endpoints of this study are listed in Table 1 and Table 2.

(Statistical) Methods

<u>Determining the MTD/RP2D</u>

An open label, Phase I/II, dose escalation (3+3) design was chosen to determine the MTD/RP2D and was followed by dose expansion parts to further evaluate the safety and tolerability of the chosen doses. The following dose levels were planned for Part A; Dose Level 1 – 0.0125 mg/kg/day (equivalent to 50% of the approved adult dose), dose level 2- 0.025 mg/kg/day, dose level 3- 0.04

mg/kg/day (equivalent to adult MTD). Additional dose levels- protocol amendment to explore additional dose according to observed PK values relative to target concentrations

MTD was defined as the dose level below that which produced a DLT in two or more of the initial 3-6 subjects enrolled during cycle 1 of treatment.

RP2D was based on PK criteria (PK target dose), defined as achieving in children a steady state (Day 15) mean C_T of trametinib that is equivalent to a mean steady state (Day 15) C_T of 10 ng/mL trametinib observed in adults at the recommended dose of 2 mg once daily. During dose escalation, children were closely monitored for drug-related toxicity. If MTD was determined, the RP2D was defined by the MTD rather than by PK criteria. In the absence of an MTD, the RP2D was the PK target dose defined as the dose that meets the PK criteria for adequate exposure (Day 15 trametinib Ct $\geq$ 10 ng/mL in at least 80% of subjects in a cohort of at least 6 subjects (i.e. 5 out of 6 subjects) treated at that dose level.

- Part A extension was added as an amendment to test the intermediate trametinib dose level of 0.032 mg/kg/day in subjects under 6 years of age.
- Part B was to use the starting dose of trametinib as determined in Part A.
- The trametinib dose administered in Part C was based on the trametinib monotherapy RP2D from Part A (0.025 mg/kg/day).

The RP2D of monotherapy dabrafenib in children was established in a separate study ([CDRB436A2102] BRF116013): <12 years old subjects: 5.25 mg/kg/day dabrafenib administered orally, divided into two equal doses;≥ 12 years old subjects: 4.5 mg/kg/day dabrafenib administered orally, divided into two equal doses.

For the evaluation of combination therapy in this study, the starting dose of dabrafenib (dose level 1) was 50% of the established monotherapy RP2D, divided into two equal doses.

- Part C used the trametinib dose determined from Part A extension with 100% paediatric RP2D of dabrafenib in subjects under 6 years of age.
- The RP2D of the combination treatment determined in Part C (0.025 mg/kg/day trametinib and the full RP2D of dabrafenib) in subjects 6 years to < 18 years (which includes the adolescents) was used in Part D.

The target average plasma concentration of dabrafenib for efficacy was defined to be ~300 ng/mL, based on the adult population.

Analysis sets

All treated population- all subjects who received at least one dose of trametinib for Part A and Part B or at least one dose of any component of the combination for Part C and Part D.

Safety population - all subjects who received at least one dose of trametinib in Part A and Part B or at least one dose of any component of the combination in Part C and Part D.

Pharmacokinetic population -subjects fulfilling the 'All treated' population criteria and from whom a PK sample was obtained and analyzed and was evaluable.

DLT Evaluable Population -subjects participating in the dose determining portion of the study, fulfill the 'All treated' population criteria and received an adequate treatment in the first 28 days which enabled an appropriate evaluation of study treatment related to DLTs. Any subject in the 'All treated' population that experienced a DLT was included in the DLT evaluable population regardless of exposure.

Response Evaluable Population - subjects who fulfilled the 'All treated' population criteria with a pre-dose and at least one post-dose disease efficacy assessment (unless disease progression was observed before that time) or have discontinued for any reason.

Efficacy analysis

Objective response rate (ORR) was defined as the proportion of subjects with best overall response rate (BOR) with confirmation of CR or PR according to criteria for a specific disease type, among subjects with disease assessment at baseline. ORR was calculated based on the 'All treated' population using investigator assessment of tumour response data and will be based on confirmed responses.

The response assessment method for glioma patients was the RANO criteria, for neuroblastoma patients RECIST 1.1, the Curie scale and bone marrow assessment were used, for patients with NF-1 with PN, LCH, melanoma and other solid tumours RECIST 1.1 was used.

Results

Recruitment/ Number analysed

A total of 139 paediatric subjects were enrolled, 50 (36.0%) of whom were receiving benefit from treatment and subsequently enrolled in a separate rollover study, 1 subject died during post-treatment follow-up, and 88 subjects (63.3%) were withdrawn or discontinued. The primary reasons for study discontinuation were 'other' reasons (30 subjects, 21.6%) and adverse events (28 subjects, 20.1%).

Baseline data

The most important baseline data is shown in Table 3.

Table 3 Baseline data

Table 10-5 Demographics and baseline characteristics Part A and Part B (All treated population)

	Part A					Part B				
	TMT 0.0125 mg/kg/day N=3 n (%)	TMT 0.025 mg/kg/day N=19 n (%)	TMT 0.032 mg/kg/day N=12 n (%)	TMT 0.04 mg/kg/day N=16 n (%)	All Part A subjects N=50 n (%)	Neuro-blastoma N=11 n (%)	LGG fusion N=10 n (%)	NF-1 with PN N=10 n (%)	BRAF V600 mutant solid tumor^ N=10 n (%)	All Part B subjects N=41 n (%)
Age (years)										
n	3	19	12	16	50	11	10	10	10	41
Mean	9.7	7.2	3.3	9.7	7.2	8.2	7.0	6.6	7.9	7.4
SD	6.43	5.16	1.18	4.99	5.04	5.18	3.56	4.86	5.20	4.62
Median	7.0	6.0	3.5	9.0	6.0	7.0	6.5	5.5	6.0	6.0
Minimum	5	0.6	1.8	0.4	0.4	1.8	2	1	2	1
Maximum	17	17	5	17	17	17	12	16	17	17
Age category n (%)										
< 2 years	0	4 (21.1)	1 (8.3)	2 (12.5)	7 (14.0)	1 (9.1)	0	1 (10.0)	0	2 (4.9)
2 - < 6 years	1 (33.3)	5 (26.3)	11 (91.7)	0	17 (34.0)	3 (27.3)	4 (40.0)	4 (40.0)	5 (50.0)	16 (39.0)
6 - < 12 years	1 (33.3)	4 (21.1)	0	9 (56.3)	14 (28.0)	5 (45.5)	5 (50.0)	3 (30.0)	1 (10.0)	14 (34.1)
≥ 12 years	1 (33.3)	6 (31.6)	0	5 (31.3)	12 (24.0)	2 (18.2)	1 (10.0)	2 (20.0)	4 (40.0)	9 (22.0)
Sex n (%)										
Female	1 (33.3)	7 (36.8)	6 (50.0)	7 (43.8)	21 (42.0)	6 (54.5)	5 (50.0)	5 (50.0)	5 (50.0)	21 (51.2)
Male	2 (66.7)	12 (63.2)	6 (50.0)	9 (56.3)	29 (58.0)	5 (45.5)	5 (50.0)	5 (50.0)	5 (50.0)	20 (48.8)
Weight (kg)										
n	3	19	12	16	50	11	10	10	10	41
Mean	40.50	27.20	15.03	34.82	27.52	29.65	28.02	24.08	40.64	30.57
SD	37.500	15.387	2.492	19.523	18.123	22.984	17.005	11.521	34.193	22.974
Median	19.10	24.90	15.35	29.95	20.80	20.90	21.95	21.75	29.00	22.10
	N=3 n (%)	N=19 n (%)	N=12 n (%)	N=16 n (%)	N=50 n (%)	N=11 n (%)	N=10 n (%)	N=10 n (%)	N=10 n (%)	N=41 n (%)
Minimum	18.6	6.1	9.0	6.3	6.1	10.1	12.2	10.2	13.2	10.1
Maximum	83.8	55.8	17.9	73.5	83.8	92.8	63.3	43.4	128.0	128.0
Karnofsky and Lansky performance status n (%)										
100	1 (33.3)	5 (26.3)	6 (50.0)	5 (31.3)	17 (34.0)	5 (45.5)	5 (50.0)	6 (60.0)	6 (60.0)	22 (53.7)
90	0	7 (36.8)	2 (16.7)	5 (31.3)	14 (28.0)	4 (36.4)	4 (40.0)	4 (40.0)	1 (10.0)	13 (31.7)
80	1 (33.3)	5 (26.3)	2 (16.7)	4 (25.0)	12 (24.0)	2 (18.2)	1 (10.0)	0	2 (20.0)	5 (12.2)
70	1 (33.3)	1 (5.3)	1 (8.3)	1 (6.3)	4 (8.0)	0	0	0	1 (10.0)	1 (2.4)
<70	0	1 (5.3)	1 (8.3)	1 (6.3)	3 (6.0)	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0

- ^Only LGG subjects enrolled in this cohort.
- Source: Table 14.1-3.1.1, Table 14.1-3.1.2

Table 10-6 Demographics and baseline characteristics Part C and Part D (All treated population)

	Part C				Part D		
	TMT 0.025 mg/kg/day + 50% DRB RP2D N=3 n (%)	TMT 0.025 mg/kg/day + 100% DRB RP2D N=9 n (%)	TMT 0.032 mg/kg/day + 100% DRB RP2D N=6 n (%)	All Part C subjects N=18 n (%)	LGG N=20 n (%)	LCH N=10 n (%)	All Part D subjects N=30 n (%)
Age (years)							
n	3	9	6	18	20	10	30
Mean	12.7	10.6	2.7	8.3	10.5	5.6	8.8
SD	3.06	5.15	1.28	5.57	3.79	3.63	4.35
Median	12.0	12.0	2.5	8.0	10.5	4.0	9.0
Minimum	10	2	1.4	1.4	2	2	2
Maximum	16	17	5	17	16	13	16
Age category n (%)							
< 2 years	0	0	1 (16.7)	1 (5.6)	0	0	0
2 - < 6 years	0	2 (22.2)	5 (83.3)	7 (38.9)	2 (10.0)	6 (60.0)	8 (26.7)
6 - < 12 years	1 (33.3)	2 (22.2)	0	3 (16.7)	9 (45.0)	3 (30.0)	12 (40.0)
≥ 12 years	2 (66.7)	5 (55.6)	0	7 (38.9)	9 (45.0)	1 (10.0)	10 (33.3)
Sex n (%)							
Female	0	6 (66.7)	4 (66.7)	10 (55.6)	10 (50.0)	2 (20.0)	12 (40.0)
Male	3 (100)	3 (33.3)	2 (33.3)	8 (44.4)	10 (50.0)	8 (80.0)	18 (60.0)
Weight (kg)							
n	3	9	6	18	20	10	30
Mean	58.30	46.42	15.80	38.19	50.54	20.64	40.57
SD	31.173	24.602	4.568	26.258	25.628	8.049	25.610
Median	54.00	41.30	13.90	30.70	50.15	19.60	33.05
Minimum	29.5	14.8	12.8	12.8	15.3	11.5	11.5
Maximum	91.4	101.5	24.9	101.5	116.6	36.2	116.6
Karnofsky and Lansky performance status n (%)							
100	3 (100)	4 (44.4)	2 (33.3)	9 (50.0)	13 (65.0)	7 (70.0)	20 (66.7)
90	0	3 (33.3)	3 (50.0)	6 (33.3)	6 (30.0)	1 (10.0)	7 (23.3)
80	0	2 (22.2)	1 (16.7)	3 (16.7)	0	1 (10.0)	1 (3.3)
70	0	0	0	0	1 (5.0)	0	1 (3.3)
<70	0	0	0	0	0	1 (10.0)	1 (3.3)

- Source: Table 14.1-3.1.3, Table 14.1-3.1.4

Part A - trametinib monotherapy dose escalation (n=50)

The primary tumour type for 26 subjects (52.0%) was low-grade glioma (including 3 patients with BRAF V600 mutant glioma; and including 9 with pilocytic astrocytoma), followed by 16 subjects with NF1 with plexiform neurofibroma. The median time since initial diagnosis was 34.3 months (range: 22 days to 179.8 months). **Part B** - trametinib monotherapy expansion cohort (n=41)

Disease characteristics were as expected for the enrolled disease cohorts. The primary tumour type for 10 subjects (24.4%) was LGG with BRAF fusion, 10 subjects (24.4%) with LGG with BRAF V600 mutation, 11 subjects (26.8%) with neuroblastoma and 10 subjects with NF1 with PN (24.4%). The median time since initial diagnosis was 41.8 months (range: 17 days to 176.7 months).

Part C - combination therapy dose escalation (n=18) in BRAF V600 mutated tumours

The majority of subjects (14 subjects, 77.8%) had low-grade gliomas. There were 2 high-grade gliomas (aPXA, aGG), 1 LCH, and a juvenile xanthogranulomatosis tumour. The median time since initial diagnosis was 39.1 months (range: 3.4 to 112.6 months).

Part D - combination therapy expansion cohort (n=30) in BRAF V600 mutated tumours

The primary tumour type was low-grade glioma (20 subjects, 66.7%), including 11 pilocytic astrocytomas and 5 gangliogliomas. Ten subjects (33.3%) had LCH and the median time since initial diagnosis was 33.9 months (range: 5.8 to 137.0 months).

Pharmacokinetic results

Non-compartmental analysis

Steady state (Cycle 1, Day 15) PK parameters for dabrafenib and trametinib were calculated. Due to limited dabrafenib and trametinib PK data for Day 1 and Day 22, no PK parameters were calculated for these time points. Pharmacokinetic parameters for trametinib observed in part A, B, C and D are displayed per dose (Table 4, Table 6, Table 8 and Table 12) and steady state concentrations are displayed per age group and per dose (Table 5), per patient population (Table 7), for combination therapy (Table 10) and per population/combination therapy (Table 14). Pharmacokinetic parameters for dabrafenib observed in part C and D are displayed per dose (Table 9 and Table 13) and steady state concentrations are displayed per age group and combination therapy (Table 11) and per population/combination therapy (Table 15).

Part A: On Day 15, following the administration of trametinib at a dose level of 0.0125, 0.025, 0.032 and 0.04 mg/kg/day, the geometric mean of trametinib average steady-state plasma concentration (Cavg) was 5.76, 13.9, 15.2 and 21.3 ng/mL, respectively. The Cavg increased with dose levels as expected. The efficacy target (~10 ng/mL) was achieved in the trametinib 0.025, 0.032 and 0.04 mg/kg/day dose cohorts in Part A. The interpretation of PK data for individual age groups was limited by small numbers of subjects within the cohorts.

Table 4. Summary of trametinib PK parameters; Cycle 1 Day 15 – Part A

	Tramatenib Dose			
Parameter	0.0125 mg/kg/day (n=3)	0.025 mg/kg/day (n=19)	0.032 mg/kg/day (n=9)	0.040 mg/kg/day (n=16)
AUC_{last} (hr*ng/mL)	138 (24.8)	341 (28.3)	364 (16.9)	413 (76.2)
AUC_{tau} (hr*ng/mL)	138 (24.8)	334 (27.1)	364 (16.9)	511 (20.7)
CL/F (mL/h)	2750 (69.4)	1530 (64.5)	1240 (25.5)	2040 (71.5)
C_{avg} (ng/mL)	5.76 (24.8)	13.9 (27.1)	15.2 (16.9)	21.3 (20.7)
C_{max} (ng/mL)	9.61 (32.9)	21.1 (33.3)	26.1 (16.8)	32.6 (28.9)
C_{trough} (ng/mL)	4.37 (30.6)	11.1 (44.0)	10.2 (19.4)	15.6 (30.1)
T_{max} (hr)	1.0 [1.0 – 2.0]	2.0 [1.0 – 4.0]	1.0 [1.0 – 2.0]	2.0 [1.0 – 24.0]

Results are presented as geometric mean (CV%) or median [minimum – maximum]

Table 5. Per age group - Summary of trametinib average steady state plasma concentration; Cycle 1 Day 15 - Part A

	Tramatenib Dose			
Age Group	0.0125 mg/kg/day	0.025 mg/kg/day	0.032 mg/kg/day	0.040 mg/kg/day
<2 years	N/E (n = 0)	10.9 (18.0%, n = 4)	13.4 (n = 1)	20.5 (36.5%, n = 2)
2 - < 6 years	5.64 (n = 1)	13.5 (13.9%, n = 5)	15.4 (17.4%, n = 8)	N/E (n = 0)
6 - < 12 years	4.56 (n =1)	17.3 (33.9%, n = 3)	N/E (n = 0)	22.5 (18.6%, n = 8)
≥ 12 years	7.44 (n = 1)	15.0 (28.3%, n = 6)	N/E (n = 0)	19.7 (20.7%, n = 5)

Results are presented as geometric mean (CV%, n)

Part B: On Cycle 1 Day 15, following the administration of trametinib 0.025 mg/kg/day, the geometric mean of trametinib average steady-state plasma concentration was 14.3 ng/mL. The efficacy target (~10 ng/mL) was achieved in Part B. No clear differences are visible between patient populations. The interpretation of PK data for individual age groups was limited by small numbers of subjects within cohorts.

Table 6. Summary of trametinib PK parameters; Cycle 1 Day 15 – Part B

	Patient Population				
Parameter	Neuroblastoma (n = 9)	LGG fusion (n = 10)	NF-1 with PN (n = 10)	BRAF V600 mutant solid tumour (n = 10)	All subjects 0.025 mg/kg/day (n = 39)
AUC_{last} (hr*ng/mL)	362 (36.0%)	316 (40.4%)	304 (36.9%)	379 (42.8%)	337 (38.6%)
AUC_{tau} (hr*ng/mL)	362 (36.0%)	316 (40.4%)	323 (25.1%)	379 (42.8%)	343 (35.8%)
CL/F (mL/h)	1710 (55.6%)	1910 (47.8%)	1590 (65.3%)	1820 (42.6%)	1750 (51.5%)
C_{avg} (ng/mL)	15.1 (36.0%)	13.2 (40.4%)	13.5 (25.1%)	15.8 (42.8%)	14.3 (35.8%)
C_{max} (ng/mL)	26.6 (39.6%)	22.1 (41.9%)	21.6 (26.1%)	27.5 (31.6%)	24.2 (35.6%)
C_{trough} (ng/mL)	10.7 (43.3%)	9.5 (53.6%)	9.3 (29.0%)	11.3 (50.3%)	10.1 (43.6%)

T_{max} (hr)	1.0 [1.0 – 4.0]	1.5 [1.0 – 2.0]	1.0 [1.0 - 2.0]	1.0 [1.0 - 2.0]	1.0 [1.0 – 4.0]

Results are presented as geometric mean (CV%) or median [minimum – maximum]

Table 7. Per age group - Summary of trametinib average steady state plasma concentration; Cycle 1 Day 15 - Part B

	Patient Population				
Age Group	Neuroblastoma	LGG fusion	NF-1 with PN	BRAF V600 mutant solid tumour	All subjects 0.025 mg/kg/day
<2 years	15.9 (n =1)	N/E (n = 0)	16.9 (n = 1)	N/E (n = 0)	16.4 (4.3%, n = 2)
2 - < 6 years	14.0 (n = 1)	9.9 (16.1%, n = 4)	12.9 (35.3%, n = 4)	14.3 (16.0, n = 5)	12.5 (26.2%, n = 14)
6 - < 12 years	13.2 (31.5%, n = 5)	14.9 (40.2%, n = 5)	14.3 (22.6%, n = 3)	36.0 (n = 1)	15.1 (40.0%, n = 14)
≥ 12 years	21.2 (55.8%, n = 2)	22.2 (n = 1)	12.0 (3.7, n = 2)	14.2 (52.1, n = 3)	15.9 (43.7%, n = 8)

Results are presented as geometric mean (CV%, n)

Part C: On Cycle 1 Day 15, following the administration of trametinib 0.025 mg/kg/day + 50% dabrafenib RP2D, trametinib 0.025 mg/kg/day + 100% dabrafenib RP2D and trametinib 0.032 mg/kg/day + 100% dabrafenib RP2D, the geometric mean of trametinib average steadystate plasma concentration was 12.1, 13.8, and 9.8 ng/mL (CV of 28%), respectively. The geometric mean of dabrafenib average steady-state plasma concentration was 239, 347, and 337 ng/mL, respectively. Dabrafenib RP2Ds were 5.25 mg/kg/day and divided into two equal doses for < 12 years old subjects and 4.5 mg/kg/day and divided into two equal doses for ≥ 12 years old pediatric subjects. The trametinib efficacy target (~10 ng/mL) was achieved in all dose cohorts in Part C. The trametinib 0.025 mg/kg/day + 100% dabrafenib RP2D and trametinib 0.032 mg/kg/day + 100% dabrafenib RP2D dose cohorts achieved the dabrafenib efficacy target (~300 ng/mL). However, the trametinib 0.025 mg/kg/day + 50% dabrafenib RP2D dose cohort did not achieve the dabrafenib efficacy target because of using only 50% of the dabrafenib RP2D dose (Cavg of 239 ng/mL). The interpretation of PK data for individual age groups was limited by small numbers of subjects within the cohorts.

Table 8. Summary of trametinib PK parameters; Cycle 1 Day 15 – Part C

	Dose		
Parameter	0.025 mg/kg/day + 50% DRB RP2D (n = 1)	0.025 mg/kg/day + 100% DRB RP2D (n = 1)	0.032 mg/kg/day + 100% DRB RP2D (n = 6)
AUC_{last} (hr*ng/mL)	290	331	122 (29.0%)
AUC_{tau}	290	331	236 (28.4%)

(hr*ng/mL)			
CL/F (mL/h)	2590	3770	2010 (38.5%)
C_{avg} (ng/mL)	12.1	13.8	9.83 (28.4%)
C_{max} (ng/mL)	26.0	24.5	23.7
C_{trough} (ng/mL)	8.3	10.2	3.9 (34.9%)
T_{max} (hr)	1.0	1.0	1.5 [1.0 – 2.0]

Results are presented as geometric mean (CV%) or median [minimum – maximum]

Table 9. Summary of dabrafenib PK parameters; Cycle 1 Day 15 – Part C

	Dose		
Parameter	0.025 mg/kg/day + 50% DRB RP2D (n = 3)	0.025 mg/kg/day + 100% DRB RP2D (n = 7)	0.032 mg/kg/day + 100% DRB RP2D (n = 6)
AUC_{last} (hr*ng/mL)	2560 (157.1%)	4160 (24.6%)	3910 (48.8%)
AUC_{tau} (hr*ng/mL)	2870 (116.6%)	4160 (24.6%)	4040 (47.9%)
CL/F (L/h)	22.9 (191.2%)	20.4 (45.4%)	10.1 (67.0%)
C_{avg} (ng/mL)	239 (116.6%)	347 (24.6%)	337 (47.9%)
C_{max} (ng/mL)	630 (235.2%)	1560 (35.3%)	1440 (43.3%)
C_{trough} (ng/mL)	88.9 (99.6%)	28.6 (203.5%)	8.1 (159.6%)
T_{max} (hr)	2.0 [2.0 – 4.0]	1.0 [1.0 – 2.0]	2.0 [1.0 – 2.0]

Results are presented as geometric mean (CV%) or median [minimum – maximum]

Table 10. Per age group - Summary of trametinib average steady state plasma concentration; Cycle 1 Day 15 - Part C

Age Group	0.025 mg/kg/day + 50% DRB RP2D	0.025 mg/kg/day + 100% DRB RP2D	0.032 mg/kg/day + 100% DRB RP2D
<2 years	N/E (n = 0)	N/E (n = 0)	11.5 (n = 1)
2 - < 6 years	N/E (n = 0)	N/E (n = 0)	9.5 (30.7%, n = 5)
6 - < 12 years	12.1 (n = 1)	13.8 (n = 1)	N/E (n = 0)
≥ 12 years	N/E (n = 0)	N/E (n = 0)	N/E (n = 0)

Results are presented as geometric mean (CV%, n)

Table 11. Per age group - Summary of dabrafenib average steady state plasma concentration; Cycle 1 Day 15 - Part C

Age Group	0.025 mg/kg/day + 50% DRB RP2D	0.025 mg/kg/day + 100% DRB RP2D	0.032 mg/kg/day + 100% DRB RP2D
<2 years	N/E (n = 0)	N/E (n = 0)	360 (n = 1)
2 - < 6 years	N/E (n = 0)	324 (15.4%, n = 2)	332 (n = 5)
6 - < 12 years	294 (n = 1)	449 (n = 1)	N/E (n = 0)
≥ 12 years	215 (205.4%, n =2)	336 (301%, n = 4)	N/E (n = 0)

Results are presented as geometric mean (CV%, n)

Part D: On Day 15, following the administration of trametinib 0.032 mg/kg/day + 100% dabrafenib RP2D for subjects <6 years, and trametinib 0.025 mg/kg/day + 100% dabrafenib RP2D for subject ≥ 6 years, the geometric mean of trametinib average steady-state plasma concentration was 9.50 and 11.9 ng/mL, respectively, and the geometric mean of dabrafenib average steady-state plasma concentration was 346 and 332 ng/mL, respectively. The trametinib efficacy target (~10 ng/mL) was achieved in both dose levels. The dabrafenib efficacy target (~300 ng/mL) was also achieved for both dose levels in Part D. The interpretation of PK data for individual age groups was limited by small numbers of subjects within the cohorts.

Table 12. Summary of trametinib PK parameters; Cycle 1 Day 15 – Part D

	Population			
Parameter	LGG (n = 20)	LCH (n = 9)	All subjects TMT 0.032 mg/kg/day + 100% DRB RP2D (n = 7)	All subjects TMT 0.025 mg/kg/day + 100% DRB RP2D (n = 22)
AUC_{last} (hr*ng/mL)	70 (35.8%)	118 (53.4%)	126 (30.7%)	255 (49.2%)
AUC_{tau} (hr*ng/mL)	308 (20.0%)	186 (23.7%)	228 (33.1%)	286 (28.4%)
CL/F (mL/h)	3540 (54.0%)	3060 (44.9%)	2180 (23.9%)	3810 (49.6%)
C_{avg} (ng/mL)	12.8 (20.0%)	7.8 (23.7%)	9.5 (33.1%)	11.9 (28.4%)
C_{max} (ng/mL)	22.9 (29.2%)	15.6 (52.5%)	25.9 (35.8%)	20.0 (38.1%)
C_{trough} (ng/mL)	8.6 (42.2%)	3.7 (66.3%)	3.1 (50.7%)	8.7 (38.6%)
T_{max} (hr)	2.0 [1.0 – 3.0]	1.0 [1.0 – 4.0]	1.0 [1.0 – 1.0]	2.0 [1.0 – 4.0]

Results are presented as geometric mean (CV%) or median [minimum – maximum]

Table 13. Summary of dabrafenib PK parameters; Cycle 1 Day 15 – Part D

	Population			
Parameter	LGG (n = 20)	LCH (n = 9)	All subjects TMT 0.032 mg/kg/day + 100% DRB RP2D (n = 7)	All subjects TMT 0.025 mg/kg/day + 100% DRB RP2D (n = 22)
AUC_{last} (hr*ng/mL)	4030 (46.4%)	3800 (35.4%)	3990 (28.3%)	3950 (46.9%)
AUC_{tau} (hr*ng/mL)	3070 (46.7%)	3910 (37.4%)	4150 (30.2%)	3990 (47.3%)
CL/F (L/h)	25.4 (70.5%)	12.5 (63.0%)	10.2 (41.6%)	25.1 (69.3%)
C_{avg} (ng/mL)	339 (46.7%)	326 (37.4%)	346 (30.2%)	332 (47.3%)
C_{max} (ng/mL)	1360 (55.6%)	1490 (88.1%)	1840 (35.2%)	1290 (68.7%)
C_{trough} (ng/mL)	38.2 (130.9%)	11.8 (869.4%)	5.4 (429.6%)	42.7 (137.4%)
T_{max} (hr)	2.0 [1.0 – 3.0]	1.0 [1.0 – 3.0]	1.0 [1.0 – 3.0]	2.0 [1.0 – 3.0]

Results are presented as geometric mean (CV%) or median [minimum – maximum]

Table 14. Per age group - Summary of trametinib average steady state plasma concentration; Cycle 1 Day 15 - Part D

	Population			
Age Group	LGG	LCH	All subjects TMT 0.032 mg/kg/day + 100% DRB RP2D	All subjects TMT 0.025 mg/kg/day + 100% DRB RP2D
2 - < 6 years	13.3 (2.0%, n = 2)	7.6 (13.5%, n = 3)	9.5 (33.1%, n = 5)	N/E (n = 0)
6 - < 12 years	13.4 (16.6%, n = 9)	9.1 (35.3%, n = 2)	N/E (n = 0)	12.5 (24.3%, n = 11)
≥ 12 years	12.2 (25.0%, n = 9)	6.0 (n = 1)	N/E (n = 0)	11.4 (33.2%, n = 10)

Results are presented as geometric mean (CV%, n)

Table 15. Per age group - Summary of dabrafenib average steady state plasma concentration; Cycle 1 Day 15 - Part D

	Population			
Age Group	LGG	LCH	All subjects TMT 0.032 mg/kg/day + 100% DRB RP2D	All subjects TMT 0.025 mg/kg/day + 100% DRB RP2D

2 - < 6 years	278 (n = 1)	362 (31.5%, n = 5)	346 (30.2%, n = 6)	N/E (n = 0)
6 - < 12 years	387 (44.2, n = 9)	354 (6.7%, n = 2)	N/E (n = 0)	381 (39.4%, n = 11)
≥ 12 years	304 (50.6%, n = 9)	165 (n = 1)	N/E (n = 0)	286 (52.1%, n = 10)

Results are presented as geometric mean (CV%, n)

Population pharmacokinetic analyses

Population pharmacokinetic models for dabrafenib and trametinib in the adult population were previously established based on data from both the monotherapy and combination settings.

The popPK of trametinib can be described using a two-compartment model with dual sequential 1st order absorption (Ka1, Ka2) and 1st order elimination (CL/F). Sex and weight are significant covariates on CL/F, and weight is also a significant covariate on Q/F. Use of dabrafenib, yes or no, is a covariate on the relative bioavailability of trametinib, reflecting the effect of dabrafenib on the PK of trametinib. Combination effect was tested on clearance (CL/F), F, and absorption rate constants (Ka1 and Ka2). The effect of concomitant administration of dabrafenib resulted in a decrease in oral bioavailability with a ratio (95% CI) of 0.876 (0.841, 0.911). Trametinib CL/F was estimated as 5.07 L/hr and was dependent on gender and weight. The typical CL/F of trametinib in male subjects was 24% higher than that observed in female subjects.

This trametinib popPK model was re-run on the data from this study, and subsequently covariate effects were re-estimated to adequately describe the paediatric population receiving trametinib. Performance of the models for this dataset was assessed based on diagnostic plots such as observations (DV) vs. population (PRED) and individual predictions (IPRED) (Figure 1), and the decrease of the objective function. In addition, a visual predictive check (VPC) plots were generated, to verify the agreement between the observed data and the simulated time-course profiles (not provided).

The effect of weight of CL/F was estimated as 0.788 (in adult population, this effect was estimated as 0.194), the effect of weight on Q/F was estimated as 0.679 (adult model: 3.30). In addition, the effect of weight on apparent central volume of distribution (Vc/F) was tested and added in the model, as well as the effect of the formulation (suspension) on relative bioavailability and the absorption constant Ka2. The remaining parameters were fixed to the previously estimated values in the adults (see Table 16 for all parameter estimates).

The study specific PopPK analysis support the weight-based dosing used in the study. Exposure of trametinib in paediatric subjects the RP2Ds were comparable those previously observed in adult population.

Table 16. Trametinib PopPK model parameter estimates for paediatric population

Parameter	Notation	Estimate
Fixed effects		
Apparent clearance	CL/F (L/h)	5.07
Apparent central volume	Vc/F (L)	184
Apparent intercompartmental clearance	Q/F (L/h)	60
Apparent peripheral volume	Vp/F (L)	433
Absorption rate constant 1	Ka1 (1/h)	0.134
Absorption rate constant 2	Ka2 (1/h)	1.55
Time when Ka1 transitions to Ka2	MTime (h)	0.404
Effect of weight on CL/F	WTCL	0.788
Effect of sex on CL/F	SEXCL	1.24
Effect of weight on Q/F	WTQ	0.679
Effect of weight on Vc/F	WTVC	1.13
Effect of formulation on F1	FORMF1	1.09
Effect of formulation on Ka2	FORMKa2	2.93
Effect of combination with dabrafenib on relative bioavailability F1	$F1_{COMBINATION}$	0.876
Variance parameter	M	0.1
Random effects		
Variance of CL/F	ω^2_{CL}	0.0903
Variance of Vc/F	ω^2_{Vc}	0.474
Covariance of CL/F and Vc/F	$\omega_{CL}\omega_{Vc}$	0.143
Variance of Q/F	ω^2_{Q}	0.0225 Fixed
Variance of Vp/F	ω^2_{Vp}	0.0225
Variance of Ka1	ω^2_{Ka1}	0.941
Variance of Ka2	ω^2_{Ka2}	0.0225
Variance of MTime	ω^2_{MTIME}	0.0225
Variance of the 1st component of the double exponential error model	$\sigma^2_{first,deem}$	0.0698
Variance of the 2nd component of the double exponential error model	$\sigma^2_{second,deem}$	143

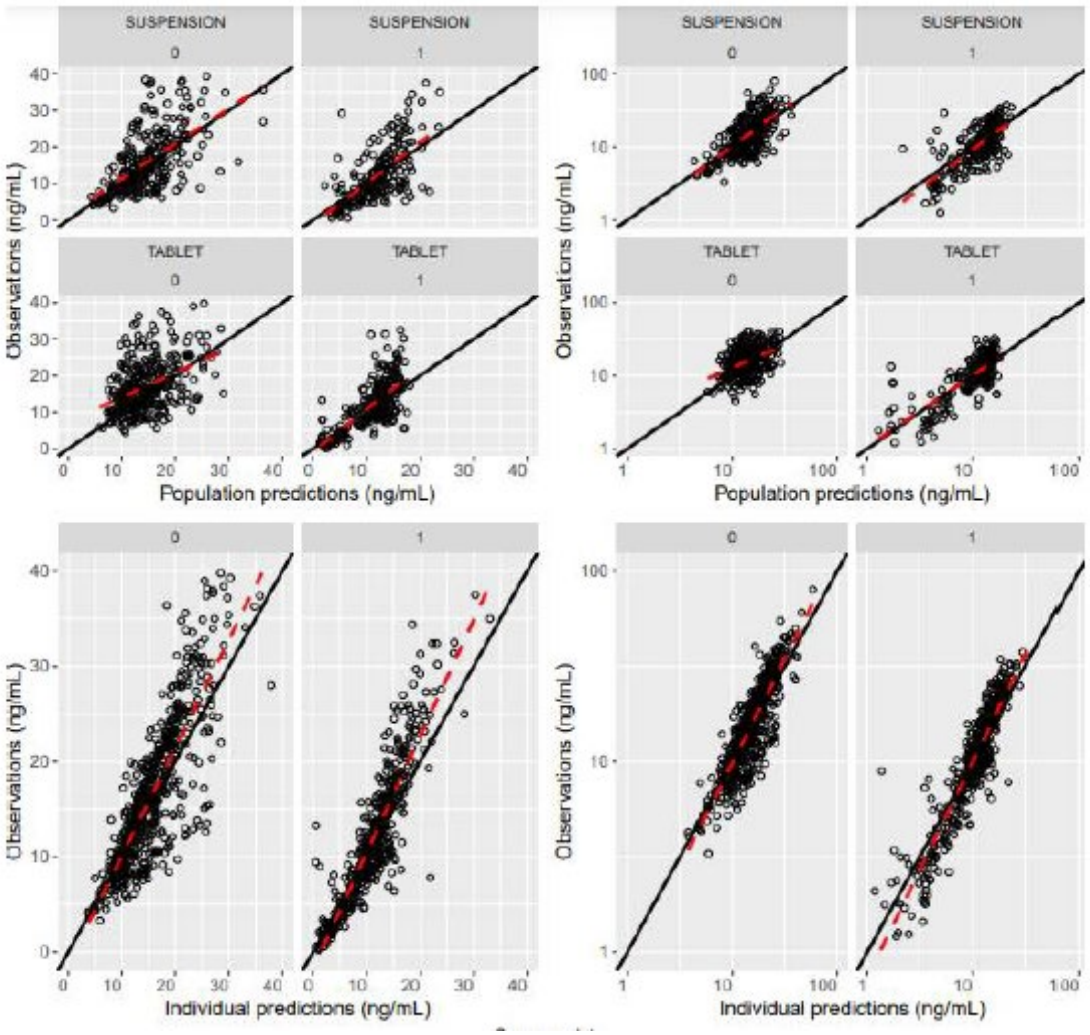

Figure 1. Individual and population predicted trametinib concentration over time overlaid with the observed data points (linear and log scale)

Efficacy results

Median exposure to trametinib across all parts ranged from 19.1 months in Part B to 24.4 months in Part A and Part D. Median exposure for dabrafenib was 20.8 months on Part C and 24.9 months in Part D.

Responses per part of the study

The response rates per part of the study are shown in Table 4 and Table 5.

Table 17 Inv- assessed best overall response Part A and B (all treated population)

	Part A					Part B				
	TMT 0.0125 mg/kg/day N=3 n (%)	TMT 0.025 mg/kg/day N=19 n (%)	TMT 0.032 mg/kg/day N=12 n (%)	TMT 0.04 mg/kg/day N=16 n (%)	All Part A subjects N=50 n (%)	Neuro-blastoma N=11 n (%)	LGG fusion N=10 n (%)	NF-1 with PN N=10 n (%)	BRAF V600 mutant solid tumors^ N=10 n (%)	All Part B subjects N=41 n (%)
Best overall response										
Complete response (CR)	0	0	0	0	0	0	0	0	0	0
Partial response (PR)	0	1 (5.3)	1 (8.3)	0	2 (4.0)	1 (9.1)	3 (30.0)	0	5 (50.0)	9 (22.0)
Stable disease (SD)	1 (33.3)	2 (10.5)	3 (25.0)	4 (25.0)	10 (20.0)	1 (9.1)	7 (70.0)	8 (80.0)	4 (40.0)	20 (48.8)
Progressive disease (PD)	0	0	2 (16.7)	0	2 (4.0)	5 (45.5)	0	0	1 (10.0)	6 (14.6)
Non-CR/Non-PD (NN)	0	0	0	0	0	0	0	0	0	0
Unknown	0	0	0	2 (12.5)	2 (4.0)	1 (9.1)	0	0	0	1 (2.4)
Missing	2 (66.7)	16 (84.2)	6 (50.0)	10 (62.5)	34 (68.0)	3 (27.3)	0	2 (20.0)	0	5 (12.2)
Objective response rate (ORR: CR+PR)	0	1 (5.3)	1 (8.3)	0	2 (4.0)	1 (9.1)	3 (30.0)	0	5 (50.0)	9 (22.0)
ORR 95% CI	(0.0, 70.8)	(0.1, 26.0)	(0.2, 38.5)	(0.0, 20.6)	(0.5, 13.7)	(0.2, 41.3)	(6.7, 65.2)	(0.0, 30.8)	(18.7, 81.3)	(10.6, 37.6)
Clinical benefit rate (CBR: CR+PR+SD)	1 (33.3)	3 (15.8)	4 (33.3)	4 (25.0)	12 (24.0)	2 (18.2)	10 (100)	8 (80.0)	9 (90.0)	29 (70.7)
CBR 95% CI	(0.8, 90.6)	(3.4, 39.6)	(9.9, 65.1)	(7.3, 52.4)	(13.1, 38.2)	(2.3, 51.8)	(69.2, 100)	(44.4, 97.5)	(55.5, 99.7)	(54.5, 83.9)

- ^Only LGG subjects enrolled in this cohort.
- ORR is calculated as the number of subjects deemed to have treatment response relative to the total number of subjects treated in that cohort which is complete response + partial response.
- The 95% CI for the frequency distribution of each variable was computed using two-sided exact binomial 95% CIs.
- Source: Table 14.2-1.1.1a, Table 14.2-1.1.1b

Table 18 Inv- assessed best overall response Part C and D (all treated population)

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

- ORR is calculated as the number of subjects deemed to have treatment response relative to the total number of subjects treated in that cohort which is complete response + partial response.
- The 95% CI for the frequency distribution of each variable was computed using two-sided exact binomial 95% CIs.
- Source: Table 14.2-1.1.1c, Table 14.2-1.1.1d

Responses per subtype

The objective response rate (ORR) assessed by Investigator in the trametinib treated cohorts for glioma fusion (n=26) was 19.2% (5/26; 95% CI: 6.6, 39.4), and for subjects with BRAF V600 mutant glioma (n=13) was 38.5% (5/13; 95% CI: 13.9, 68.4). Note that independent review was used for efficacy analysis for subjects with NF1 associated PNs. For the dabrafenib + trametinib combination arms, Investigator-assessed ORR for subjects with BRAF V600 glioma was 52.8% (95% CI: 35.5, 69.6) and with LCH was 58.3% (95% CI: 27.7, 84.8).

Independent reviewer assessed ORR for trametinib-treated cohorts for subjects with glioma fusion was 3.8% (95% CI: 0.1, 19.6), for subjects with NF-1 with PN was 58.1% (95% CI: 39.1, 75.5), and for subjects with BRAF V600 mutant glioma was 15.4% (95% CI: 1.9, 45.4) using Response Assessment in Neuro-Oncology (RANO) 2010 (Wen et al 2010) criteria and RANO 2017 (Wen et al 2017) criteria. For the dabrafenib + trametinib combination arm, independent reviewer assessed ORR for subjects

with BRAF V600 glioma was 19.4% (95% CI: 8.2, 36.0) using RANO 2010 and 25.0% (95% CI: 12.1, 42.2) using RANO 2017). Note that for subjects with gliomas, only those determined to have measurable disease at baseline were eligible to achieve PR or CR; measurable disease was not an eligibility requirement for this study.

- Concordance of response determination between Investigator and independent review assessments of BOR for trametinib monotherapy cohorts with glioma fusion monotherapy was 73.1% using RANO 2010 and 66.7% for subjects with BRAF V600 glioma using both RANO 2010 and RANO 2017. For the dabrafenib + trametinib combination, concordance between investigator and independent review assessments of BOR for subjects with BRAF V600 glioma was 58.3% per RANO 2010 and 69.4% per RANO 2017.

Safety results

Determining the MTD and RP2D

No DLTs were observed for the 0.0125 mg/kg/day dose cohort.

In the 0.025 mg/kg/day dose cohort, 3 out of 19 subjects had a protocol defined DLT. One subject had hyponatremia and 1 subject had hypotension (2 to < 6 years age group) and 2 subjects had mucosal inflammation (one each in the 6 to < 12 years age group and 12 to < 18 years age group).

In the trametinib 0.040 mg/kg/day dose cohort, 5 out of 15 subjects had a protocol defined DLT. One subject, age 4.8 months, had pelvic abscess. In the 6 to < 12 years age group, one subject had mucosal inflammation and one subject had hyponatremia. In the 12 to < 18 years age group one subject had increased ALT and increased AST and one subject had dermatitis acneiform. The dose level of trametinib 0.040 mg/kg/day was not tolerated.

Results from completed and ongoing cohorts (Parts A, B and C) of this study had shown that the trametinib 0.025 mg/kg/day dose level also achieved target exposures that are associated with the recommended efficacious adult dose for melanoma treatment in most subjects older than 6 years of age, however not in subjects under 6 years. In addition, the exposure-efficacy relationship for trametinib when combined with dabrafenib in adult melanoma patients demonstrates an apparent threshold effect and provides further rationale to optimize trametinib exposures in paediatric subjects. Therefore, Part A extension was added by protocol amendment to test the intermediate trametinib dose level of 0.032 mg/kg/day in subjects under 6 years of age for safety, tolerability and pharmacokinetics. No DLTs were observed for the 0.032 mg/kg/day dose cohort.

The RP2Ds for trametinib monotherapy were determined as 0.032 mg/kg/day for subjects< 6 years old and 0.025 mg/kg/day for subjects ≥ 6 years old.

AEs

For the most frequently reported AEs per monotherapy and combination therapy with dabrafenib, see below. No on-treatment deaths or SAEs with fatal outcome were reported. One death, with a primary reason of aspiration, occurred during the post-treatment period, > 28 days from last dose of study drug (see below). For a summary of safety per study part, refer to Table 6, Table 7, Table 8 and Table 9.

Five subjects receiving monotherapy had AEs of hyponatremia of grade 3 or 4, which were manageable. Two subjects had notable ECG values that were also considered adverse events, 1 subject in Part B , and 1 subject in Part C. In part A 3 subjects, in Part B 3 subjects, in Part C 6 subjects and in part D 3 subjects had a LVEF decrease ≥20%. No subject had a more than 20% decrease in LVEF that was also below LLN.

Analysis of growth parameters for subjects over time demonstrated gain in height and weight similar to that expected for their ages, as most height and weight velocities were within one standard deviation of the norm at most time intervals.

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

Subjects Tanner stage of development was assessed every 6 months. The expected outcome was that a portion of the paediatric subjects that were pre-pubertal would progress through 1 or more tanner stages over the time of participation in the study. However, Tanner stage did not change for subjects during study participation.

Table 19 Adverse events overview- Part A (Safety population)

	TMT 0.0125 mg/kg/day N=3		TMT 0.025 mg/kg/day N=19		TMT 0.032 mg/kg/day N=12		TMT 0.04 mg/kg/day N=16		All subjects N=50	
Category	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)
All deaths [a]	0	0	0	0	1 (8.3)	1 (8.3)	0	0	1 (2.0)	1 (2.0)
On-treatment deaths [b]	0	0	0	0	0	0	0	0	0	0
Adverse events	3 (100)	1 (33.3)	19 (100)	10 (52.6)	12 (100)	4 (33.3)	16 (100)	10 (62.5)	50 (100)	25 (50.0)
Suspected to be drug related	3 (100)	0	19 (100)	6 (31.6)	12 (100)	3 (25.0)	16 (100)	9 (56.3)	50 (100)	18 (36.0)
Serious adverse events	1 (33.3)	1 (33.3)	8 (42.1)	7 (36.8)	3 (25.0)	2 (16.7)	11 (68.8)	7 (43.8)	23 (46.0)	17 (34.0)
Suspected to be drug related	0	0	5 (26.3)	4 (21.1)	1 (8.3)	0	6 (37.5)	5 (31.3)	12 (24.0)	9 (18.0)
Fatal serious adverse events	0	0	0	0	0	0	0	0	0	0
Suspected to be drug related	0	0	0	0	0	0	0	0	0	0
AEs leading to discontinuation	1 (33.3)	0	4 (21.1)	0	1 (8.3)	0	6 (37.5)	4 (25.0)	12 (24.0)	4 (8.0)
AEs requiring dose interruptions	0	0	12 (63.2)	4 (21.1)	6 (50.0)	0	14 (87.5)	9 (56.3)	32 (64.0)	13 (26.0)
AEs requiring dose reductions	0	0	9 (47.4)	2 (10.5)	5 (41.7)	0	9 (56.3)	4 (25.0)	23 (46.0)	6 (12.0)
AEs requiring dose reductions or interruptions	0	0	13 (68.4)	4 (21.1)	7 (58.3)	0	14 (87.5)	9 (56.3)	34 (68.0)	13 (26.0)

- MedDRA v 23.1, CTCAE v 4.03.
- Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events more than 1 category are counted once in each of those categories.
- [a]: All deaths including those > 30 days after the last dose of study drug.
- [b]: Deaths occurring more than 30 days after the last dose of study drug are not included.
- AEs occurring more than 30 days after the last dose of study drug are not summarized.
- Missing grades are included under 'All grades' column.
- Source: Table 14.3.1-1

Category	Neuroblastoma N=11		LGG fusion N=10		NF-1 with PN N=10		BRAF V600 mutant solid tumor^ N=10		All subjects N=41	
	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)
All deaths [a]	0	0	0	0	0	0	0	0	0	0
On-treatment deaths [b]	0	0	0	0	0	0	0	0	0	0
Adverse events	11 (100)	9 (81.8)	10 (100)	6 (60.0)	10 (100)	5 (50.0)	10 (100)	7 (70.0)	41 (100)	27 (65.9)
Suspected to be drug related	10 (90.9)	4 (36.4)	10 (100)	5 (50.0)	10 (100)	3 (30.0)	10 (100)	4 (40.0)	40 (97.6)	16 (39.0)
Serious adverse events	6 (54.5)	6 (54.5)	6 (60.0)	3 (30.0)	6 (60.0)	4 (40.0)	5 (50.0)	5 (50.0)	23 (56.1)	18 (43.9)
Suspected to be drug related	1 (9.1)	1 (9.1)	2 (20.0)	1 (10.0)	2 (20.0)	2 (20.0)	3 (30.0)	3 (30.0)	8 (19.5)	7 (17.1)
Fatal serious adverse events	0	0	0	0	0	0	0	0	0	0
Suspected to be drug related	0	0	0	0	0	0	0	0	0	0
AEs leading to discontinuation	4 (36.4)	4 (36.4)	1 (10.0)	0	1 (10.0)	0	5 (50.0)	4 (40.0)	11 (26.8)	8 (19.5)
AEs requiring dose interruptions	3 (27.3)	2 (18.2)	8 (80.0)	4 (40.0)	5 (50.0)	3 (30.0)	8 (80.0)	4 (40.0)	24 (58.5)	13 (31.7)
AEs requiring dose reductions	2 (18.2)	1 (9.1)	4 (40.0)	1 (10.0)	3 (30.0)	1 (10.0)	7 (70.0)	1 (10.0)	16 (39.0)	4 (9.8)
AEs requiring dose reductions or interruptions	3 (27.3)	2 (18.2)	8 (80.0)	4 (40.0)	6 (60.0)	3 (30.0)	9 (90.0)	5 (50.0)	26 (63.4)	14 (34.1)

- ^Only LGG subjects enrolled in this cohort.
- MedDRA v 23.1, CTCAE v 4.03.
- Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events more than 1 category are counted once in each of those categories.
- [a]: All deaths including those > 30 days after the last dose of study drug.
- [b]: Deaths occurring more than 30 days after the last dose of study drug are not included.
- AEs occurring more than 30 days after the last dose of study drug are not summarized.
- Missing grades are included under 'All grades' column.
- Source: Table 14.3.1-2

Table 21 Adverse event overview - Part C (safety population)

Category	TMT 0.025 mg/kg/day + 50% DRB RP2D N=3		TMT 0.025 mg/kg/day + 100% DRB RP2D N=9_		TMT 0.032 mg/kg/day + 100% DRB RP2D N=6		All subjects N=18	
	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)
All deaths [a]	0	0	0	0	0	0	0	0
On-treatment deaths [b]	0	0	0	0	0	0	0	0
Adverse events	3 (100)	3 (100)	9 (100)	6 (66.7)	6 (100)	3 (50.0)	18 (100)	12 (66.7)
Suspected to be drug related	3 (100)	1 (33.3)	9 (100)	5 (55.6)	6 (100)	2 (33.3)	18 (100)	8 (44.4)
Serious adverse events	1 (33.3)	1 (33.3)	5 (55.6)	2 (22.2)	2 (33.3)	1 (16.7)	8 (44.4)	4 (22.2)
Suspected to be drug related	0	0	2 (22.2)	1 (11.1)	1 (16.7)	0	3 (16.7)	1 (5.6)
Fatal serious adverse events	0	0	0	0	0	0	0	0
Suspected to be drug related	0	0	0	0	0	0	0	0
AEs leading to discontinuation	0	0	3 (33.3)	2 (22.2)	1 (16.7)	1 (16.7)	4 (22.2)	3 (16.7)
AEs requiring dose interruptions	1 (33.3)	1 (33.3)	6 (66.7)	4 (44.4)	4 (66.7)	2 (33.3)	11 (61.1)	7 (38.9)
AEs requiring dose reductions	1 (33.3)	0	3 (33.3)	3 (33.3)	1 (16.7)	1 (16.7)	5 (27.8)	4 (22.2)
AEs requiring dose reductions or interruptions	1 (33.3)	1 (33.3)	7 (77.8)	5 (55.6)	4 (66.7)	2 (33.3)	12 (66.7)	8 (44.4)

- MedDRA v 23.1, CTCAE v 4.03.
- Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events more than 1 category are counted once in each of those categories.
- [a]: All deaths including those > 30 days after the last dose of study drug.
- [b]: Deaths occurring more than 30 days after the last dose of study drug are not included.
- AEs occurring more than 30 days after the last dose of study drug are not summarized.
- Missing grades are included under 'All grades' column.
- Source: Table 14.3.1-3

Table 22 Adverse event overview - Part D (Safety population)

	LGG N=20		LCH N=10		All subjects N=30	
Category	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)	All grades n (%)	Grade 3/4/5 n (%)
All deaths [a]	0	0	0	0	0	0
On-treatment deaths [b]	0	0	0	0	0	0
Adverse events	20 (100)	12 (60.0)	10 (100)	7 (70.0)	30 (100)	19 (63.3)
Suspected to be drug related	20 (100)	7 (35.0)	10 (100)	4 (40.0)	30 (100)	11 (36.7)
Serious adverse events	8 (40.0)	6 (30.0)	6 (60.0)	5 (50.0)	14 (46.7)	11 (36.7)
Suspected to be drug related	5 (25.0)	3 (15.0)	3 (30.0)	2 (20.0)	8 (26.7)	5 (16.7)
Fatal serious adverse events	0	0	0	0	0	0
Suspected to be drug related	0	0	0	0	0	0
AEs leading to discontinuation	5 (25.0)	2 (10.0)	1 (10.0)	1 (10.0)	6 (20.0)	3 (10.0)
AEs requiring dose interruptions	16 (80.0)	10 (50.0)	8 (80.0)	4 (40.0)	24 (80.0)	14 (46.7)
AEs requiring dose reductions	6 (30.0)	2 (10.0)	1 (10.0)	1 (10.0)	7 (23.3)	3 (10.0)
AEs requiring dose reductions or interruptions	16 (80.0)	10 (50.0)	8 (80.0)	4 (40.0)	24 (80.0)	14 (46.7)

- MedDRA v 23.1, CTCAE v 4.03
- Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events more than 1 category are counted once in each of those categories.
- [a]: All deaths including those > 30 days after the last dose of study drug.
- [b]: Deaths occurring more than 30 days after the last dose of study drug are not included.
- AEs occurring more than 30 days after the last dose of study drug are not summarized.
- Missing grades are included under 'All grades' column.
- Source: Table 14.3.1-4

For trametinib monotherapy (Parts A and B):

- SAEs were reported in a total of 46 subjects (50.5%) who received trametinib monotherapy; the SAEs that were reported in at least 2 subjects in each part included pyrexia, pneumonia, seizure, viral infection, vomiting, gastroenteritis, hypernatremia, hyponatremia, hypoxia, device-related infection, aspiration, upper respiratory tract infection, varicella, and skin infection.
- The most frequently reported AEs in monotherapy (at least in 35% of all subjects per part) included paronychia, diarrhea, pyrexia, vomiting, dry skin, fatigue, rash, eczema, anemia, decreased appetite, epistaxis, abdominal pain, AST increased, dermatitis acneiform, headache, constipation and cough.
- The majority of subjects (up to 63.4%-86.0%) had grade 1 or 2 hematology abnormalities at baseline and during the course of treatment. The observed new or worsened grade 3 or grade 4 hematology abnormalities based on CTC grade (in ≥ 2% of subjects) included decreased neutrophils (n=4), increased lymphocytes (n=2), decreased lymphocytes (n=1), decreased platelets (n=1), and decreased hemoglobin (n=5).
- The majority of subjects (up to 92.0%- 92.7%) had grade 1 or 2 biochemistry abnormalities at baseline and during the course of treatment. The observed new or worsened grade 3 or grade 4 biochemistry abnormalities based on CTC grade (in ≥ 2% of subjects) included increased ALT (n=1), increased ALP (n=2), decreased sodium (n=3), increased potassium (n=1), decreased potassium (n=2), decreased calcium (n=1), increased AST (n=1), decreased albumin (n=1), and increased glucose (n=1).

Part A

- In the trametinib 0.025 mg/kg/day dose cohort, DLTs of hyponatremia and mucosal inflammation were reported. In the trametinib 0.04 mg/kg/day dose cohort, DLTs of pelvic abscess, hyponatremia, increased ALT, increased AST, dermatitis acneiform, and mucosal inflammation were reported. The RP2Ds for trametinib monotherapy were determined as trametinib 0.032 mg/kg/day for subjects < 6 years old and trametinib 0.025 mg/kg/day for subjects ≥ 6 years old.
- One post-treatment death was reported due to aspiration in the trametinib 0.032 mg/kg/day dose cohort > 28 days from last dose of study drug. The subject (ID 001230) was a 3-year-old male with an ongoing medical condition of right side hemiparesis and history of GI tube insertion that had an SAE of grade 5 massive lung aspiration that started on study day 290 (34 days after last dose of study drug) and was ongoing at end of study.
- SAEs were reported for 23 subjects (46.0%), 12 of whom (24.0%) had SAEs suspected to be related to study drug.
- Twelve subjects (24.0%) discontinued the study due to AEs; rash and dermatitis acneiform were the most common AEs leading to discontinuation (3 subjects each).
- All subjects had at least 1 AE and 25 subjects (50.0%) had ≥ grade 3 events. Grade ≥ 3 AEs reported in more than 10% of subjects with a dose cohort were tachycardia, pneumonia, increased weight, hyponatremia, hypoxia, and rash maculo-papular.
- All subjects had at least 1 AE suspected to be related to study drug.

Part B

- SAEs were reported for 23 subjects (56.1%), 8 of whom (19.5%) had SAEs suspected to be related to study drug.
- Eleven subjects (26.8%) discontinued the study due to AEs; the most common AEs leading to discontinuation were nausea, dermatitis acneiform, and rash (2 subjects each).
- All subjects had at least 1 AE and 27 subjects (65.9%) had grade≥ 3 events. Grade ≥ 3 AEs reported in more than 10% of subjects within a disease cohort were anemia, increased weight, and device-related infection.
- Forty subjects (97.6%) had at least 1 AE suspected to be related to study drug.
- One subject (2.0%) in the neuroblastoma disease cohort had liver enzyme elevations that upon full evaluation did not Hy's law criteria.
- One subject had an AE of electrocardiogram QT prolonged, 12 days after discontinuing treatment for lack of efficacy and observed at the end of study visit.

For dabrafenib + trametinib combination therapy (Parts C and D)

- SAEs were reported in a total of 22 subjects (45.8%) who received dabrafenib + trametinib combination therapy; the SAEs that were reported in at least 2 subjects in each part included pyrexia, pneumonia, dehydration, ejection fraction decreased, hypotension and vomiting.
- The most frequently reported AEs in combination therapy (in at least 35% of all subjects per part) included pyrexia, rash, dry skin, vomiting, diarrhea, AST increased, cough, dermatitis acneiform, headache, nausea, rash maculo-papular, upper respiratory tract infection and fatigue.

- The majority of subjects (up to 63.3%- 88.9%), had grade 1 or 2 hematology abnormalities at baseline and during the course of treatment. The observed new or worsened grade 3 or grade 4 hematology abnormalities based on CTC grade (in ≥ 2% of subjects) included decreased hemoglobin (n=4), increased lymphocytes (n=1), decreased lymphocytes (n=2), decreased neutrophils (n=11), and decreased WBC (n=1).
- The majority of subjects (up to 94.4% had grade 1 or 2 biochemistry abnormalities at baseline and during the course of treatment. The observed new or worsened grade 3 or grade 4 biochemistry abnormalities based on CTC grade (in ≥ 2% of subjects) included increased ALT (n=3), increased ALP (n=3), increased sodium (n=1), increased potassium (n=2), decreased potassium (n=1), increased magnesium (n=1), decreased calcium (n=1), decreased albumin (n=1), increased AST (n=2), increased bilirubin (n=1), increased glucose (n=1), increased creatinine (n=1) and decreased magnesium (n=1).

Part C

- No DLTs were observed in the dabrafenib + trametinib dose cohorts.
- No MTD was established for combination therapy. The RP2Ds for dabrafenib + trametinib combination therapy were determined as trametinib 0.032 mg/kg/day + 100% dabrafenib for subjects < 6 years old and trametinib 0.025 mg/kg/day + 100% dabrafenib for subjects ≥ 6 years old.
- SAEs were reported for 8 subjects (44.4%); 3 (16.7%) were suspected to be related to study drug.
- Four subjects (22.2%) discontinued the study due to AEs.
- All subjects had at least 1 AE and 12 subjects (66.7%) had ≥ grade 3 events. Grade ≥ 3 AEs reported in more than 10% of subjects within a dose cohort were gamma-glutamyltransferase increased, ALT increased, brain edema, febrile neutropenia, uveitis, pyrexia, vomiting, neutrophil count decreased, abdominal pain, nausea, blood ALP increased, panniculitis, dehydration, hypotension, abdominal distension, ECG QT prolongation, upper respiratory infection, cellulitis, dental caries, upper limb fracture, and varicella.
- All subjects had at least 1 AE suspected to be related to study drug.
- Clinically significant abnormal ECG findings occurred for 1 subject with QTcB > 500 ms and were reported as grade 2 and grade 3 AEs of electrocardiogram QT prolonged. This subject had several significant confounding clinical features, including electrolyte abnormalities.

Part D

- SAEs were reported for 14 subjects (46.7%), in 8 cases these were suspected to be related to study drug.
- Six subjects (20.0%) discontinued the study due to AEs.
- All subjects had at least 1 AE and 19 subjects (63.3%) had ≥ grade 3 events. Grade ≥ 3 AEs reported in more than 10% of subjects within a disease cohort were neutropenia, pyrexia, and neutrophil count decreased.
- All subjects had at least 1 AE suspected to be related to study drug.
- Most frequent notable ECG values were HR below LLN (8 subjects, 26.7%) and QTcB increase from baseline of > 30 ms to ≤ 60 ms (15 subjects, 50.0%). One subject (3.3%) had a new QTcB value of > 500 ms. One subject (3.3%) had a new QTcF value of > 500 ms.

2.3.3. Discussion on clinical aspects

The MAH has submitted study X2101 which is part of their clinical development program.

The design of X2101 is in line with the latest PIP (EMEA-001177-PIP01-11-M06) and considered appropriate to achieve the primary objective: to determine the R2PD for trametinib and trametinib plus dabrafenib in paediatric patients that achieves similar exposures to the recommended dose in adults. Also the design is considered acceptable to evaluate the secondary objectives. The eligibility criteria are considered acceptable to select the targeted population of paediatric subjects with refractory or recurrent solid tumours and specifically to select paediatric patients with recurrent, refractory or unresectable BRAF V600 mutated LGG and LCH. The methods to determine the MTD and RP2D as well as to determine the response rates are considered acceptable.

The study subjects mostly consisted of LGG patients (80/139) and included sufficient patients younger than 6 years of age (58/139). There were 26 patients included with NF1 with PN and 11 patients with LCH.

Pharmacokinetics

The applicant conducted both non-compartmental as well as compartmental methods to determine the pharmacokinetic parameters in paediatric patients varying from 0.4 to 17 years of age. Subsequently, the applicant compared the paediatric pharmacokinetic parameters with adult pharmacokinetic parameters.

In the study report (Page 72), it was stated that: "RP2D was based on PK criteria (PK target dose), defined as achieving in children a steady state (Day 15) mean C_T of trametinib that is equivalent to a mean steady state (Day 15) C_T of 10 ng/mL trametinib observed in adults at the recommended dose of 2 mg once daily." The applicant clarified that C_T is an abbreviation for trough concentration. However, in the Applicant's response to Question 2 below, the Applicant mentions that Caverage was the main PK parameter. These statements are conflicting.

Table 11-8, 11-10, 11-13 and 11-17 of the study report and Table 5, 7, 10 and 14 of this assessment report, demonstrate results of the average steady state plasma concentrations per age group in different sub-analyses (i.e. per dose group, disease group, combination groups with dabrafenib). During assessment, it was assumed that Ctrough was meant. Sub-analyses should be provided for Ctrough, as this appears to be the pre-defined PK parameter for dosing decisions. A justification for the pre-defined PK parameter for dosing decisions is however lacking and the non-compartmental methods are difficult to interpret due to the smaller sample sizes of the individual cohorts. Compartmental methods and exposure-response models are therefore expected at the time of submission of the planned variation to justify which PK parameter should be used for dosing decisions.
Trametinib achieved the target concentration in part A (dosages > 0.025 mg/kg/day), part B (0.025 mg/kg/day), part C (dosages > 0.025 mg/kg/day + 50% dabrafenib RP2D), part D (dosages > 0.025 mg/kg/day). A justification for the pre-defined target concentration is however lacking and the non-compartmental methods are difficult to interpret due to the smaller sample sizes of the individual cohorts.

The applicant states that the RP2Ds for trametinib monotherapy were determined as 0.032 mg/kg/day for subjects < 6 years old and 0.025 mg/kg/day for subjects ≥ 6 years old. However, data of the non-compartmental methods do not allow a solid conclusion due to the limited number of patients per age range in the different parts of the study. It is unclear which PK parameter is the main parameter of interest for dosing decisions. Nonetheless, it is understood that a population pharmacokinetic model will be submitted as part of the planned variation to further substantiate paediatric posology.

A population pharmacokinetic analyses is also being conducted and minimal results have already been presented in the study report. No details of the population pharmacokinetic analyses have been provided, but the presented plots are assumed to be post-hoc fits of the paediatric data to the adult model (MAXEVAL=0). A small bias is seen in the higher concentration range, but in general the results look adequate. As the applicant states that further results will be submitted, no questions regarding the population pharmacokinetic model are currently requested. The Applicant is expected to provide a clear justification for the used target concentrations at the time of application. Additionally, details about the population pharmacokinetic model should then also be provided. In this respect, a comparison between the adult model and updated paediatric model and a justification for the updates (such as a discussion whether the paediatric data are informative enough for the updates) are expected.

Efficacy

The response rates per investigator (inv.) for trametinib monotherapy in part A and part B were respectively 4.0% (95% CI: 0.5, 13.7) and 22.0% (95% CI: 10.6, 37.6). There were no CRs seen in part A and B. The response rates for dabrafenib + trametinib in part C and B were respectively 50.0% (95% CI: 26.0, 74.0) and 56.7% (95% CI: 37.4, 74.5) including 7 CRs.

The ORR per inv. for trametinib monotherapy for subjects with glioma fusion was 19.2% (95% CI: 6.6, 39.4), and for subjects with BRAF V600 mutant glioma was 38.5% (95% CI: 13.9, 68.4). For the dabrafenib + trametinib combination arms, the ORR per inv. for subjects with BRAF V600 glioma was 52.8% (95% CI: 35.5, 69.6) and with LCH was 58.3% (95% CI: 27.7, 84.8). For subjects with NF-1 with PN the independent review ORR was 58.1% (95% CI: 39.1, 75.5). Note that the responses per independent reviewer for glioma's were consistently lower compared to investigator assessment and the concordance between Investigator and independent review ranged between 58.3% -73.1%.

The response data show preliminary clinical evidence of anti-tumour activity of trametinib monotherapy and dabrafenib + trametinib in paediatric patients with BRAF V600 mutant LGG and LCH, and of trametinib monotherapy in paediatric patients with NF1 with PN.

Safety

The RP2Ds for trametinib monotherapy were determined as 0.032 mg/kg/day for subjects< 6 years old and 0.025 mg/kg/day for subjects ≥ 6 years old. This was based on the achieved target exposures that are associated with the recommended efficacious adult dose for melanoma treatment. As states above, the methods to determine the RP2D are considered acceptable.

The AEs observed in study X2101 are consistent with the known safety profile for trametinib monotherapy and dabrafenib + trametinib combination therapy. No new safety signals were observed.

Patients had height and weight growth similar to that expected for their ages and there were no abnormalities observed in sexual maturity. There were growth plate abnormalities observed in 2 subjects. These data are expected to be monitored in the subsequent studies.

Conclusion

The MAH has submitted study X2101 in paediatric subjects with refractory or recurrent solid tumours. The RP2Ds for trametinib monotherapy were determined as 0.032 mg/kg/day for subjects <6 years old and 0.025 mg/kg/day for subjects ≥ 6 years old. The response data show preliminary clinical evidence of anti-tumour activity of trametinib monotherapy and dabrafenib + trametinib in paediatric patients with BRAF V600 mutant LGG and LCH, and of trametinib monotherapy in paediatric patients with NF1 with PN. No new safety concerns were identified. The provided efficacy and safety data do not affect

the benefit-risk for the current indications, however several questions on pharmacokinetics have been raised.

The SmPC of trametinib currently reports that there are no data in paediatric patients and the Applicant proposed no changes to the paediatric information in the SmPC. In accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 the Applicant would be expected to update the SmPC with data derived from study X2101. However, amendments to the SmPC are not considered necessary at this moment.

3. Overall conclusion and recommendation

☒ Fulfilled:

No further action required, however, further data are expected in the context of a variation prior any conclusion on product information amendments is made. The MAH should commit to submit this variation application by Q4/2022.

4. Additional clarification requested

Based on the data submitted, the MAH was requested to address the following questions:

1. In the study report, it was noted that C_T was an abbreviation for trough concentration. It is assumed that this is an error and that $C_{average}$ was meant. This needs to be clarified.
2. The applicant states that the RP2Ds for trametinib monotherapy were determined as 0.032 mg/kg/day for subjects < 6 years old and 0.025 mg/kg/day for subjects ≥ 6 years old. However, data of the non-compartmental methods do not allow a solid conclusion due to the limited number of patients per age range in the different parts of the study. This can presumably only be substantiated with the population pharmacokinetic model. The pharmacokinetic rationale for this statement needs to be provided.
3. The applicant is requested to provide a summary of the bioanalytical method used in this study, including bioanalytical reports (bioanalytical study report and validation report).

5. MAH responses to Request for supplementary information

Question 1

In the study report, it was noted that C_T was an abbreviation for trough concentration. It is assumed that this is an error and that Caverage was meant. This needs to be clarified.

Applicant's Response

We would like to clarify that C_T was not Caverage. As shown in Table 11-7 on page 155 of the CTMT212X2101 CSR, there are results for Cavg (average steady state plasma concentration) and Ctrough (trough concentration). Based on the list of abbreviations and definition of terms on page 64, C_T was an abbreviation for trough concentration, and Cavg was an abbreviation for average steady state plasma concentration.

Assessment of the Applicant's Response

In the study report (Page 72), it was stated that: *"RP2D was based on PK criteria (PK target dose), defined as achieving in children a steady state (Day 15) mean C_T of trametinib that is equivalent to a mean steady state (Day 15) C_T of 10 ng/mL trametinib observed in adults at the recommended dose of 2 mg once daily."* The applicant clarified that C_T is an abbreviation for trough concentration. However, in the Applicant's response to Question 2 below, the Applicant mentions that $C_{average}$ was the main PK parameter. These statements are conflicting.

Table 11-8, 11-10, 11-13 and 11-17 of the study report and Table 5, 7, 10 and 14 of this assessment report, demonstrate results of the average steady state plasma concentrations per age group in different sub-analyses (i.e. per dose group, disease group, combination groups with dabrafenib). During assessment, it was assumed that Ctrough was meant. Sub-analyses should be provided for Ctrough, as this appears to be the pre-defined PK parameter for dosing decisions.

A justification for the pre-defined PK parameter for dosing decisions is however lacking and the non-compartmental methods are difficult to interpret due to the smaller sample sizes of the individual cohorts. Compartmental methods and exposure-response models are therefore expected as part of the planned variation to justify which PK parameter should be used for dosing decisions.

Conclusion

Issue not further pursued.

Question 2

The Applicant states that the RP2Ds for trametinib monotherapy were determined as 0.032 mg/kg/day for subjects < 6 years old and 0.025 mg/kg/day for subjects ≥ 6 years old. However, data of the non-compartmental methods do not allow a solid conclusion due to the limited number of patients per age range in the different parts of the study. This can presumably only be substantiated with the population pharmacokinetic model. The pharmacokinetic rationale for this statement needs to be provided.

Applicant's Response

The 0.025mg/kg/day trametinib was shown to be tolerable and was declared as the recommended phase 2 dose (RP2D) for patients aged 1 month to <18 years. Results from the Parts A, B and C of this trial, which were either completed or ongoing at the time the RP2D was established, have showed that the 0.025 mg/kg/day dose level achieved target exposures that are associated with the recommended efficacious adult dose for melanoma treatment, in most patients older than 6 years of age. The preplanned dose of 0.04 mg/kg was not tolerated with DLTs occurring in each age category. However, as PK data from additional patients became available, the data showed that patients under the age of 6 are less likely to achieve the target exposure when dosed at 0.025 mg/kg/day than the older patients. The exposure-efficacy relationship for trametinib when combined with dabrafenib in adult melanoma patients demonstrates an apparent threshold effect and provides further rationale to optimize trametinib exposures in pediatric patients. Therefore, a Part A extension was added to test the intermediate trametinib dose level of 0.032 mg/kg/day in patients under 6 years of age for safety, tolerability and pharmacokinetics. This dose of 0.032 mg/kg/day was well tolerated in patients under 6 years of age, both as monotherapy and in combination with dabrafenib The pediatric posology that will be proposed for dabrafenib in combination with trametinib in an application to EMA in 2022, will be

supported by a population pharmacokinetic model which will include patients treated with trametinib monotherapy and the combination from studies CTMT212X2101 and CDRB436G2201.

The trametinib dose of 0.025mg/kg/day was shown to be tolerable and was declared as the recommended phase 2 dose (RP2D) for patients aged 1 month to <18 years in Mar-2016. The higher preplanned dose of 0.04 mg/kg was not tolerated with DLTs occurring in each age category, with 6 DLTs in 5 patients:

- Patient 000002 (age 5 months) Grade 3 Suprapubic skin abscess
- Patient 000403 (age 14 years) Grade 2 Rash acneiform
- Patient 000802 (age 8 years) Grade 3 Stomatitis/Mucositis
- Patient 205382 (age 9 years) Grade 3 Alanine aminotransferase increased
- Patient 001204 (age 17 years) Grade 4 Hyponatremia and Grade 4 Hypotension

The exposure-efficacy relationship for trametinib when combined with dabrafenib in adult melanoma patients demonstrated an apparent threshold effect, with target trametinib exposures of Cavg>=10ng/mL associated with efficacy. Preliminary results from Parts A, B and C of this trial that were either completed or ongoing at the time the RP2D was established, indicated that the 0.025 mg/kg/day dose level achieved target Cavg exposures in most patients older than 6 years of age (geo mean 15.8 ng/mL, 90% above target threshold, n=30). However, patients younger than 6 years of age were less likely to achieve the target exposure when dosed at 0.025 mg/kg/day (geo mean 11.9ng/mL, 77% above target threshold, n=22). Therefore, a Part A extension was added with protocol amendment 5 on 08-Mar-2017 to test the intermediate trametinib dose level of 0.032 mg/kg/day in patients under 6 years of age for safety, tolerability and pharmacokinetics. This dose of 0.032 mg/kg/day was well tolerated in patients under 6 years of age, both as monotherapy and in combination with dabrafenib.

We confirm that the pediatric posology that will be proposed for dabrafenib in combination with trametinib in an application to EMA in 2022, will be supported by a population pharmacokinetic model which will include data from patients treated with dabrafenib and/or trametinib in studies CDRB436A2102, CTMT212X2101 and CDRB436G2201.

Assessment of the Applicant's Response

As stated in the Assessment of Question 1, it is unclear which PK parameter should be used to justify the paediatric posology. Nonetheless, the applicant concludes that adequate exposure has been achieved in paediatric patients with the 0.025 mg/kg/day dose level (although less likely in patients 6 years of age). It is unclear whether this dose is suitable for all paediatric patients as the currently provided results of different subgroups cannot be interpreted with the unclarities around the main PK parameter. Safety appears to be the main rationale for selection of the 0.025 mg/kg/day and 0.032 mg/kg/day dosages. A population pharmacokinetic model will however be submitted as part of the planned variation to further substantiate paediatric posology.

Conclusion

Issue not further pursued.

Question 3

The Applicant is requested to provide a summary of the bioanalytical method used in this study, including bioanalytical reports (bioanalytical study report and validation report).

Applicant's Response

Plasma concentrations of dabrafenib, its three metabolites, hydroxyl-dabrafenib, carboxydabrafenib, and desmethyl-dabrafenib, and trametinib were analyzed using three different validated bioanalytical methods: GGGHPP, G83HPP and GK2HPP. The method GK2HPP has a lower LLOQ for quantification of trametinib and was only used for analysis of samples from part A and part B otherwise method GGGHPP was used to quantify trametinib.

All bioanalytical methods used to measure concentrations of dabrafenib, dabrafenib metabolites, and trametinib in human plasma were sensitive, selective, accurate and reproducible. Long term stability of the analytes (dabrafenib, hydroxyl-dabrafenib, desmethyldabrafenib and trametinib) was demonstrated for at least 1616 days (812 days for trametinib at lower LLOQ) when stored in human plasma between -10°C and -30°C. Long term stability for carboxy-dabrafenib was demonstrated for 848 days when stored in human plasma between -10°C and -30°C. Stability of all analytes was also demonstrated during sample processing. The methods are described below and method validation reports provided in addition.

Method GGGHPP to Quantify Dabrafenib, Hydroxy-dabrafenib, Desmethyl-dabrafenib and Trametinib in Human Plasma

Validation of the method was conducted by Labcorp (formerly Covance) Laboratories, Madison, WI, US. The analytical method for dabrafenib (parent), hydroxy-dabrafenib, desmethyl-dabrafenib, and trametinib was validated with a 8-point calibration curve from 1.00 ng/mL to 1000 ng/mL for dabrafenib and its two metabolites and from 0.25 to 250 ng/mL for trametinib. Dabrafenib, hydroxy-dabrafenib, desmethyl-dabrafenib, and trametinib were extracted from human plasma by liquid-liquid extraction (LLE) using ethyl acetate after the addition of isotopically labelled internal standards [2H9]-dabrafenib, [2H6 13C2]-GSK2285403, [2H6 13C2]-GSK2167542 and [13C6]-GSK1120212. Extracts were analysed using high performance liquid chromatography/mass spectrometry/mass spectrometry (HPLC-MS/MS) with a TurboIonspray™ interface and positive ion multiple reaction monitoring with a single injection. The validation procedures were conducted in accordance with Labcorp Standard Operating Procedures (SOP). The lower limit of quantitation (LLQ) was 1.00 ng/mL for dabrafenib, hydroxy-dabrafenib and desmethyl-dabrafenib and 0.25 ng/mL for trametinib, using a 50 µL aliquot of human plasma.

Method G83HPP to Quantify Carboxy-dabrafenib in Human Plasma

The method was validated at Labcorp. Carboxy-dabrafenib was extracted from human plasma by protein precipitation using 80/20 ethyl alcohol/water containing [2H6 13C2]-GSK2298683 as an internal standard. Extracts were analysed by ultra-high pressure liquid chromatography/mass spectrometry/mass spectrometry (UHPLC-MS/MS) using a TurboIonspray™ interface with positive ion multiple reaction monitoring. This method was validated according to departmental SOPs over the range 5 ng/mL to 5000 ng/mL. The LLQ was 5 ng/mL using a 25 µL aliquot of human plasma.

Method GK2HPP to Quantify Trametinib in Human Plasma

Validation of the method was conducted by Labcorp Laboratories, Madison, WI, US. The analytical method for trametinib was validated with a 9-point calibration curve from 0.100 ng/mL to 250 ng/mL. Trametinib was extracted from human plasma by liquid-liquid extraction (LLE) using ethyl acetate after the addition of isotopically labelled internal standard [13C6]-GSK1120212 and ammonium hydroxide. Extracts were analysed using ultrahigh performance liquid chromatography/mass spectrometry/mass spectrometry (UPLC-MS/MS) with a TurboIonspray™ interface and positive ion multiple reaction monitoring with a single injection. The validation procedures were conducted in accordance with Labcorp Standard Operating Procedures (SOP). The lower limit of quantitation (LLQ) was 0.100 ng/mL for trametinib, using a 50 µL aliquot of human plasma.

Within Study Quality Control Sample Analysis
Quality control (QC) samples were prepared and stored alongside the study samples. The QC samples and separately prepared calibration standards were analyzed with each batch of clinical samples. Spiked duplicate standard curve and QC samples were extracted daily to permit the determination of the concentration of dabrafenib, as well as hydroxy-, carboxy-, and desmethyldabrafenib, and of trametinib and to monitor the day-to-day performance of the method, respectively. For the analysis to be acceptable, no more than one-third of the QC sample results could deviate from the nominal concentration by more than 15%. In addition, at least 50% of the results from each QC concentration should be within 15% of nominal. All applicable analytical runs for the clinical study MEK116540 (TMT212X2101) met these predefined run acceptance criteria. The overall accuracy and precision of QC samples from each of the studies are summarized in the attached bioanalytical data report.

Assessment of the Applicant's Response
The applicant provided the bioanalytical report (DMPK RCTMT212X2101) of study CTMT212X2101 regarding the determination of dabrafenib, its three metabolites, hydroxyl-dabrafenib, carboxydabrafenib, and desmethyl-dabrafenib, and trametinib in plasma. No validation reports are however provided. These will need to be submitted as part of the planned variation in order to assess the bioanalytical method used.
Conclusion
Issue not further pursued.