Amsterdam, 26 March 2026
EMADOC-1700519818-2637645
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMA/VR/0000271728

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:
Tafinlar	dabrafenib
Mekinist	trametinib

Worksharing applicant (WSA): Novartis Europharm Limited

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AUC	Area under the concentration-time curve
BID	*bis in die*, twice a day
BOR	best overall response rate
BRAF	B-Raf proto-oncogene, serine/threonine kinase
C_{avg}	Average concentration
CDC	Centers for Disease Control
CI	Confidence interval
C_{max}	Maximum concentration
$C_{max.re}$	C_{max} with residual error
C_{min}	minimum concentration
CR	Complete Response
Ctrough	Lowest concentration
GSK	GlaxoSmithKline
HGG	High Grade Glioma
LDH	Lactate dehydrogenase
LGG	Low Grade Glioma
LVEF	left ventricular ejection fraction
MAP	Managed Access Program
MAPK	Mitogen-Activated Protein Kinase
MEK	Mitogen-activated extracellular signal-regulated kinase
pcVPCs	prediction-corrected visual predictive checks
PD	pharmacodynamics
PIP	paediatric investigation plan(s)
PK	pharmacokinetic(s)
PopPK	Population pharmacokinetics
QD	*Quaque die*, once a day
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
ss	Steady state
VPC	Visual predictive check

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 3 Jun 2025 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of unresectable or metastatic melanoma with a BRAF V600 mutation and adjuvant treatment of Stage III melanoma with a BRAF V600 mutation for adolescents aged 12 years and older for TAFINLAR and MEKINIST, based on an extrapolation report using a modelling and simulation approach to demonstrate PK, PD and efficacy of dabrafenib and trametinib in adolescent patients. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. RMP versions 13.0 and 21.0 for Tafinlar and Mekinist, respectively, have also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI and to update list of local representatives in the Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0410/2020 (Tafinlar) and P/0392/2020 (Mekinist) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0410/2020 (Tafinlar) and P/0392/2020 (Mekinist) were completed.

The PDCO issued an opinion on compliance for the PIP P/0410/2020 (Tafinlar) and P/0392/2020 (Mekinist).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH 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.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed Rapporteurs for the WS procedure:

Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	3 June 2025
Start of procedure:	21 June 2025
CHMP Rapporteur's preliminary assessment report circulated on:	14 August 2025
PRAC RMP advice and assessment overview adopted by PRAC	4 September 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	18 September 2025
WSA's responses submitted to the CHMP on:	10 November 2025
CHMP Rapporteur's preliminary assessment report on the WSA's responses circulated on:	26 November 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	11 December 2025
WSA's responses submitted to the CHMP on:	24 February 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 March 2026
CHMP opinion:	26 March 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The current worksharing procedure is to extend the approved melanoma indications in adults for dabrafenib and trametinib to adolescents aged 12 years and older.

The indications sought for dabrafenib are:

Melanoma

Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adults and adolescents aged 12 years and older with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1).

Adjuvant treatment of melanoma

Dabrafenib in combination with trametinib is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage III melanoma with a BRAF V600 mutation, following complete resection.

The indications sought for trametinib are:

Melanoma

Trametinib as monotherapy or in combination with dabrafenib is indicated for the treatment of adults and adolescents aged 12 years and older with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1).

Adjuvant treatment of melanoma

Trametinib in combination with dabrafenib is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage III melanoma with a BRAF V600 mutation, following complete resection.

Epidemiology

The incidence of BRAF V600 mutation-positive melanoma in adolescent patients is extremely low (Howlader et al 2013) but is not considered to have any major distinguishing or unique characteristics from conventional adult-type BRAF V600 mutation-positive melanoma (Wilmott et al 2019, Merkel et al 2019). BRAF mutations lead to constitutive activation of the MAPK signaling pathway, which in turn mediates several phenomena, including cell proliferation, differentiation, and secretion of signal molecules, related to melanoma occurrence and progression (Castellani et al 2023).

Based on limited data available, it is understood that the conventional adult-type melanoma in adolescents is the most prevalent BRAF V600 mutation-positive melanoma in adolescents, and this type of adolescent melanoma does not have any distinguishing or unique characteristics from conventional adult-type melanoma observed in adults (Lu et al 2015, Wilmott et al 2019, Grobner et al 2018).

Management

Targeted therapies (BRAF and MEK inhibitors) are effective and approved for treating BRAF-mutated melanoma in adults and show substantial response rates (see Mekinist and Tafinlar SmPCs). The data in adolescents are limited to isolated cases, however similar treatment strategies as for adults have been used, with similar results (Saiyed et al 2017). Generally, it is recommended that adolescents with adult-type conventional melanomas be enrolled into adult clinical studies (Kolandijan et al 2014). However, there is no currently approved therapy in the EU specifically for adolescents with BRAF V600 mutation-positive melanoma, hence there is an unmet medical need.

2.1.2. About the product

Dabrafenib is an inhibitor of RAF kinases. Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, B-Raf serine-threonine kinase (BRAF) inhibitors, ATC code: L01EC02

Trametinib is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. Trametinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity. Trametinib inhibits growth of BRAF V600 mutant melanoma cell lines and demonstrates anti-tumour effects in BRAF V600 mutant melanoma animal models.

The currently approved indications for Mekinist/Tafinlar is for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, and for the adjuvant treatment

of adult patients with Stage III melanoma with a BRAF V600 mutation following complete resection. In addition, the combination is approved for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The application is based on Tafinlar PIP01 measure 7 (Measure to demonstrate that the pharmacokinetics, pharmacodynamics and efficacy of dabrafenib in adolescent patients (aged from 12 to less than 18 years of age) with BRAF V600-mutant melanoma are similar to that in adults with BRAF V600-mutant melanoma, using a modelling and simulation approach for the purpose of extrapolation.); the same measure is captured in the Mekinist PIP01 as Study 6.

This application is covered by approved Paediatric Investigational Plans (PIP) EMEA-01147-PIP01-11-M07 (dabrafenib) and EMEA-001177-PIP01-11-M06 (trametinib). All measures for dabrafenib and for trametinib have been completed as confirmed by compliance check procedures EMEA-C-001147-PIP01-11-M07 and EMEA-C-001177-PIP01-11-M06 (for dabrafenib and trametinib, respectively) and are appropriately reflected in the respective SmPCs with this application, as detailed in the Overview Table of the Paediatric Investigation Plan.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

In the current submission, the melanoma indication is extended to include also paediatric patients, particularly from 12+ years to 18+ years. In the initial melanoma MAA, the applicant used the all ages prevalence for melanoma and therefore the calculation cover the current extension of indication and the conclusion of the previous ERA remains valid.

For clarity, the summary of main study results from the previous ERAs for the peadiatric glioma indication are provided below.

Table 1 Summary of main study results

Substance (INN/Invented Name): Trametinib dimethyl sulfoxide/Mekinist					
CAS-number (if available): 871700-17-3					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	4.04			Not Potential PBT
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, refined (overall PEC $_{surfacewater}$, calculated based on glioma and previously approved indications for NSCLC and melanoma)	0.00072	µg/L			> 0.01 threshold No
Other concerns (e.g. chemical class)					N
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test 72h/ *Pseudokirchnereriella subcapita*	OECD 201	NOEC	0,04	mg/L	
Daphnia sp. ReproductionTest 21d, semi static, *Daphnia magna*	OECD 211	NOEC	0,013	mg/L	reproduction
Fish, Early Life Stage Toxicity Test 28d, flow through/*Pimephales promelas*	OECD 210	NOEC	0,004	mg g/L	0.003mg/L (mean measured

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 glioma and previously approved indications for NSCLC and melanoma)	mg/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_{Foc} =2460 L/Kg	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:	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.

		day 59: 10.4 %/14.0 %			
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	0.0583	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 GLP	OECD 209	EC50 NOEC	>1000 312.5	mg/L	Total respiration

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.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted for this application. This is considered acceptable.

With addition of the proposed indication, based on the ERA, trametinib and dabrafenib are not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

This application is intended to support the broadening of the currently approved indication for dabrafenib and trametinib to include the paediatric patient population aged ≥12 years and to provide dosage recommendations for paediatric patients weighing ≥26 kg. The proposed adolescent posology is based on exposure similar to adults with BRAF V600-mutant melanoma and is supported by pharmacokinetic (PK) data, modelling and simulation (+ cross ref to sections below).

GCP

No new clinical data were provided by the Applicant. The clinical paediatric data referred to herein were previously submitted in the procedures Finlee (EMEA/H/C/005885/0000) and Spexotras (EMEA/H/C/005886/0000) from the same Applicant. The following statements were made by the Applicant in procedures Finlee and Spexotras.

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.

- Tabular overview of clinical studies

Table 1 Overview of studies providing adolescent data

Phase/ Objective	Population	No. of patient adolescent patients enrolled (total patients)	Study treatment	Status
Study A2102 (GlaxoSmithKline code: BRF116013): A multicenter, dose escalation/expansion, single-arm open-label clinical study.				
Phase I/IIa: safety, tolerability, PK; clinical activity (Part 2 only)	Pediatrics (≥ 12 months to < 18 years) with advanced BRAF V600 mutation-positive solid tumor	35 (Part I: 27; Part 2: 58)	Dabrafenib: total daily dose adjusted to subject's BW.	Study completed LPLV: 04-Dec-2020
Study X2101 (GlaxoSmithKline code: MEK116540): Multicenter, dose escalation, 4-part tumor cohort-expansion, open-label clinical study				
Phase I/II: safety, tolerability, PK, PD; clinical activity (Part B and D only)	Pediatrics (1 month and < 18 years of age) with solid tumor as recurrent, refractory, or unresectable histologically confirmed BRAF V600 mutant tumor or PNs harboring BRAF V600 mutation	38 (Part A: 50; Part B: 41; Part C: 18; Part D: 30)	Dabrafenib or trametinib each within age-range starting dosing. ≥ 12 y, 4.5 mg/kg/d. Trametinib for ≥ 6 y, 0.025 mg/kg/d	Study completed LPLV: 29-Dec-2020
Study G2201: Multicenter, randomized, single-arm, open-label clinical study				
Phase II: efficacy, safety, tolerability, PK	Single-arm cohort only: Pediatrics (≥12 months to <18 years of age) with BRAF V600 mutation-positive relapsed or refractory histologically confirmed high grade glioma	57 (151)	Dabrafenib+Trametinib: Dabrafenib BID: ≥ 12 y: 4.5 mg/kg/d and Trametinib≥ 6 y: 0.025 mg/kg/d	Study ongoing, as of data cut-off date of 23-Aug-2021

2.3.2. Pharmacokinetics

Pharmacokinetics have a major role for the benefit-risk assessment in the current procedure. The dose justification is based on a PK-bridge. This approach assumes extrapolation of efficacy and safety from adult melanoma patients. The proposed posology is supported by PopPK-based simulations and exposure matching.

This application is supported by historical PK data in paediatric patients previously submitted in the Finlee (EMEA/H/C/005885/0000) and Spexotras (EMEA/H/C/005886/0000) procedures for the clinical studies outlined in *Table 1*. Studies A2102, X2101 and G2201 included 130 adolescent patients with other (non-melanoma) malignancies who received dabrafenib and/or trametinib (either as single agents or in combination). Due to the rarity of the condition, no adolescent patients with melanoma were enrolled in these studies. However, the PK insights from those with available PK are applicable to patients with melanoma, as there is no evidence of any clinically relevant differences in PK across indications.

An overview of the observed PK data vs time after dose in paediatric patients aged 6 to 17 years is shown in *Figure 1* and *Figure 2* for dabrafenib and trametinib, respectively.

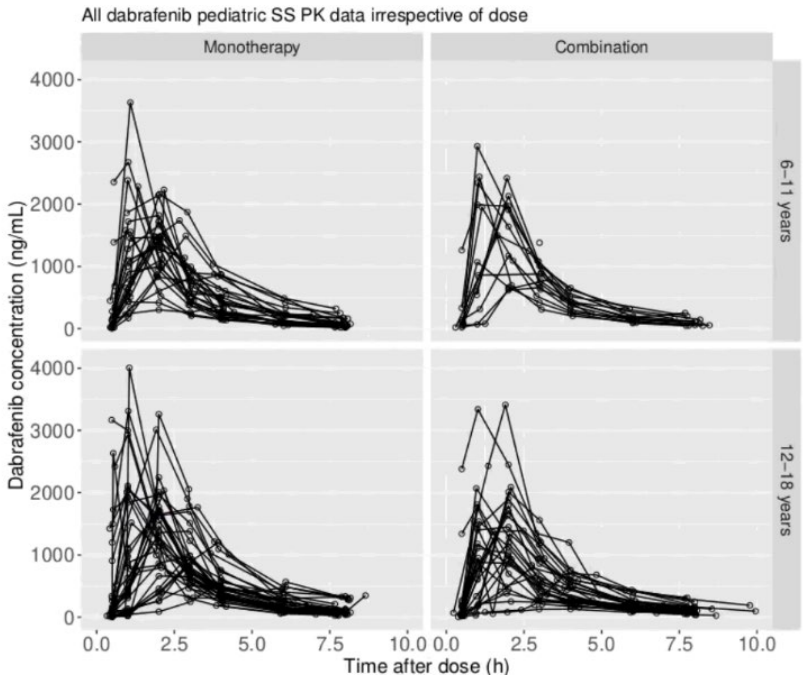

Figure 1 Dabrafenib concentration profiles across 6 to 11 and 12-17 year old patients (stratified by age group and arm)

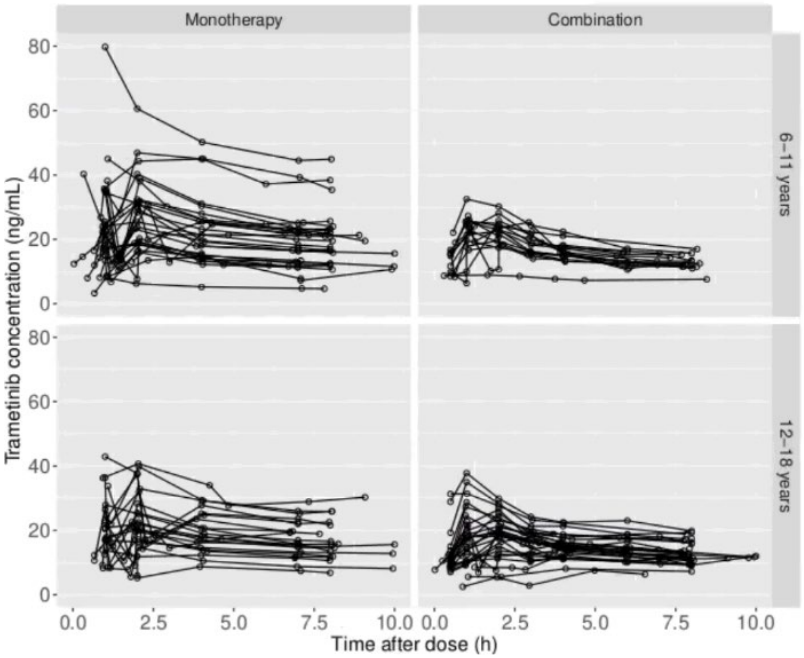

Figure 2 Trametinib concentration profiles across paediatric 6 to 17 year old patients stratified by treatment arm (mono/combo)

Population pharmacokinetics

PopPK models for dabrafenib and trametinib were already established with dense PK data in adult patients with BRAF V600 mutation-positive melanoma. The existing PopPK models in adults were updated with PK data from pediatric patients aged 6 to 17 years in Studies A2102, X2101 and G2201 (data not shown).

Previously developed paediatric PopPK models based on paediatric data including patients 1-17 years are described below. These models were previously assessed in the procedures Finlee (EMEA/H/C/005886/0000) and Spexotras (EMEA/H/C/005886/0000). These models are summarized below. Refer to the Finlee and Spexotras EPARs for more details.

The obtained PK parameters for the PopPK models developed on patients 1-17 years were used to run simulations at different doses of dabrafenib and trametinib to determine the required doses of dabrafenib capsule formulation and the trametinib tablet formulation in adolescent patients to reach similar exposures as those in adult patients. The body weight range used in the simulations (≥ 26 kg) covers the expected weight range for the target population of adolescent patients aged 12 years and older. Consistent weight categories were used for both dabrafenib and trametinib posology to the extent possible.

PopPK models in patients 1-17 years

The population PK models summarized below are based on data from paediatric patients aged 1-17 years and were submitted and assessed in the procedures Finlee and Spexotras. The PopPK models in patients 6-17 years and 1-17 years were built on data from the same paediatric clinical studies. The main difference is that the model based on patients 1-17 years include additional data (in younger subjects <6 years).

Dabrafenib

A total of 2185 dabrafenib PK observations across 243 patients (47 patients in X2101, 111 patients in G2201, and 85 patients in A2102) were available for the model development.

The parameters of the final PopPK model with 1 to 17 year old patients' data are shown in *Table 2*. The final PopPK model with 1 to 17 year old patients' data evaluation included prediction-corrected visual predictive checks (pcVPCs) shown in *Figure 3* (stratified on formulation), and *Figure 4* (stratified on weight).

Table 2 Parameter posteriors and covariate effects by the dabrafenib PopPK model with 1 to 17 year old patients' data

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.

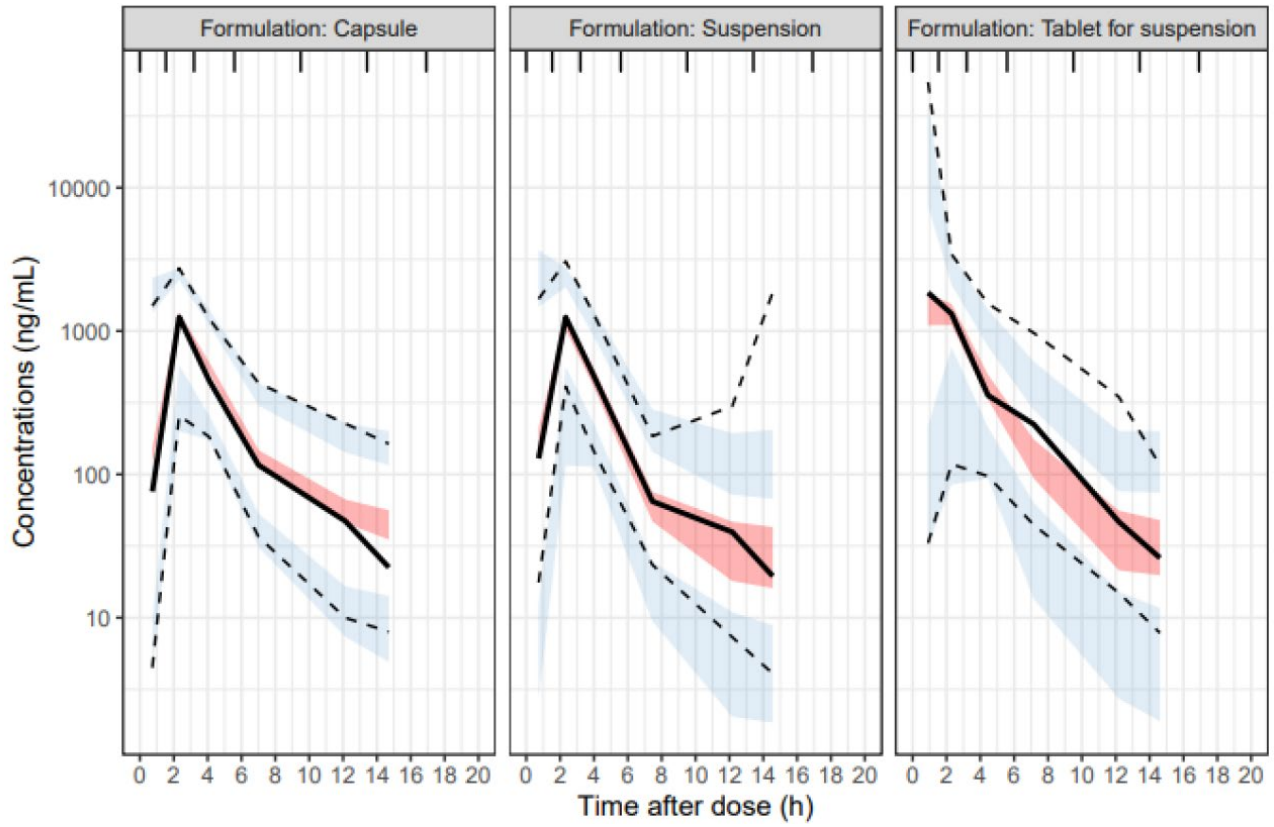

Figure 3 Prediction-corrected VPC for dabrafenib final the PopPK model with 1 to 17 year old patients' data stratified by formulation.

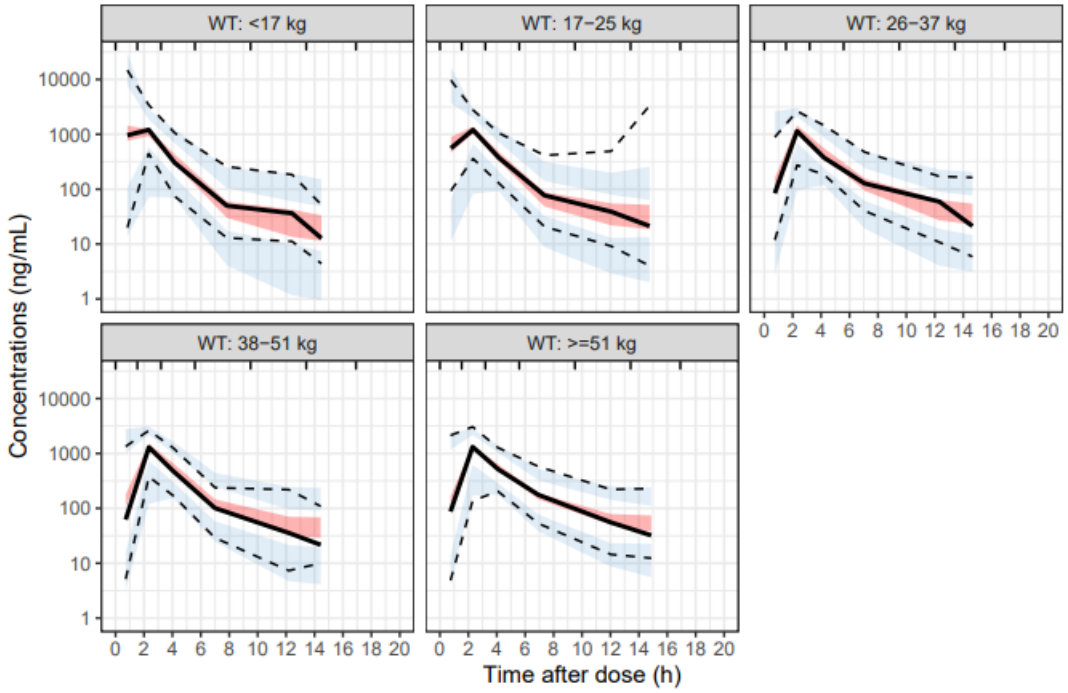

Figure 4 Prediction-corrected VPC for dabrafenib final PopPK model with 1 to 17 year old patients' data stratified by weight.

Trametinib

A total of 1943 trametinib PK observations across 244 patients (133 patients in X2101 study, and 111 patients in G2201 study) were available for the model development.

The parameters of the final PopPK model with 1 to 17 year old patients' data are shown in *Table 3*. The final PopPK model with 1 to 17 year old patients' data evaluation included prediction-corrected visual predictive checks (pcVPCs) shown in *Figure 5* (stratified on formulation), and *Figure 6* (stratified on weight).

Table 3 Parameter posteriors and covariate effects by the trametinib PopPK model with 1 to 17 year old patients' data

Parameter Name	Mean	95% Confidence Interval
Q (L/h)	60	NA
M (-)	0.1	NA
CL (L/h)	5.212	(4.661 - 5.788)
VC (L)	118.285	(81.746 - 158.281)
VP (L)	371.939	(294.231 - 455.501)
KA1 (1/h)	0.026	(0.018 - 0.037)
KA2 (1/h)	1.432	(0.993 - 1.96)
MTIME (h)	0.372	(0.316 - 0.425)
WT_CL (-)	0.472	(0.393 - 0.548)
WT_Q (-)	0.586	(0.366 - 0.807)
SEX_CL (-)	0.862	(0.798 - 0.929)
Combo_F1 (-)	0.721	(0.666 - 0.778)
Form1_F1(-)	1.234	(1.135 - 1.338)
WT_VC (-)	0.966	(0.704 - 1.248)
WT_VP (-)	0.995	(0.809 - 1.17)
Form1_KA 2 (-)	2.232	(1.67 - 2.837)
ω^2_{CL}	0.038	(0.023 - 0.056)
$\omega_{CL}\omega_{Vc}$	0.095	(0.054 - 0.144)
ω^2_{Vc}	0.522	(0.347 - 0.772)
ω^2_Q	0.54	(0.306 - 0.875)
$\omega^2_{V_p}$	0.059	(0.011 - 0.145)
$\omega^2_{K_{A_1}}$	0.618	(0.33 - 1.084)
$\omega^2_{K_{A_2}}$	0.04	(0.009 - 0.137)
ω^2_{MTIME}	0.146	(0.063 - 0.28)
SIGMA.1.1.	0.049	(0.044 - 0.053)
MCMCOBJ	-5007.743	(-5478.655 - -4520.511)

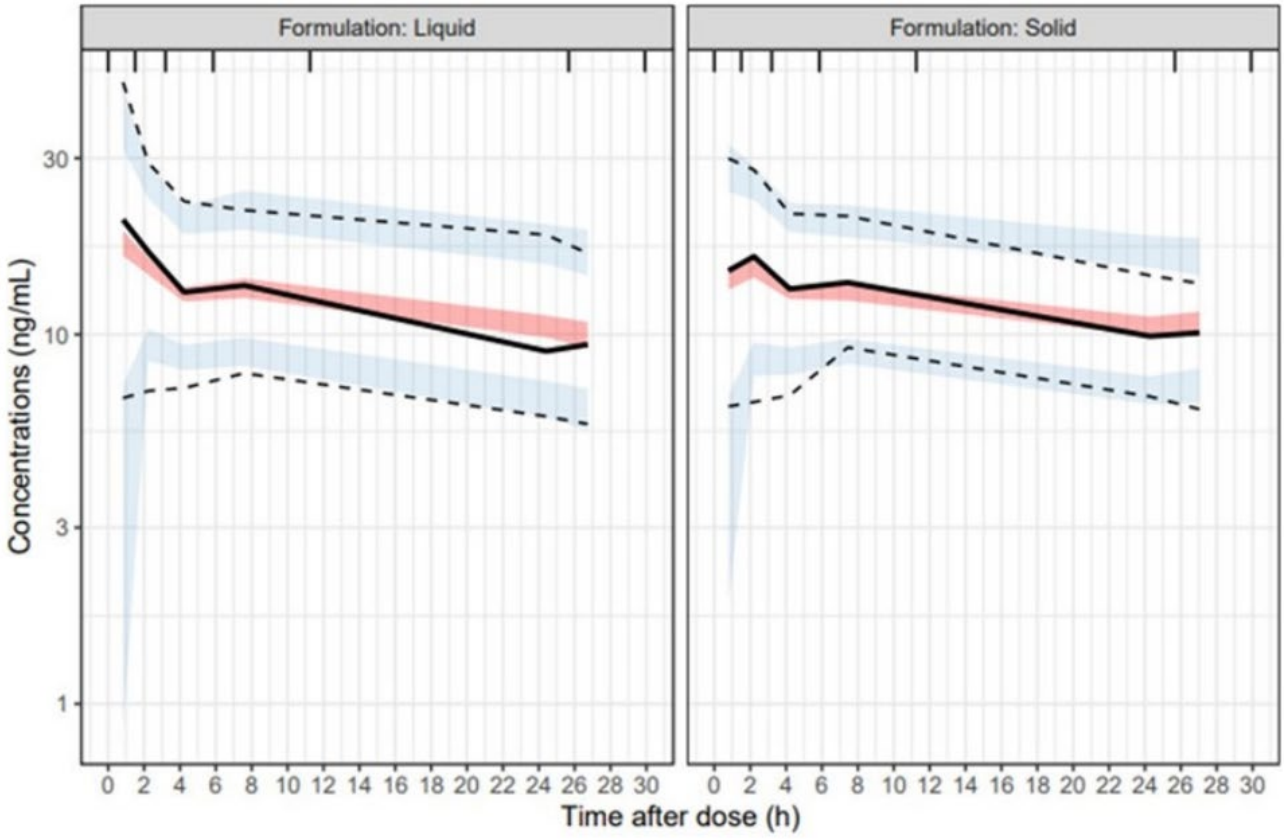

Figure 5 Prediction-corrected VPC for trametinib final the PopPK model with 1 to 17 year old patients' data stratified by formulation.

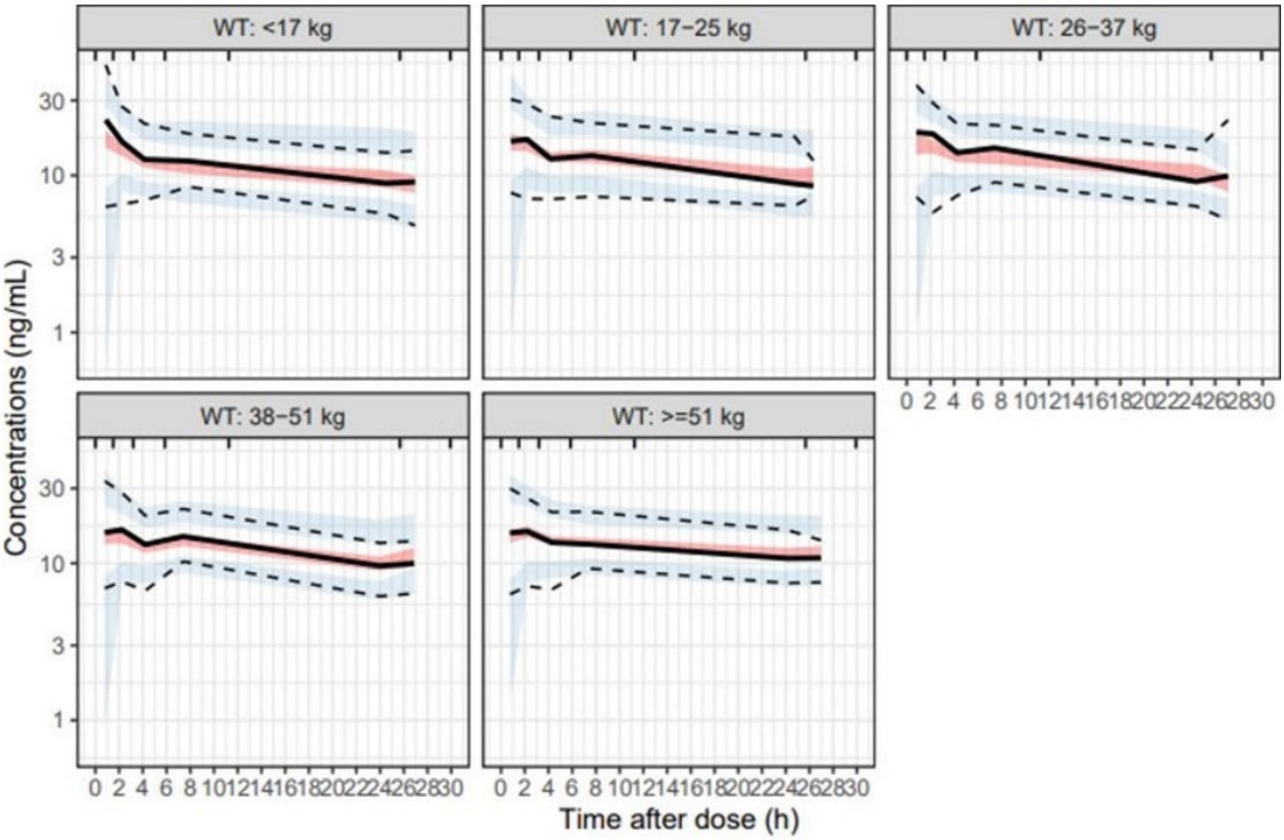

Figure 6 Prediction-corrected VPC for trametinib final PopPK model with 1 to 17 year old patients' data stratified by weight.

Simulations

The simulations were based on the PopPK models based on PK data from patients aged 1-17 years. The recommended doses of dabrafenib and trametinib in adolescent subjects, aged 12 to 17 years obtained from simulations from the developed models are those that yield similar exposures to those exposures of the adults, and are demonstrated to be safe, based on the previous paediatric clinical trials using dabrafenib, trametinib, or the combination. The proposed doses were constrained to not exceed the highest clinically tested dose of 0.04 mg/kg for trametinib and the upper recommended dose of 5.9 mg/kg for dabrafenib to ensure patient safety.

In addition, the proposed doses for dabrafenib and trametinib are stratified by patients' body weight range, and are achieved using the currently marketed capsule strengths of 50 mg and 75 mg; and tablet strengths of 0.5 mg and 2 mg, respectively.

The concentration profiles at steady-state were simulated. Only the approved solid formulations were simulated in patients of body weight ≥26 kg.

Due to the constraint of not exceeding 0.04 mg/kg doses of trametinib, the approved dose of 2 mg in the adult patients, and the possible doses that can be achieved with 2 mg and 0.5 mg tablets, the following body weight cut-offs were introduced for trametinib: ≥51 kg, 38-50 kg, and 26-37 kg.

2 mg dose cannot be given to patients in the body weight range of 38-50 kg to avoid exceeding 0.04 mg/kg threshold. Thus, 1.5 mg can be tested for patients in the body weight range of 38-50 kg. Similarly, for patients in the body weight range of 26-37 kg, 1 mg can be used to avoid exceeding 0.04 mg/kg. 1 mg cannot be given to patients with a body weight < 25 kg without exceeding 0.04 mg/kg.

The dabrafenib posology was grouped by the same body-weight groups, to ensure the maximum combination alignment with trametinib posology's body-weight groups.

A total of 250000 virtual pediatric patients were sampled from CDC growth chart (https://www.cdc.gov/growthcharts/cdc-data-files.htm), for whom the popPK simulated PK metrics were generated with the above mentioned popPK models. The exposure metrics of interest included steady-state Cmax and Cavg (AUCtau divided by 12 h for dabrafenib; AUCtau divided by 24 h for trametinib).

Adult exposure targets

The adult exposure range in adult patients with melanoma was derived for monotherapy and combination from the respective pivotal studies in adults (*Table 4*).

Table 4 Summary of studies and popPK models used

Study	Treatment	Study population	PopPK model used
[BRF113683]	Dabrafenib monotherapy	adult unresectable or metastatic melanoma	[2012N144949_02-PopPK report]
[MEK114267]	Trametinib monotherapy	adult unresectable or metastatic melanoma	
[MEK115306]	D + T combination	adult unresectable or metastatic melanoma	
[BRF115532]	D + T combination	adult adjuvant melanoma	

The target exposure ranges were based on popPK-predicted PK metrics, including Cavg, using the adult melanoma model for adult melanoma patients who had contributed at least one PK sample (*Table 5*).

Table 5 Median and estimated (5th and 95th percentiles) of the steady-state PK metrics

	Cavg		
	Observed	**Full popPK**	**Updated popPK**
D mono	N=29 381 (202.0, 717.1)	N=766 371.81 (239.93, 520.74)	N=182 367.98 (256.20, 464.67)
D combo	N=12 504 (264.3, 961.0)	N=766 466.37 (275.77, 700.08)	N=510 443.53 (237.26, 724.84)
T mono	N=13 15.4 (11.6, 20.4)	N=588 14.44 (10.08, 20.50)	N=197 14.60 (11.02, 19.78)
T combo	N=13 14.4 (10.7, 19.4)	N=588 12.65 (8.83, 17.96)	N=262 12.30 (8.27, 17.79)

Dabrafenib

This section graphically summarizes and compares exposure metric of main interest: steady-state C_{avg} (AUC_{tau} divided by 12) across adolescent patients in different weight groups and compare them to the reference adult exposures.

Based on the simulations (*Figure 4*), the following BID dosing scheme is simulated from the developed popPK model: flat dose of 150 mg BID (corresponding to ≤5.9 mg/kg/day doses) for subjects weighing ≥51 kg, dose of 100 mg BID (corresponding to doses between 4.0-5.26 mg/kg/day) for those with body weight in the range 38-50 kg, and 75 mg BID (corresponding to 4.1-5.8 mg/kg/day) for 26-37 kg.

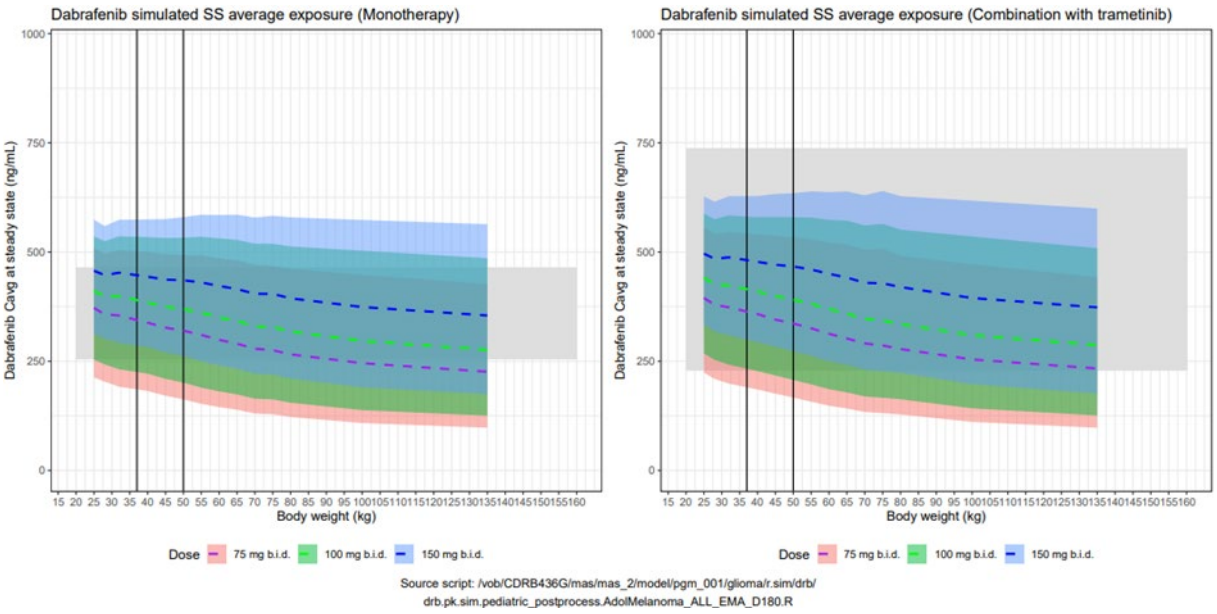

Figure 7 PopPK simulated dabrafenib C_{avg}, as monotherapy and in combination with trametinib, as a function of body weight relative to the adult exposure range in metastatic melanoma. Grey horizontal shaded band: 5th to 95th percentiles of popPK-predicted adult exposure range in patients with metastatic melanoma treated with 150 mg BID dabrafenib in monotherapy (left) and combination (right) with 2 mg QD trametinib tablet. Dashed lines represent the simulated medians from the corresponding dose levels. Colored shaded areas represent the corresponding 90% prediction intervals.

Trametinib

This section graphically summarizes and compares exposure metric of interest: steady-state C_{avg} (AUC_{tau} divided by 24) across adolescent patients in different weight groups and compare them to the reference adult exposures.

Based on the simulation results (

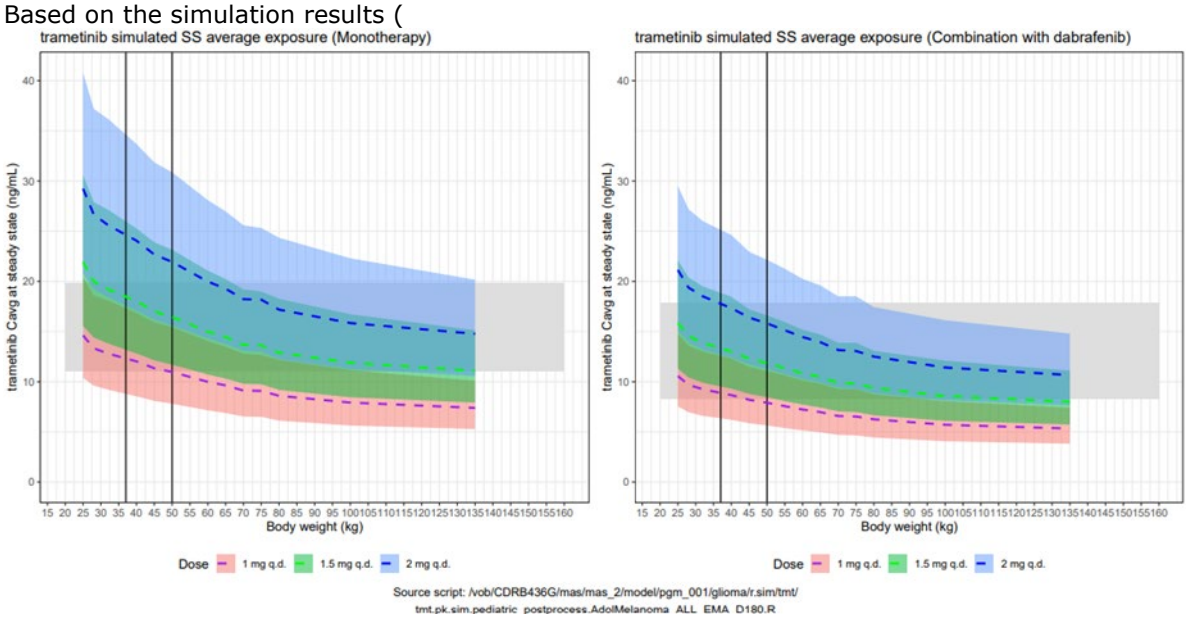

Figure 8) and the limited choices for solid formulation (0.5, 1, 1.5, 2 mg), the following doses allow to meet the efficacy target C_{avg} guidance of ~10 ng/mL, with the constraint of the upper recommended dose-range of 0.039 mg/kg/day: flat dose of 2 mg QD for subjects weighing 51 kg or more, dose of 1.5 mg QD for those with body weight in the range 38-50 kg, and 1 mg QD for 26-37 kg.

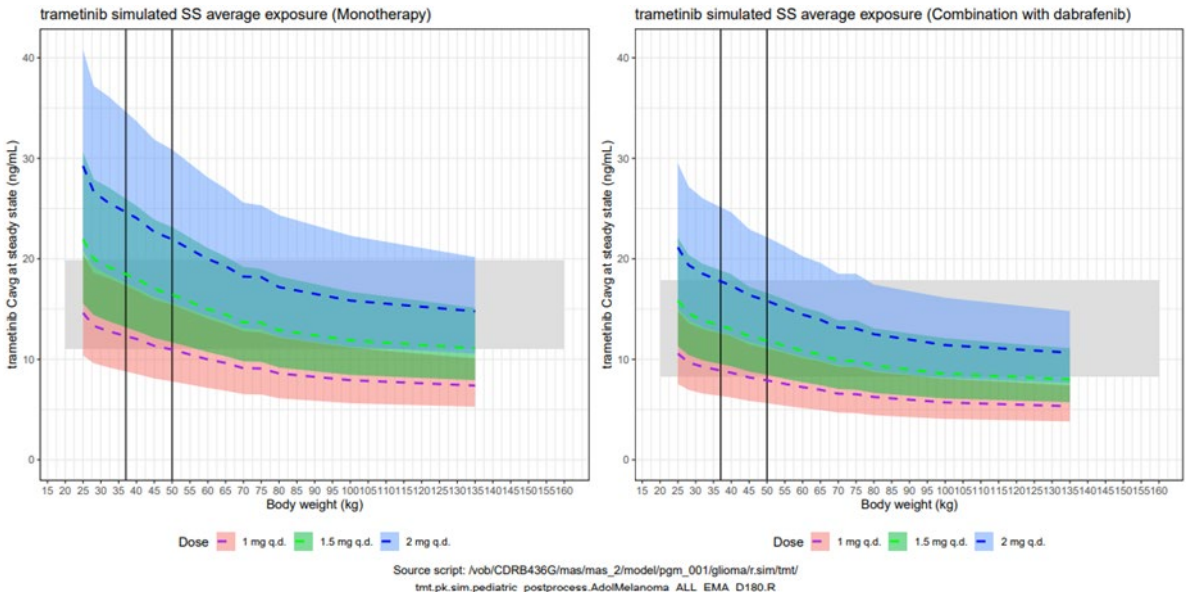

Figure 8 PopPK simulated trametinib C_{avg}, as monotherapy and in combination with dabrafenib, as a function of body weight relative to the adult exposure range in metastatic melanoma. Grey horizontal shaded band: 5^{th} to 95^{th} percentiles of popPK-predicted adult exposure range in patients with metastatic melanoma treated with 2 mg QD trametinib in monotherapy (left) and combination (right) with 150 mg BID dabrafenib. Dashed lines represent the simulated medians from the

corresponding dose levels. Colored shaded areas represent the corresponding 90% prediction intervals.

2.3.3. Exposure-response modelling

Exposure-response simulations of ORR were submitted to support the proposed posologies (see Clinical Efficacy).

2.3.4. Dose justification

The proposed weight-based posology shown below (*Table 6* and *Table 7*) for adolescent patients with BRAF V600 mutation-positive melanoma is supported by the *in-silico* extrapolation (see section "Simulations" above). The popPK model, developed using available PK data from adolescents, predicts that the proposed posology would achieve similar drug exposures as that observed in adult patients with melanoma (see Section **Error! Reference source not found.**). This proposed dosing regimen allows for accurate body weight-adjusted dosing in adolescent patients, including indicated dose reduction steps.

Table 6 Recommended dose levels and reductions for dabrafenib capsules (by body weight range)

	Body weight 26 - 37 kg	**Body weight 38 - 50 kg**	**Body weight ≥ 51 kg**
Dose level	**75 mg BID**	**100 mg BID**	**150 mg BID**
Dose reductions			
1st dose reduction	50 mg BID	75 mg BID	100 mg BID
2nd dose reduction	NA	50 mg BID	75 mg BID
3rd dose reduction	NA	NA	50 mg BID
Source: Tafinlar SmPC			

The proposed dose reductions for dabrafenib follow the established algorithm in adult patients, with up to 3 dose reduction levels and reductions by approximately 33% (from 150 mg BID to 100 mg BID in adults), 50% (to 75 mg BID in adults) and 66% (to 50 mg BID in adults) from the starting dose.

Table 7 Recommended dose levels and reductions for trametinib tablets (by body weight range)

	Body weight 26 - 37 kg	**Body weight 38 - 50 kg**	**Body weight ≥ 51 kg**
Dose level	**1 mg QD**	**1.5 mg QD**	**2 mg QD**
Dose reductions			
1st dose reduction	0.5 mg QD	1 mg QD	1.5 mg QD
2nd dose reduction	NA	0.5 mg QD	1 mg QD
Source: Mekinist SmPC			

The dose reductions for trametinib also follow the established algorithm in adult patients, with up to 2 dose reduction levels and reductions by approximately 25% (from 2 mg to 1.5 mg QD in adults) and by 50% (to 1 mg QD in adults).

2.3.5. Discussion on clinical pharmacology

The Applicant has submitted paediatric population PK analyses and simulations to support posologies for Tafinlar and Mekinist. The benefit-risk in patients 12-17 years is mainly based on a

PK-bridging strategy with extrapolation of efficacy/safety from adult melanoma patients by means of exposure matching.

Notably, the paediatric population PK models were developed based on paediatric PK data collected in glioma patients (Studies A2102, X2101 and G2201) submitted in the previous regulatory procedures Finlee (dabrafenib, EMEA/H/C/005885/0000) and Spexotras (trametinib, EMEA/H/C/005886/0000). This is acceptable based on the assumption that there are no clinically relevant differences between the dabrafenib and trametinib PK profiles between paediatric patients with glioma or melanoma.

Finlee and Spexotras concern liquid formulations of dabrafenib and trametinib. However, the paediatric PK data submitted in Finlee and Spexotras included a considerable amount of PK data for tablets and capsules, which is the subject of the current procedure. Thus, a sufficient amount of paediatric PK data is available to support the relevant tablet and capsule formulations. There were sufficient number of patients across the entire intended age and body weight groups.

Regarding the approach, the PK-bridging strategy with extrapolation of efficacy/safety from adult melanoma patients by means of exposure matching is acceptable as such.

The bioanalysis methods for dabrafenib and trametinib was previously assessed in the procedures Finlee (EMEA/H/C/005885/0000) and Spexotras (EMEA/H/C/005886/0000) and was found acceptable. Thus, no concerns are raised regarding bioanalysis in the current procedure.

The Applicant has developed paediatric PopPK models for dabrafenib and trametinib in patients aged 1-17 years in procedures Finlee and Spexotras. The PopPK models in patients 1-17 years includes patients in the Low Grade Glioma (LGG) cohort of Study G2201. The PopPK models in patients aged 1-17 years are acceptable; the PopPK models in patients aged 1-17 years were adequately validated using pcVPCs stratified both on formulation and body weight. The pcVPCs show acceptable description of the observed PK data both across formulation and body weight for dabrafenib and trametinib. The dose-dependency for the dabrafenib autoinduction was implemented as the body-weight-normalized dose (i.e. the dose expressed as mg/kg) which is acceptable (see above). Thus, the PopPK models in patients aged 1-17 years are considered fit-for-purpose to support a posology for tablets and capsules in paediatric melanoma patients.

Of note, the Applicant submitted PopPK models in patients aged 6-17 years in the first round of the current procedure (data not shown). However, these models are not described in the current report since the PopPK models in patients aged 1-17 years are considered fit-for-purpose and described in the current report.

The Applicant simulated body weight and age from the CDC growth charts which is acceptable.

The Applicant submitted PopPK simulations to support the proposed posology. This is considered a reasonable approach to support the posology. The simulations were based on the PopPK models in patients aged 1-17 years which is adequate and the simulations were presented in a reasonable format.

The Applicant derived adult exposure targets from observed data and using a PopPK model-based approach where individual PK parameters (also known as Empirical Bayes Estimates (EBEs)) were used. This is considered as a reasonable strategy. The Applicant derived target exposures which is based on the pivotal studies for the adult approval which is considered appropriate.

The exposure targets were derived as the 5^{th} to 95^{th} percentile which is reasonable. This means that the observed variability in PK exposures will be accounted for in the exposure comparison.

The simulated paediatric exposures overlapped with the corresponding adult target exposure range for both trametinib and dabrafenib at the proposed weight bands. A trend of slightly higher paediatric C_{ave} was noted at lower body weights for trametinib monotherapy in the ≥51 kg weight band. A trend of slightly lower C_{ave} was noted at the highest body weights in the 26-37 kg weight band for the trametinib combination therapy. However, taken together this is considered acceptable and supports the proposed posology.

The discussion above is based on the exposure metric Cave and Simulations provided also for C_{max} (data not shown). Exposure matching based on Cave was considered a more relevant exposure metric compared to C_{max}. This is considered a reasonable assumption for the kinase inhibitors trametinib and dabrafenib. Of note, exposure matching based on C_{ave} was considered more important than C_{max} when corresponding liquid formulations of trametinib and dabrafenib were approved for paediatric glioma patients (see procedures Spexotras and Finlee). For C_{max}, the simulated paediatric exposure generally overlapped with the corresponding adult target exposure range for both trametinib and dabrafenib at the proposed weight bands.

The simulations were also be provided in a tabular format (data not shown).

The proposed posologies are in overall agreement with the posologies for the liquid dabrafenib and trametinib formulations in Finlee and Spexotras considering the available tablet and capsule strengths (Table 8). For trametinib, the liquid formulation has ~10% relatively higher AUC than the solid formulation (Spexotras SmPC). For dabrafenib, the liquid formulation has ~20% lower AUC than the solid formulation (Finlee SmPC).

Table 8: Comparison of weight-based paediatric posologies for liquid and solid formulations of dabrafenib and trametinib in EU

Weight-band liquid formulations	**Corresponding weight band for solid formulations**	**Dose Finlee**	**Proposed dose Tafinlar**	**Dose Spexotras**	**Proposed dose Mekinist**
26 to 29 kg		70 mg BID		0.90 mg QD	
30 to 33 kg	26 to 37 kg	80 mg BID	75 mg BID	1 mg QD	1 mg QD
34 to 37 kg		90 mg BID		1.15 mg QD	
38 to 41 kg		100 mg BID		1.25 mg QD	
42 to 45 kg	38 to 50 kg	110 mg BID	100 mg BID	1.40 mg QD	1.5 mg QD
46 to 50 kg		130 mg BID		1.60 mg QD	
≥51 kg	≥51 kg	150 mg BID	150 mg BID	2 mg QD	2 mg QD

The Applicant proposed dose reductions for paediatric patients which are reasonable. The proposed starting doses are also acceptable. Bearing this in mind, the recommended dose reductions are acceptable considering the available tablet and capsule strengths. These are adequately reflected in SmPC 4.2.

The Applicant defined exposure targets for efficacy based on C_{avg} derived from exposure-efficacy analyses. These targets are considered supportive evidence with low impact on the overall benefit-risk assessment as this procedure is viewed as a PK bridge with exposure comparisons to adults (see discussion above).

The proposed Mekinist SmPC 5.2 states that "*The pharmacokinetic exposures of trametinib at a weight-adjusted dosage in adolescent patients were within range of those observed in adults*". The proposed Tafinlar SmPC 5.2 states that "*The pharmacokinetic exposures of dabrafenib at a weight-adjusted dosage in adolescent patients were within range of those observed in adults*". These statements are acceptable.

In addition to PK simulations, the Applicant also included exposure-response simulations of ORR in adolescents which are discussed under Clinical efficacy.

2.3.6. Conclusions on clinical pharmacology

The proposed posologies in paediatric melanoma patients are mainly supported by a PopPK-based PK-bridge with exposure comparison versus adult melanoma patients. Paediatric PopPK models developed in paediatric glioma patients are available which is acceptable. The paediatric PopPK simulations show that the paediatric doses give exposures which match the exposure in adult patients.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose-response studies in adolescent patients with BRAF V600 mutation-positive melanoma have been performed. Please refer to the dose justification in section 9.5.

2.4.2. Main study(ies)

There are no clinical studies performed in adolescent patients with BRAF V600 mutation-positive melanoma given the rarity of this condition in adolescents. Therefore, a modelling extrapolation approach was pursued to identify doses that match adult exposures at approved doses and predicted efficacy in the adolescent population under the assumption of disease similarity. The proposal is based on the histopathological and molecular similarity of BRAF V600 mutation-positive melanoma in adolescents with that in adults and presumed similar clinical behaviour.

The extrapolation approach was based on safety and pharmacokinetic data obtained in three paediatric studies in non-melanoma indications. Supplementary supportive efficacy data is provided from an external publication on adolescent patients with BRAF V600 mutation-positive melanoma treated experimentally with dabrafenib and trametinib outside clinical trials.

Methods

The existing population PK models in adults were updated, in particular the effect of body weight on PK parameters, for dabrafenib and trametinib with PK data from paediatric (aged 6 to 17 years) patients. Simulations were done at various dose levels to obtain exposure metrics of interest, which were used in the extrapolation of efficacy.

The logistic regression models, that characterize the relationship between dabrafenib/trametinib exposure and objective response rate, were previously developed in adults and were used to predict the ORR at different adolescent exposure levels.

Study participants

The data sources for extrapolation included clinical experience in approved adult melanoma indications over past decade and previously developed PopPK models in adults, previously established adult exposure-efficacy models, and PK and safety data collected in 3 paediatric studies in non-melanoma indications.

Results

Extrapolation of efficacy results

Dabrafenib

Cumulative logistic regression model for response (CR+PR) was used to estimate the probability of response (CR+PR) at different predicted adolescent dabrafenib C_{avg} levels when used in combination with trametinib.

The estimated probabilities of response (CR+PR) in adolescents are consistent with the results in adult patients.

Trametinib

Similarly, for trametinib cumulative logistic regression models were used to estimate the probability of response (CR+PR) across a range of predicted trametinib C_{min} and C_{avg} levels in combination with dabrafenib for C_{min}, and for C_{avg}. The estimated probabilities are consistent with the results in adult patients.

Summary of main study(ies)

N/A

Supportive study(ies)

No adolescent patients with BRAF V600 mutation-positive melanoma could be enrolled into the paediatric Phase I studies and therefore no efficacy data from prospective clinical trials are available in this setting. However, a recent publication describes the observations from a paediatric melanoma case series at an Italian referral site. The treatment was made available to the patients under the applicant's global compassionate use program (or Managed Access Program (MAP)).

As described by Chiaravalli et al 2025, 6 patients were included in in this program (three female and three male patients) and received dabrafenib and trametinib for 12 months (adjuvant setting) or until disease progression, unacceptable toxic effects or patients' decision (metastatic setting). The median age at diagnosis was 15 years (range: 9.5-17.6 years). At the time of diagnosis, one patient had Stage IIB, five had Stage III disease (two patients had IIIA, two patients had IIIB, and one patient had IIID). The disease stage at the beginning of treatment was III in four patients and IV in two patients. All patients had BRAF V600E mutation. None of the patients had received prior systemic therapy for melanoma. Three patients received dabrafenib 300 mg/day plus trametinib 2 mg/day, two dabrafenib 250 mg/day plus trametinib 1.5 mg/day, and one dabrafenib 300 mg/day plus trametinib 1.5 mg/day.

After a median follow-up of 22 months (range 5.4 - 42.4 months) from the beginning of treatment, all 4 patients treated with adjuvant targeted therapy were alive with no evidence of disease. One patient with metastatic disease was still under treatment with prolonged complete response (treatment duration: 19.3 months); one patient died due to disease progression 5.4 months after starting targeted therapy.

2.4.3. Discussion on clinical efficacy

Indications

This procedure extends the indications of dabrafenib and trametinib to include treatment of unresectable or metastatic melanoma with a BRAF V600 mutation and adjuvant treatment of Stage III melanoma with a BRAF V600 mutation for adolescents aged 12 years and older.

Modelling and simulation approach to support efficacy

The strategy put forward by the applicant to support an adolescent indication involved extrapolation of safety and efficacy of dabrafenib and of trametinib from adults with BRAF V600-mutation positive melanoma to adolescent patients with BRAF V600-mutation positive melanoma based on population PK, and exposure-response, modelling. Furthermore, due to very limited PK data from adolescent patients with BRAF V600-mutation positive melanoma, PK in adolescent patients with melanoma was extrapolated from non-melanoma paediatric patients (3 clinical studies).

This strategy was applied given the rarity of malignant melanoma diagnosis in adolescents making the initially planned PIP clinical studies unfeasible, as agreed in the modification of the two PIPs by PDCO for Tafinlar (EMEA-001147-PIP01-11-M07) and Mekinist (EMEA-001177-PIP01-11-M06).

Extrapolation of efficacy

In accordance with the Reflection paper on the use of extrapolation in the development of medicines for paediatrics EMA/189724/2018, the extrapolation concept should be based on the existing information about the disease, the drug pharmacology and the clinical response to treatment across the target populations. The applicant argued for feasibility of the extrapolation of efficacy primarily based on assumptions of similarity of the molecular features of BRAF V600 mutation-positive melanoma and the exposure-efficacy relationship between adolescents and adults. The proposed strategy to support extrapolation of efficacy, safety and finally of the extension of the indications from adults to adolescents is considered adequate, given the approved indications for dabrafenib and trametinib in adults with malignant melanoma in adjuvant and metastatic settings and availability of data from clinical trials in adults. Hence, the ethical imperative outlined in EMA's reflection paper to avoid unfeasible or unethical studies given the rarity of certain paediatric cancers by relying on appropriate adult data may be achieved.

Similarity of Disease: BRAF V600-mutated malignant melanoma shares many core molecular and clinical characteristics between adults and adolescents (Wilmott et al 2019, Merkel et al 2019):

- **Molecular and Pathological Features**
    - Both adults and adolescents with malignant melanoma frequently harbor the BRAF V600 mutation, most commonly the V600E variant.
    - The BRAF V600 mutation activates the MAPK/ERK pathway, driving tumour growth and progression in both age groups.

    - Melanomas in both populations exhibit increased aggressiveness and metastatic potential when BRAF mutations are present.

- **Therapeutic Approach**
    - Targeted therapies (BRAF and MEK inhibitors) are effective and approved for treating BRAF-mutated melanoma in adults and show substantial response rates. The data in adolescents are limited to isolated cases, however similar treatment strategies as for adults have been used, with similar results. No therapy is however approved in the EU in adolescents with malignant melanoma besides the ICI.
- **Immunogenicity and Tumour Microenvironment**
    - BRAF-mutant melanomas in both groups display alterations in their immunogenicity and tumour microenvironment, including immune escape mechanisms and changes in antigen expression.

Some differences exist, particularly in mutation frequency and histological presentation. Thus, adolescents are more likely to harbor BRAF-mutated melanoma (68% vs 46% in adults) and often exhibit thinner tumours and a higher proportion of superficial spreading melanoma at diagnosis with a tendency to be diagnosed at a slightly earlier stage, although they can be aggressive when advance. These factors are not deemed relevant effect modifiers of treatment.

Similarity of Drug Pharmacology: The drugs' mechanism of action, consisting in BRAF 600- and MEK(ERK1/2) inhibition, will not differ between the adult and the adolescent population, and is considered as relevant for the adolescent population as for the adult population, particularly taking into account the higher prevalence of BRAF 600 mutation in adolescent melanoma than in adult melanoma (~68% vs ~46%). Furthermore, no differences in pharmacology are expected between paediatric patients with melanoma and paediatric patients with other solid tumours (Suhail, Cohen 2024, Corley et al 2022).

Given the similarity in aetiology, pathophysiology, clinical manifestation, and disease progression (Lu et al 2015, Wilmott et al 2019, Grobner et al 2018), an extrapolation approach based on exposure matching of the adolescent population and the adult population is considered appropriate to predict efficacy of dabrafenib and trametinib in adolescent patients with BRAF V600 mutation-positive melanoma.

Results of modelling and simulation in support of efficacy

To support similar exposure with the proposed doses in adolescent patients as with the approved doses in adult patients, the Applicant has provided a population PK analysis.

To further support similar efficacy, the Applicant has provided simulations of ORR in adolescents based on exposure-response models previously developed in adults. Exposures used in these simulations were derived using the inadequate population PK models. However, since simulations of ORR are considered of limited importance (the simulated ORR will be the same as long as the exposure is the same), no updated simulations of ORR are requested, and the models are not described in any detail (data not shown).

Supportive efficacy data from single cases of adolescents with BRAF V600 mutation-positive melanoma

Supportive evidence is provided from an external publication (Chiaravalli et al 2025) on case series of adolescent patients with BRAF V600 mutation-positive melanoma treated experimentally with dabrafenib and trametinib outside clinical trials under the applicant's global compassionate use

program (or Managed Access Program (MAP). The 6 patients were 15 years old (range: 9.5-17.6) at the time of diagnosis and had stage III and IV at the beginning of the treatment with dabrafenib and trametinib combination given as adjuvant therapy in 4 patients and until disease progression or death in 2 patients with metastatic disease. After a median follow-up of 22 months (range 5.4 - 42.4 months) all 4 patients treated with adjuvant therapy were disease-free. Out of the two patients with metastatic disease, one had complete response with ongoing treatment (treatment duration: 19.3 months), while the other patient died due to disease progression 5.4 months after starting targeted therapy.

The descriptive outcomes in these 6 real world cases suggest the anticipated activity of dabrafenib and trametinib combination in adolescents treated with doses in the sought ranges.

The proposed doses in adolescents provide exposures within the same range as the approved doses in adults. Since the extrapolation concept relays on adult data from the clinical pivotal studies in BRAF V600 mutation positive melanoma, and given the similarities in disease biology, clinical aspects, and drug mechanism of action between adolescents and adults, the indications in adults may be fully extended to the adolescent patients for dabrafenib and trametinib, in combination across adjuvant and metastatic settings and as monotherapy in metastatic settings.

2.4.4. Conclusions on the clinical efficacy

Given the rarity of BRAF V600 mutation-positive melanoma in the adolescent population as well as the similarity in aetiology, pathophysiology, clinical manifestation, and disease progression, an extrapolation approach based on exposure matching of the adolescent population and the adult population is considered appropriate to predict efficacy of dabrafenib and trametinib in adolescent patients with BRAF V600 mutation-positive melanoma.

2.5. Clinical safety

Introduction

The safety profile of dabrafenib and trametinib combination therapy has been extensively assessed in adult patients in clinical trials (since 2009) and in the post-marketing setting (since 2013). The safety of dabrafenib and/or trametinib therapy in paediatric patients was assessed in studies G2201, X2101 and A2102.

Patient exposure

In adult patients, the safety profile of dabrafenib and trametinib has been established across indications and the post-marketing setting, with over 120,000 patient treatment years recorded for both dabrafenib and trametinib since the initial approvals in 2013.

Subsequent to the development of age-appropriate formulations (dabrafenib dispersible tablets and trametinib powder for oral solution), dabrafenib and trametinib combination therapy has also been approved for the treatment of paediatric patients with BRAF V600E mutation-positive glioma or other solid tumours worldwide.

Patients received study treatments based on their body weight and age. Maximum daily doses for patients weighing ≥ 51 kg were capped at the adult doses (150 mg BID for dabrafenib and 2 mg QD for trametinib).

The median duration of exposure to dabrafenib and trametinib, administered as combination therapy, exceeded 1 year (62.14 weeks for dabrafenib and 59.43 weeks to trametinib) with more than 60% of the subjects receiving dabrafenib and trametinib combination therapy beyond 48 weeks. The cumulative exposure to dabrafenib and trametinib in combination therapy pool was comparable (5419.29 and 5334.0 subject-weeks, respectively).

Demography and baseline characteristics were generally similar amongst subjects receiving combination or monotherapy treatment. In the combination therapy pool, the median age of subjects was 14.0 years, and the median weight was 59.35 kg (range: 27.8 - 155.6).

Adverse events

Table 9 Adverse event categories with dabrafenib and/or trametinib in adolescents (Pooled Adolescents Safety set)

Category	Dabrafenib N=35		Trametinib N=21		Combination therapy N=74		All Subjects N=130	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Adverse events	33 (94.3)	16 (45.7)	21 (100)	12 (57.1)	73 (98.6)	45 (60.8)	127 (97.7)	73 (56.2)
Treatment-related	31 (88.6)	8 (22.9)	21 (100)	7 (33.3)	67 (90.5)	27 (36.5)	119 (91.5)	42 (32.3)
SAEs	13 (37.1)	9 (25.7)	9 (42.9)	7 (33.3)	32 (43.2)	23 (31.1)	54 (41.5)	39 (30.0)
Treatment-related	5 (14.3)	2 (5.7)	4 (19.0)	4 (19.0)	15 (20.3)	11 (14.9)	24 (18.5)	17 (13.1)
All deaths	1 (2.9)	1 (2.9)	0 (0.0)	0 (0.0)	12 (16.2)	10 (13.5)	13 (10.0)	11 (8.5)
Treatment-related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal SAEs	1 (2.9)	1 (2.9)	0 (0.0)	0 (0.0)	3 (4.1)	3 (4.1)	4 (3.1)	4 (3.1)
Treatment-related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to discontinuation	2 (5.7)	1 (2.9)	9 (42.9)	4 (19.0)	7 (9.5)	2 (2.7)	18 (13.8)	7 (5.4)
Treatment-related	2 (5.7)	1 (2.9)	8 (38.1)	3 (14.3)	5 (6.8)	1 (1.4)	15 (11.5)	5 (3.8)
AEs leading to dose adjustment/ interruption	14 (40.0)	5 (14.3)	16 (76.2)	7 (33.3)	51 (68.9)	27 (36.5)	81 (62.3)	39 (30.0)

- 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 4.0 (A2102,X2101) and CTCAE version 4.03 (G2201)
Source: [SCS Appendix 1-Table 3-1].

Most frequently occurring adverse events

Table 10 Adverse events by preferred term (greater than or equal to 20% for all grades in all subjects) - (Pooled Adolescents Safety set)

Preferred term	Dabrafenib N=35		Trametinib N=21		Combination therapy N=74		All subjects N=130	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Total	33 (94.3)	16 (45.7)	21 (100)	12 (57.1)	73 (98.6)	45 (60.8)	127 (97.7)	73 (56.2)
Pyrexia	15 (42.9)	1 (2.9)	6 (28.6)	2 (9.5)	43 (58.1)	6 (8.1)	64 (49.2)	9 (6.9)
Headache	18 (51.4)	2 (5.7)	8 (38.1)	1 (4.8)	34 (45.9)	5 (6.8)	60 (46.2)	8 (6.2)
Dry skin	11 (31.4)	0 (0.0)	9 (42.9)	0 (0.0)	29 (39.2)	0 (0.0)	49 (37.7)	0 (0.0)
Fatigue	16 (45.7)	0 (0.0)	7 (33.3)	0 (0.0)	26 (35.1)	0 (0.0)	49 (37.7)	0 (0.0)
Vomiting	14 (40.0)	0 (0.0)	6 (28.6)	0 (0.0)	22 (29.7)	2 (2.7)	42 (32.3)	2 (1.5)
Nausea	11 (31.4)	0 (0.0)	5 (23.8)	0 (0.0)	25 (33.8)	1 (1.4)	41 (31.5)	1 (0.8)
Diarrhea	6 (17.1)	0 (0.0)	13 (61.9)	0 (0.0)	14 (18.9)	0 (0.0)	33 (25.4)	0 (0.0)
Rash	9 (25.7)	0 (0.0)	10 (47.6)	0 (0.0)	14 (18.9)	0 (0.0)	33 (25.4)	0 (0.0)
Dermatitis acneiform	3 (8.6)	0 (0.0)	12 (57.1)	1 (4.8)	17 (23.0)	0 (0.0)	32 (24.6)	1 (0.8)

- 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 4.0 (A2102, X2101) and CTCAE version 4.03 (G2201)
Source: [SCS Appendix 1-Table 3-3]

Serious adverse event/deaths/other significant events

In the combination pool, 43.2% patients reported at least one SAE, which was similar to that of the dabrafenib or trametinib monotherapies or overall population. The most frequently reported SAEs with the combination therapy pool were pyrexia (14.9%) and headache (6.8%). The frequency of

SAEs that were suspected to be related to the study treatments in the combination pool was low (20.3%) and were similar to monotherapies (14.3% with dabrafenib and 19.0% with trametinib) and the overall adolescent population (18.5%).

Deaths

Table 11 All deaths – (Pooled Adolescent Safety Set)

	Dabrafenib N=35 n (%)	Trametinib N=21 n (%)	Combination therapy N=74 n (%)	All Subjects N=130 n (%)
Number of subjects who died	1 (2.9)	0 (0.0)	12 (16.2)	13 (10.0)
Study Indication	1 (2.9)	0 (0.0)	10 (13.5)	11 (8.5)
Other	0 (0.0)	0 (0.0)	2 (2.7)	2 (1.5)
Disease progression	1 (2.9)	0 (0.0)	0 (0.0)	1 (0.8)
Encephalomyelitis	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.8)
Intracranial pressure increased	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.8)
Apnea	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.8)

- Includes both on-treatment deaths, and those that occurred more than 30 days after the last treatment.
- MedDRA version 24.0
Source: [SCS Appendix 1-Table 3-10].

Safety topics of interest

Adverse events of special interest (AESIs)

Table 12 Adverse events of special interest - Pooled Adolescents Safety set

	Dabrafenib N=35		Trametinib N=21		Combination therapy N=74		All subjects N=130	
Safety topic	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of subjects with at least one event	24 (68.6)	3 (8.6)	20 (95.2)	3 (14.3)	71 (95.9)	24 (32.4)	115 (88.5)	30 (23.1)
Bleeding events	0 (0.0)	0 (0.0)	9 (42.9)	0 (0.0)	18 (24.3)	1 (1.4)	27 (20.8)	1 (0.8)
Cardiac related events	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	10 (13.5)	1 (1.4)	12 (9.2)	1 (0.8)
Hepatic disorders	0 (0.0)	0 (0.0)	10 (47.6)	1 (4.8)	18 (24.3)	6 (8.1)	28 (21.5)	7 (5.4)
Hyperglycemia	7 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (9.5)	1 (1.4)	14 (10.8)	1 (0.8)
Hypersensitivity	6 (17.1)	0 (0.0)	3 (14.3)	0 (0.0)	11 (14.9)	0 (0.0)	20 (15.4)	0 (0.0)
Neutropenia	8 (22.9)	1 (2.9)	3 (14.3)	0 (0.0)	20 (27.0)	10 (13.5)	31 (23.8)	11 (8.5)
Ocular events	0 (0.0)	0 (0.0)	3 (14.3)	0 (0.0)	12 (16.2)	0 (0.0)	15 (11.5)	0 (0.0)
Pancreatitis	1 (2.9)	1 (2.9)	0 (0.0)	0 (0.0)	3 (4.1)	2 (2.7)	4 (3.1)	3 (2.3)
Pneumonitis and interstitial lung disease	0 (0.0)	0 (0.0)	1 (4.8)	1 (4.8)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)
Pre-renal and intrinsic renal failure	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Pyrexia	15 (42.9)	1 (2.9)	0 (0.0)	0 (0.0)	46 (62.2)	6 (8.1)	61 (46.9)	7 (5.4)
Skin toxicity	0 (0.0)	0 (0.0)	20 (95.2)	1 (4.8)	61 (82.4)	0 (0.0)	81 (62.3)	1 (0.8)
Uveitis	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.1)	1 (1.4)	4 (3.1)	1 (0.8)
Venous Thromboembolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.8)	0 (0.0)
Hypertension	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	4 (5.4)	2 (2.7)	5 (3.8)	2 (1.5)

- 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 4.0 (A2102, X2101) and CTCAE version 4.03 (G2201), Case Retrieval Strategy version released 2021-10-10 (dabrafenib), 2021-10-07 (trametinib).
source: [SCS Appendix 1-Table 3-13].

Pediatric-specific safety topics of interest

Evaluation of pediatric-specific safety topics of interest (i.e. growth and development toxicity, reproductive toxicity and renal toxicity) in the combination therapy pool that are designated based on the current safety information available for the dabrafenib and trametinib combination did not reveal any significant safety concern, except for an observed greater than expected median weight gain velocity standard deviation score at 6 months ranging from 1.31 to 2.39 months in the paediatric patients.

Laboratory findings

Hematology

Table 13 Worst post-baseline hematology abnormalities based on CTC grades - (Pooled Adolescents Safety set)

	Dabrafenib N=35		Trametinib N=21		Combination therapy N=74		All Subjects N=130	
	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)
Hemoglobin (G/L) - (Decrease)	18 (51.4)	0	16 (76.2)	0	42 (56.8)	2 (2.7)	76 (58.5)	2 (1.5)
Leukocytes (10E9/L) - (Decrease)	16 (45.7)	2 (5.7)	7 (33.3)	0	49 (66.2)	1 (1.4)	72 (55.4)	3 (2.3)
Lymphocytes (10E9/L) - (Decrease)	20 (57.1)	6 (17.1)	6 (28.6)	1 (4.8)	27 (36.5)	6 (8.1)	53 (40.8)	13 (10.0)
Lymphocytes (10E9/L) - (Increase)	2 (5.7)	0	2 (9.5)	0	6 (8.1)	0	10 (7.7)	0
Neutrophils (10E9/L) - (Decrease)	10 (28.6)	2 (5.7)	7 (33.3)	1 (4.8)	35 (47.3)	12 (16.2)	52 (40.0)	15 (11.5)
Platelets (10E9/L) - (Decrease)	7 (20.0)	0	5 (23.8)	0	21 (28.4)	1 (1.4)	33 (25.4)	1 (0.8)

- Numbers (n) represent counts of subjects. 'All grades' represents subjects with any grade 1, 2, 3 or 4 post-baseline.
- Each patient is counted only for the worst grade observed post-baseline.
- Grades based on CTCAE version 4.03.

Source: [SCS Appendix 1-Table 4-1].

Clinical chemistry

Table 14 Worst post-baseline biochemistry abnormalities (greater than or equal to 20% in all grades in combination pool) based on CTC grades (Pooled Adolescents Safety set)

	Dabrafenib N=35		Trametinib N=21		Combination therapy N=74		All Subjects N=130	
	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)
Alanine Aminotransferase (U/L) - (Increase)	11 (31.4)	0	11 (52.4)	1 (4.8)	35 (47.3)	2 (2.7)	57 (43.8)	3 (2.3)
Alkaline Phosphatase (U/L) - (Increase)	6 (17.1)	0	10 (47.6)	1 (4.8)	28 (37.8)	0	44 (33.8)	1 (0.8)
Aspartate Aminotransferase (U/L) - (Increase)	7 (20.0)	0	13 (61.9)	0	37 (50.0)	2 (2.7)	57 (43.8)	2 (1.5)
Calcium (CORRECTED) (MG/DL) - (Decrease)	6 (17.1)	0	8 (38.1)	0	16 (21.6)	4 (5.4)	30 (23.1)	4 (3.1)
Glucose (MMOL/L) - (Increase)	21 (60.0)	0	17 (81.0)	1 (4.8)	16 (21.6)	1 (1.4)	54 (41.5)	2 (1.5)
Magnesium (MMOL/L) - (Decrease)	8 (22.9)	1 (2.9)	9 (42.9)	0	31 (41.9)	3 (4.1)	48 (36.9)	4 (3.1)
Magnesium (MMOL/L) - (Increase)	9 (25.7)	0	3 (14.3)	0	37 (50.0)	0	49 (37.7)	0
Phosphate (MMOL/L) - (Decrease)	16 (45.7)	2 (5.7)	0	0	15 (20.3)	2 (2.7)	31 (23.8)	4 (3.1)
Potassium (MMOL/L) - (Increase)	2 (5.7)	0	6 (28.6)	0	15 (20.3)	4 (5.4)	23 (17.7)	4 (3.1)

- Numbers (n) represent counts of subjects. 'All grades' represents subjects with any grade 1, 2, 3 or 4 post-baseline.
- Each patient is counted only for the worst grade observed post-baseline.
- Grades based on CTCAE version 4.03.

Source: [SCS Appendix 1-Table 4-2].

Vital signs and electrocardiograms

Overall, 4/75 subjects (5.3%) had new post-baseline QTcF intervals between > 450 ms to ≤480 ms (including 1/62 adolescent on combination therapy). There was no new post-baseline increase in QTcF duration >480 ms. Five (7.4%) subjects had increase in QTcF duration >60 ms including 3 subjects (4.8%) on the combination therapy. One subject on combination therapy had SBP ≥180 mmHg and increase by >20 mmHg and 2 subjects had DBP ≥105 mmHg and increase ≥15 mmHg.

Safety in special populations

Pregnancy

No cases of pregnancy were reported.

Supportive literature safety data in adolescents with BRAF 600-positive malignant melanoma

Of the six patients treated with dabrafenib and trametinib in the global compassionate use program (or Managed Access Program (MAP), five reported mild treatment-related AEs, including fever and increased creatine-phosphokinase, with two experiencing reversible asymptomatic decreases in left ventricular ejection fraction (LVEF), which resolved after temporary treatment interruption, and both patients resumed at a reduced dose without further cardiac toxicity. One discontinued trametinib due to non-treatment-related intestinal bleeding. Although limited by the sample size, the MAP data suggests that treatment with dabrafenib and trametinib in the adolescent melanoma

patients has a safety profile comparable to that in adults and in the previous published pediatric studies (Chiaravalli et al 2025).

2.5.1. Discussion on clinical safety

There are no safety data from studies in adolescents with BRAF 600mutation positive malignant melanoma treated with dabrafenib and trametinib monotherapy or in combination.

In adult patients, the safety profile of dabrafenib and trametinib has been well established across indications and is well known from the post-marketing setting, with both dabrafenib and trametinib in use since the initial approvals in 2013.

In the current application, the pooled safety data from three non-melanoma paediatric studies in patients with glioma and solid tumours (N=130 adolescent patients: 74 on combination therapy, 35 on dabrafenib, and 21 on trametinib) support the characterization of the safety profile of dabrafenib and trametinib in adolescents.

The median duration of exposure to the combination therapy exceeded 1 year, with similar cumulative exposure for both drugs. Patients received treatments based on body weight and age.

The most frequently reported AESI were pyrexia and skin toxicity. Overall, in the pooled three studies, 13 deaths (10%) were reported, mainly with the dabrafenib and trametinib combination (n=12). The incidence of the SAEs suspected to be related to the study treatments in the overall adolescent population was 18.5%, in line with the frequency for the combination pool (20%). The most frequently reported SAEs were pyrexia and headache.

Overall, across the pooled data from the paediatric studies, the safety profile of dabrafenib and trametinib was consistent with the safety profile in adult patients with BRAF V600 mutation-positive melanoma. However, the AE of weight increase (abnormal weight gain) has only been reported in the paediatric population, of which, according to the applicant, in 15% of adolescent patients including grade 3 cases in 4% of patients. Weight increase (abnormal weight gain) has been included as an ADR for the dabrafenib and trametinib combination in 4.8 section of the SmPC with frequency 'very common' for both products during the current procedure. This is also reflected in the SmPCs of Finlee and Spexotras. Long-term safety is missing and this is included in the RMP. To complete the safety dataset, a further post-authorisation study in the children and adolescents (CDRB436G2401) is expected to provide data on long-term safety.

2.5.2. Conclusions on clinical safety

The safety profile across the pooled analysis from three paediatric studies with 130 non-melanoma patients treated with dabrafenib and trametinib in combination or monotherapy is consistent with the established safety profile in adults. To complete the safety data for the malignant melanoma indication in adolescents, the safety data from the proposed Category 3 PASS in children and adolescents with expected report May 2027 will be submitted as post-marketing commitment (see RMP).

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted two updated RMP versions with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the RMP for Mekinist version 23 and the RMP for Tafinlar version 15 are acceptable.

Safety concerns

Dabrafenib

Table 15 Summary of safety concerns

Important identified risks for dabrafenib (including combination therapy)	● Pre-renal and Intrinsic Renal failure ● Uveitis
Important potential risks for dabrafenib (including combination therapy)	● Testicular Toxicity ● Developmental toxicity ● Long-term safety in patients <18 years of age (including potential adverse effects on skeletal maturation and sexual maturation)
Missing Information for dabrafenib	● None

Trametinib

Table 16 Summary of safety concerns

Important identified risks for trametinib	• Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachment)
Important potential risks for trametinib	• Developmental toxicity • Long-term safety in patients < 18 years old (including potential adverse effects on skeletal maturation and sexual maturation)
Missing information for trametinib	• None

Pharmacovigilance plan

Additional pharmacovigilance activities

A long-term follow-up roll-over study is ongoing; CDRB436G2401, details of which are provided below:

Study CDRB436G2401- An open label, multi-center roll-over study to assess long-term effect in pediatric patients treated with Tafinlar (dabrafenib) and/or Mekinist (trametinib).

The study is a global single-arm, open-label, multi-center study to collect data on the long-term effects of dabrafenib, trametinib or the combination in paediatric subjects who have been treated in clinical trials with dabrafenib and trametinib.

Parent studies include:

- CDRB436A2102:

Phase I/IIa, 2-part, multi-center, single-arm, open-label study to determine the safety, tolerability and pharmacokinetics of oral dabrafenib in children and adolescent patients with advanced BRAF

V600-mutation positive solid tumours.

- CTMT212X2101:

Pharmacodynamics and clinical activity of the MEK inhibitor trametinib in children and adolescents patients with cancer or plexiform neurofibromas and trametinib in combination with dabrafenib in children and adolescents with cancers harboring V600 mutation.

- CDRB436G2201:

Phase II open-label global study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600-mutation positive LGG or relapsed or refractory High Grade Glioma (HGG).

The Final CSR is planned for May-2027.

The study protocol was assessed and agreed in a previous procedure. It is considered that the proposed study is appropriate to further follow up and characterize the safety in adolescents with BRAF V600-mutation positive malignant melanoma concerned by the current application.

Consequently, the additional pharmacovigilance activities outlined in RMP Part III.3 Summary Table of additional pharmacovigilance activities remain unchanged for both dabrafenib and trametinib as follows:

Table 17 Ongoing and planned additional pharmacovigilance activities

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

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

The planned and ongoing additional pharmacovigilance activities are similar for both active substances.

Risk minimisation measures

No updated risk minimisation measures were introduced with this application.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the Mekinist and Tafinlar SmPCs have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) and accepted by the CHMP.

In addition, the list of local representatives in the Package Leaflet (PL) has been revised to amend contact details.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- For this type II variation for the extension of the age range of the currently approved melanoma indications from "adult" to "adult and adolescent (ages 12 years and older)", no significant changes are made to the PL. The information proposed in the PL included in this variation maintains the currently approved layout and format and is not considered to require further consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This application concerns the extension of indication for Tafinlar and Mekinist to also include the treatment of paediatric patients (12 years to less than 18 years of age) with BRAF-600 mutation positive malignant melanoma.

The incidence of melanoma in adolescent patients is extremely low (Howlader et al 2013). BRAF V600 activating mutations are the most commonly identified mutations in paediatric and adolescent melanoma with a prevalence of approximately 60% of adolescent melanoma. The adolescent BRAF V600 mutation-positive melanoma is not considered to have any major distinguishing or unique characteristics differing from conventional adult-type BRAF V600 mutation-positive melanoma (Wilmott et al 2019, Merkel et al 2019).

3.1.2. Available therapies and unmet medical need

Targeted therapies (BRAF and MEK inhibitors) are approved for treating BRAF-mutated melanoma in adults and show substantial response rates. Given the rarity of such disease, data in adolescents are limited to isolated cases. However similar treatment strategies as for adults have been used, with similar results. Apart from ICI (Keytruda, Opdivo, Yervoy, Opdualag) no other therapies are presently approved in the EU in adolescents with malignant melanoma. Hence there is an unmet medical need in adolescents with BRAF V600 mutation-positive melanoma.

Similar driver mutation and disease characteristics supports the bridging to adult data on BRAF V600 mutation-positive melanoma to inform the benefit-risk in adolescent BRAF V600 mutation-positive melanoma. Moreover, as the specific malignancy is not a modifier of exposure, PK data from other paediatric indications may be used for bridging.

3.1.3. Main clinical studies

No dedicated efficacy and safety clinical studies in the target population have been submitted.

This application is based on PK results from paediatric clinical studies A2101, X2101 and G2201. These paediatric patients had various tumour diseases with very limited data in paediatric melanoma patients.

Study A2101 is a Phase I/IIa study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Subjects with Advanced BRAF V600-Mutation Positive Solid Tumours. The study included 85 patients (27 patients in Part 1 [dose escalation] and 58 patients in Part 2 [tumour specific expansion]). 63 patients with PK information were between 6 and 17 years of age and 22 were 5 years and below. PK sampling of dabrafenib was included at Days 1 (0.5, 2, 4 h after dose) and 15 (pre-dose, 0.5, 1, 2, 3, 4, 6, 8h after dose).

Study X2101 is a 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 Harbouring V600 mutation. The study included 133 patients with PK information, with 21 patients older than 12 years receiving trametinib alone 28 between 6 and 11 years old receiving trametinib alone; 17 older than 12 years receiving combination, and 15

between 6 and 11 year old receiving the combination. PK sampling was included on Days 1 (0.5, 2, 4 h after dose), 15 (pre-dose, 0.5, 1, 2, 3, 4, 6, 8 h after dose) and 22 (pre-dose).

Study G2201 is Phase II study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive LGG or relapsed or refractory HGG. The study included 111 patients with PK information, 53 older than 12 years, N=34 between 6 and 11 years old, and N=24 between 1 and 5 years old. PK sampling was included on Days 1 (0.5, 2, 4 h after dose), 15 (pre-dose, 0.5, 1, 2, 3, 4, 6, 8 h after dose) and 22 (pre-dose).

Given the rarity of BRAF-mutation positive malignant melanoma in adolescents, very limited PK data in the target population were available. Thus, Studies A2101, X2101 and G2101 were used to support inferences on PK in the target population. Efficacy and safety assumptions in the paediatric population are based on extrapolation from the adult population via PK bridging.

A modelling and simulation approach was employed where PopPK models for dabrafenib and trametinib were developed on PK data from paediatric patients. Subsequently, PK simulations were performed to support the proposed posologies. PK simulations included the steady state PK exposures at various dose levels stratified by body weight.

Further supportive evidence for efficacy is provided from an external publication (Chiaravalli et al 2025) on case series of adolescent patients with BRAF V600 mutation-positive melanoma treated experimentally with dabrafenib and trametinib outside clinical trials under the applicant's global compassionate use program (or Managed Access Program (MAP)).

3.2. Favourable effects

Efficacy assumptions in the target population are based on extrapolation from the adult population via PK bridging. Since there are very limited PK data in the target population, paediatric studies A2101, X2101 and G2101 were used to support inferences on dabrafenib and trametinib PK in the target population.

The PK analyses included population pharmacokinetic (PopPK) analyses for dabrafenib and trametinib. For dabrafenib, a PopPK model was developed on patients aged 1-17 years and included 2185 dabrafenib PK observations across 243 patients. For trametinib, a PopPK model was developed on patients aged 1-17 years and included a total of 1943 trametinib PK observations across 244 patients.

The simulation-based PK comparison is considered pivotal for the overall benefit-risk assessment. The most important PK exposure metric from an efficacy perspective is the Cavg (or AUC) at steady state.

Supportive efficacy evidence was available from an external publication (Chiaravalli et al 2025). The descriptive outcomes in the 6 real world cases of adolescent patients with BRAF V600 mutation-positive melanoma treated experimentally with dabrafenib and trametinib outside clinical trials suggest the anticipated activity of dabrafenib and trametinib combination in adolescents treated with doses in the sought ranges.

3.3. Uncertainties and limitations about favourable effects

The PK-bridging strategy assumes that the PK in adolescent melanoma patients can be inferred from paediatric patients with mostly other tumour diseases. This is considered an acceptable approach since it can be assumed that there are no clinically relevant PK differences between peadiatric patients with melanoma and other solid tumours. This assumption is underpinned by the

adult and paediatric PopPK analyses where disease/indication has not been identified as a clinically relevant covariate on the dabrafenib and trametinib PK profiles. Dabrafenib and trametinib are both small molecule drugs without target mediated PK. This is in agreement with the regulatory precedents of Finlee and Spexotras where data from other solid tumours were accepted as supportive evidence for characterizing the PK in paediatric glioma patients.

3.4. Unfavourable effects

The data sources for safety represent the safety data collected in 3 paediatric studies in non-melanoma indications (studies G2201, X2101 and A2102) (N=130).

All grade treatment related adverse events (TEAEs) were reported in 97.7% of paediatric patients. Treatment related SAEs were reported in 41.5% of paediatric patients. Treatment related deaths were reported in 10% of paediatric patients. Treatment related AEs leading to discontinuations were reported in 13.8% of paediatric patients. All grades pyrexia AEs were reported in 49.2% of paediatric patients. All grades dry skin AEs were reported in 37.7% of paediatric patients. The AE of weight increase (abnormal weight gain) has been reported in 15% of adolescent patients including 4% of patients with grade 3 cases.

3.5. Uncertainties and limitations about unfavourable effects

Currently, there are no safety data in adolescents with BRAF 600 mutation-positive melanoma. The safety data from the proposed Category 3 PASS CDRB436G2401 in children and adolescents with expected report May 2027 will be submitted as post-marketing commitment (see RMP).

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The need for new therapeutic options to treat adolescent BRAF V600 mutation-positive melanoma is high.

The current application is based on extrapolation of efficacy and safety from adult melanoma patients. Given the low prevalence and incidence of BRAF V600 mutation-positive melanoma in the adolescent population as well as the similarity in aetiology, pathophysiology, clinical manifestation, and disease progression to the adult population, an extrapolation approach based on popPK simulations with exposure matching is considered appropriate. This is supported by EMA guidance (EMEA/CHMP/EWP/147013/2004) and regulatory precedent.

To this end, PK data and resulting analyses are pivotal to this submission. The exposure comparisons between paediatric and adult patients were based on PopPK simulations, which is supported. The paediatric PK simulations were compared with target exposure intervals based on PopPK model-based PK exposures in adults. The proposed paediatric posology gave matching exposure compared to adult patients.

The PK-bridging strategy assumes that the PK in adolescent melanoma patients can be inferred from paediatric patients with mostly other tumour diseases. This is considered an acceptable approach since it can be assumed that there are no clinically relevant PK differences between peadiatric patients with melanoma and other solid tumours.

The safety profile across the pooled analysis from three paediatric studies with 130 non-melanoma patients treated with dabrafenib and trametinib in combination or monotherapy is consistent with

the established safety profile in adults. The most frequently reported AESI were pyrexia and skin toxicity

3.6.2. Balance of benefits and risks

Considering the similarity in aetiology, pathophysiology, clinical manifestation, and disease progression of BRAF V600 mutated melanoma in adults and adolescents, as well as in the pharmacology of dabrafenib and trametinib, the extrapolation of efficacy and safety for indications in adults to adolescents is possible.

The same extrapolation approach based on similarity in disease and pharmacology of the product has been accepted by the CHMP for the extension of malignant melanoma indication from adults to adolescents in case of Opdivo, Yervoy and Opdualag. These approvals using similar arguments for extrapolation strategy represent relevant precedents for the current application.

The balance of benefits and risk for the extension of indication of treatment of adolescent melanoma is positive.

Given the absence of safety data in adolescents with BRAF 600 mutation-positive melanoma, the safety data from the proposed Category 3 PASS CDRB436G2401 in children and adolescents with expected report May 2027 will be submitted as post-marketing commitment (see RMP).

3.6.3. Additional considerations on the benefit-risk balance

N/A

3.7. Conclusions

The overall B/R of Tafinlar and Mekinist is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of unresectable or metastatic melanoma with a BRAF V600 mutation and adjuvant treatment of Stage III melanoma with a BRAF V600 mutation for adolescents aged 12 years and older for TAFINLAR and MEKINIST, based on an extrapolation report using a modelling and simulation approach to demonstrate PK, PD and efficacy of dabrafenib and trametinib in adolescent patients. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. RMP versions 15.0 and 23.0 for Tafinlar and Mekinist, respectively, have also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI and to update list of local representatives in the Package Leaflet.

The worksharing procedure leads to amendments to the annexes I and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annexes I and IIIB, and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The 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.

In addition, 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/0410/2020 (Tafinlar) and P/0392/2020 (Mekinist), and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.