NOVARTIS

Patient Safety & Pharmacovigilance

Dabrafenib

DRB436

EU Safety Risk Management Plan

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Product(s) concerned (brand name(s)):	Tafinlar®, Finlee®
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Rationale for submitting an updated RMP: This update to the EU Risk Management Plan is in response to the PRAC PSUR assessment report, dated 18-Nov-2024 (Procedure number: EMEA/H/C/PSUSA/00010084/202405).

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v 11.1
Part I	Table 1-1 updated to reflect the current approved indications
Part II	Removal of well characterized risks in line with PSUR assessment report Exposure updated according to PSUR DLP
Part III	No update
Part IV	No update
Part V	Removal of well characterized risks in line with PSUR assessment report Correction in Table 12-2 to better reflect the classification of risk "Long-term safety in patients <18 years of age (including potential adverse effects on skeletal maturation and sexual maturation)"
Part VI	Removal of well characterized risks in line with PSUR assessment report
Part VII	CCI

Other RMP versions under evaluation

No other RMP versions are currently under evaluation.

Details of the currently approved RMP:

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Approved with procedure: EMEA/H/C/005885/0000

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QPPV name: Dr. Justin Daniels, PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse event
AHR	Adjusted hazard ratios
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AOR	Adjusted odds ratio
ARR	Adjusted risk ratio
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BMI	Body mass index
BRAF	B-Raf proto-oncogene, serine/threonine kinase
CNS	Central nervous system
CI	Confidence Interval
CSR	Clinical Study Report
CTCAE	Common terminology criteria for adverse events
CuI	Cumulative incidence
DTIC	Dacarbazine
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERK	Extracellular related kinase
ESRD	End stage renal disease
EU	European Union
FDA	Food and Drug Administration
FU	Follow up
GALT	Gut-associated lymphoid tissue
HGG	High-grade glioma
HR	Hazard ratio
ISP	Integrated safety population
LCH	Langherhans Cell Histiocytosis
LGG	Low-grade glioma
LVEF	Left ventricular ejection fraction
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated extracellular related kinase
NCCN	National Comprehensive Cancer Network
NF1	Neurofibromatosis type 1
NOS	Not otherwise specified
NR	Not reported
NSCLC	Non-small cell lung cancer
OPG	Optic pathway gloma
OR	Odds ratio
OS	Overall survival
PFS	Progression free survival
PPES	Palmar-plantar erythrodysaesthesia syndrome

PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PSUSA	PSUR Single Assessment
PTY	Patient Treatment Years
RFS	Relapse free survival
RP2D	Recommended phase 2 dose
RMP	Risk Management Plan
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SEER	Surveillance, Epidemiology and End Results
SmPC	Summary of Product Characteristics
US	United States
WHO	World Health Organization

1 Part I: Product(s) Overview

Table 1-1 Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Dabrafenib
Pharmacotherapeutic group(s) (ATC Code)	L01EC02
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Tafinlar, Finlee
Marketing authorization procedure	Centralized Procedure
Brief description of the product	Chemical class: Antineoplastic agent – Protein kinase inhibitor. ATC code: L01EC02
	Summary of mode of action: potent and selective inhibitor of V600 mutation-positive BRAF kinase
	Important information about its composition: N/A. No new information.
Hyperlink to the Product Information	[SmPC]
Indications in the EEA	Current: • Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. • Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with BRAF V600 mutation. • Adjuvant treatment of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection. • Dabrafenib in combination with trametinib powder for oral solution is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy. • Dabrafenib in combination with trametinib powder for oral solution is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment.
Dosage in the EEA	Current: • 150 mg twice daily p.o. (capsule formulation) • Weight-based dosing, twice daily p.o. administration (dispersible tablet formulation; see Finlee SmPC for details)
Pharmaceutical forms and strengths	Current: • 50 mg and 75 mg hydroxypropyl methylcellulose (HPMC) hard capsules • 10 mg dispersible tablets
Is the product subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indications: treatment of adult patients with unresectable or metastatic melanoma with BRAF V600E mutation and adjuvant treatment of patients with stage III melanoma with a BRAF V600 mutation, following complete resection

2.1.1 Indication: treatment of adult patients with unresectable or metastatic melanoma with BRAF V600E mutation

Incidence:

Cutaneous melanoma is the most aggressive form of all skin cancers, with approximately 232000 new cases and approximately 55000 disease-related deaths worldwide each year (Globocan 2012a). In Europe, malignant melanoma is the 9th most common cancer, with more than 100000 new cases diagnosed in 2012 (Ferlay et al 2013).

According to EUCAN, the age-standardized incidence rate (per 100000) of skin melanoma, in 2012 was 11.1 (males – 11.4, females – 11.0) in Europe (40 countries), and 13.0 (males – 13.2, females - 13.1) in the European Union (EU) (27 countries in 2012) (EUCAN 2012d, EUCAN 2012e, EUCAN 2012f). In the US, it was estimated that 87110 individuals will be diagnosed with skin melanoma and an estimated 9730 people will die of this disease in 2017 (SEER 2017a). The age-standardized incidence rate was 22.3 per 100000 individuals per year based on cases diagnosed in 2010-2014 in the geographical area of the Surveillance, Epidemiology and End Results (SEER) registries (SEER 2017a).

Table 2-1 Incidence of cutaneous melanoma

	Incidence		
Country/Region	Number of patients	Annual Rate (per 100000)	Source of data/ reference
Europe	100339	11.1	EUCAN* / Ferlay et al (2013)
France	9871	13.0	EUCAN* / Ferlay et al (2013)
Germany	16884	14.8	EUCAN* / Ferlay et al (2013)
Italy	10012	13.4	EUCAN* / Ferlay et al (2013)
Spain	5004	8.6	EUCAN* / Ferlay et al (2013)
United Kingdom	14445	19.0	EUCAN* / Ferlay et al (2013)
US	87110	22.3	SEER (2017a)**

*EUCAN incidence rates are age-adjusted to the European standard population;**SEER incidence rates are age-adjusted to the 2000 US population

Although the number of cases of incident malignant melanoma is large, a small percentage of subjects are considered to have unresectable or metastatic disease (unresectable Stage IIIC or Stage IV disease). According to the SEER Program in the US, stage IIIC and stage IV melanoma, respectively, comprise 1.6% and 4.2% of all new melanoma cases with known stage information (SEER 2017b).

Prevalence:

The 2012 estimated 1-year prevalence of melanoma is 13.9 per 100000 for Europe, corresponding to 87280 prevalent cases; and 24.0 per 100000 for the US, corresponding to 60518 prevalent cases; and 53.6 per 100000 in Australia/New Zealand, corresponding to 11846 prevalent cases (Globocan 2012c, Globocan 2012d).

Table 2-2 Prevalence of cutaneous melanoma

	Number of prevalent cases			
Country/Region	**1-year**	**3-year**	**5-year**	**Source of data/ reference**
Europe	87285	247837	391316	EUCAN 2012d
France	8601	24760	39533	EUCAN 2012d
Germany	14735	42207	66997	EUCAN 2012d
Italy	8719	25154	40248	EUCAN 2012d
Spain	4309	12425	19792	EUCAN 2012d
United Kingdom	12602	36005	57163	EUCAN 2012d
US	60518	175103	281577	Globocan 2012d

The 2012 unresectable and metastatic prevalent population of melanoma (i.e. unresectable Stage IIIC and IV) that is considered eligible for drug treatment is estimated to be 15120 patients in the US. Of these, 5380 patients are estimated to harbor the BRAF mutation and be eligible for 1st or 2nd line treatment (Webster and Hughes 2012). Similarly, the drug-treatable, unresectable and metastatic prevalent melanoma population in the EU-5 is expected to number 16414 cases, of which 5260 patients would have BRAF mutation and be eligible for 1st or 2nd line treatment (Webster and Hughes 2012).

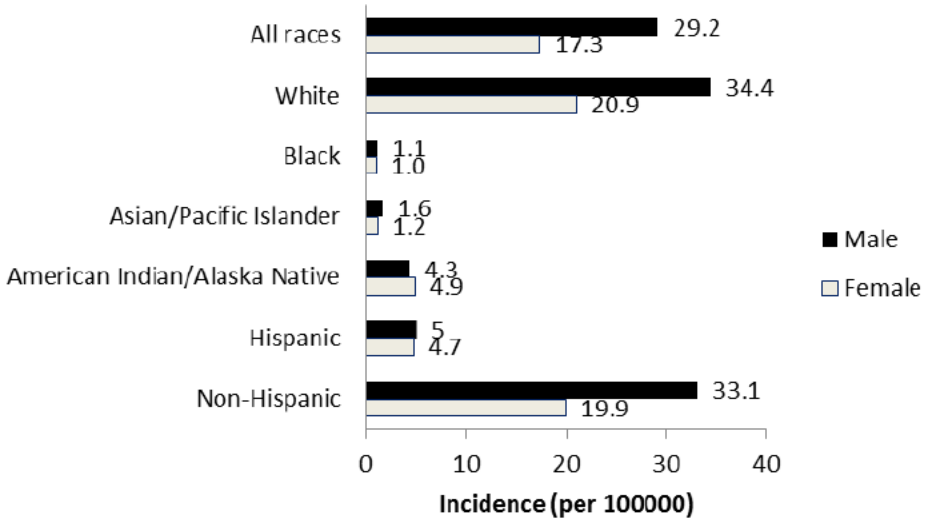
The frequency of BRAF mutations in melanoma has been reported to be approximately 50% (range: 27% to 70%) (Garnett and Marais 2004, Chapman 2011a).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Melanoma risk varies by age and gender. Based on 2006 to 2008 SEER cancer registry data among Whites, the probability of developing melanoma is higher among women than men from birth to age 39 (0.27 and 0.15, respectively), but reverses thereafter (0.56 and 0.63, respectively, from ages 40 to 59; 0.39 and 0.75, respectively, from ages 60 to 69; 0.82 and 1.94, respectively, from age 70 onwards) (Siegel 2012).

The overall incidence (per 100000) is 29.2 among men and 17.3 among women in the US. The corresponding incidence rates (male and females) across race/ethnicity is shown in Figure 2-1 (SEER 2017a).

Figure 2-1 Incidence of cutaneous melanoma by race/ethnicity and gender



SEER 18 registries (2010-2014), Age-adjusted rates
Based on SEER Cancer Stat Facts: Melanoma of the skin (SEER 2017a)

From 2010-2014, the median age at diagnosis of skin melanoma was 64 years in the US. Approximately 22.2% were diagnosed between 55 and 64 years; 22.7% between 65 and 74 years; 17.1% between 75 and 84 years. About 8.2% were diagnosed over 84 years of age (SEER 2017a).

The US SEER cancer registry included 4210 melanoma patients diagnosed in 2005-2009 initially as Stage IIIC to Stage IV, which can be considered as a proxy for unresectable and metastatic melanoma patients. Of these, 48% of patients diagnosed with unresectable and metastatic melanoma were at age 65 years and above, 28% at 75 years and above, and 8% at 85 years and above (Table 2-3). Similar age distribution was observed among unresectable and metastatic melanoma subjects in Denmark.

Table 2-3 Age distribution of unresectable and metastatic melanoma subjects

	US SEER 2005-2009[a] Unresectable/metastatic (stage IIIC+IV) melanoma		Denmark 1997-2010[b] Metastatic (stage IV) melanoma	
Age at diagnosis	**N**	**%**	**N**	**%**
<55 years	1209	28.7	801	28.4
55-64 years	973	23.1	669	23.8
65-74 years	836	19.9	629	22.4
75-84 years	849	20.2	536	19.0
85+ years	343	8.1	179	6.4
Total	4210	100.0	2814	100.0

a. Data Source: Software: Surveillance Research Program, SEER*Stat software (www.seer.cancer.gov/seerstat) version 8.0.1. Data: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2011 Sub (1973-2009 varying) - Linked To County Attributes - Total U.S., 1969-2010 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2012, based on the November 2011 submission.

	US SEER 2005-2009[a] Unresectable/metastatic (stage IIIC+IV) melanoma		Denmark 1997-2010[b] Metastatic (stage IV) melanoma	
Age at diagnosis	**N**	**%**	**N**	**%**

b. Data Source: Danish cancer registry and Danish Pathology Registry. GSK sponsored study (ID: WEUSKOP6139), unpublished.

Cutaneous melanoma is a multi-factorial disease with both genetic and environmental risk factors - a personal or family history of melanoma, the presence of atypical or numerous moles (>50), sun sensitivity (sun burning easily, tanning minimally, natural blond or red hair color), a history of high intermittent sun exposure, including sunburns, use of tanning booths, diseases that suppress the immune system, and past history of basal or squamous cell carcinoma (American Cancer Society 2012a).

The main existing treatment options:

The treatment choice for malignant melanoma depends on cancer stage, whether the tumor is resectable, BRAF mutation status, patient health status and drug toxicity profile (Solanki 2012). Patients who have unresectable Stage III melanoma are generally treated like those with metastatic disease (Solanki 2012).

Systemic treatment with chemotherapy has been the traditional way to treat unresectable and metastatic melanoma, although with little to no impact on survival for subjects. The alkylating agent, dacarbazine, is the most widely used chemotherapy for advanced disease with a response rate of 5-12% and median duration of response of 6 months (Solanki 2012, Avril et al 2004, Middleton et al 2000a, Bedikian et al 2006, Schadendorf et al 2006, Chapman et al 2011a, Robert et al 2011).

Current treatment options for unresectable and metastatic melanoma include:

- immunotherapy,
- chemotherapy,
- targeted therapy.

The approvals of ipilimumab, vemurafenib, dabrafenib, trametinib, pembrolizumab and nivolumab in the US and EU in 2011 to 2014 for the treatment of unresectable and metastatic malignant melanoma as well as more recent approval of cobimetinib in combination with vemurafenib in US and EU in 2015, and talimogene laherparepvec (an oncolytic virus therapy, also known as T-vec) in US with positive opinion in EU marks the start of a new era for the treatment of this disease. Prior to these, immunotherapy and chemotherapy both as single agents and combination regimens had failed to significantly improve survival for advanced malignant melanoma subjects. In patients with BRAF V600E or K mutation, the combination of a BRAF inhibitor and a MEK inhibitor, including dabrafenib plus trametinib, is the treatment with highest level of medical evidence(category 1) recommended by National Comprehensive Cancer Network (NCCN) guideline as first line treatment for unresectable or metastatic disease (NCCN 2016).

On 29-May-2013, Tafinlar® (dabrafenib) and Mekinist® (trametinib) were approved by the US Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E (dabrafenib monotherapy and trametinib monotherapy)

or BRAF V600K (trametinib monotherapy only) mutations. Tafinlar® and Mekinist® were also approved in Canada as monotherapies (16-Jul-2013 and 18-Jul-2013, respectively), Australia (21-Aug-2013 and 11-Feb-2014, respectively) and in the European Union (EU) (26-Aug-2013 and 30-Jun-2014, respectively). Tafinlar® and Mekinist® have subsequently been approved in multiple additional countries as single agents.

The combination of Tafinlar® and Mekinist® was first approved by the FDA on 08-Jan-2014 (accelerated approval), Australia TGA on 11-Feb-2014, Canada on 06-Mar-2015 (conditional approval), and New Zealand on 20-Mar-2015 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. The combination was approved on 25-Aug-2015 in the EU and the FDA granted conversion of the accelerated approval to regular approval on 20-Nov-2015 based on Phase III data. The combinations of Tafinlar® and Mekinist® have subsequently been approved in multiple additional countries.

The purpose of the medicinal product covered by this EU RMP, including trametinib monotherapy and trametinib in combination with dabrafenib, is to reduce progression of disease in patients with a BRAF V600 mutation.

Natural history of the indicated condition in the population, including mortality and morbidity:

The melanoma mortality rate in Europe is 1.5 per 100000 (Forsea et al 2012). Due to early detection, a majority of melanoma patients are cured with surgery alone. Historically, the median survival time for subjects with Stage IV melanoma was short, at approximately 6 months with 26% of subjects alive at 1 year, and a median progression-free survival (PFS) of 1.7 months with 14.5% of subjects progression-free at 6 months (Korn et al 2008). With the advances in immune check-point inhibitor, such as the combination treatment of nivolumab and ipilimumab, the median PFS for metastatic melanoma patients can reach 11.5 months and response rate reached 57.6% (Larkin et al 2015). The mean age at baseline was 59 years. On average, an individual loses 20.4 years of potential life as a result of melanoma mortality, compared to 16.6 years for all malignancies (NCCN 2016).

In the US, the mortality rates for skin melanoma are 4.0 per 100000 men and 1.7 per 100000 women. The mortality rates (per 100000) in men and women respectively, are 4.6 and 1.9 among Caucasians, 0.5 and 0.4 among Blacks, 0.4 and 0.3 among Asian/Pacific Islanders, 1.4 and 0.5 among American Indian/Alaska Natives, and 1.0 and 0.6 among Hispanics (SEER 2017a).

From 2010-2014, the median age at death for cancer of melanoma was 70 years of age. Approximately 2.0% died between ages 20 and 34; 4.6% between 35 and 44; 11.2% between 45 and 54; 20.1% between 55 and 64; 22.8% between 65 and 74; 24.1% between 75 and 84; and 15.1% for those over 84 years of age (SEER 2017a).

The age-adjusted death rate was 2.7 per 100000 men and women per year based on data from patients who died between 2010 and 2014 in the US. Based on 2007-2013 data, 5-year survival rate of melanoma was 91.7% (SEER 2017a).

Cutaneous melanoma accounts for less than 5% of all skin cancers, which also includes basal cell carcinoma and squamous cell carcinoma (American Cancer Society 2012a), but it causes 75% of skin cancer deaths (Jerant et al 2000).

Mortality is worse among Whites compared with African Americans - the death rates (per 100000 persons) in males were 4.6 versus 0.5, respectively, and in females, 1.9 versus 0.4, respectively (SEER 2017a).

Overall, death rate has been decreasing among Whites, younger than age 50, by 2.9% annually in men and 2.3% annually in women from 2004 to 2008, whereas the rates among Whites, 50 years and older, has increased 1% per year for males and remained stable for females during the same time period (American Cancer Society 2012a).

Melanoma is highly curable if detected in its earliest stages and treated properly (usually surgery). However, the prognosis for metastatic melanoma patients has been historically poor because of limited treatment options and efficacy, which up until recently, included mainly alkylating agents, dacarbazine and temozolomide, and immunotherapy with IL-2 and/or interferon-alpha (IFN-α) (American Cancer Society 2012b).

The melanoma mortality rate in Europe is 1.5 per 100000 (Forsea et al 2012). Due to early detection, a majority of melanoma patients are cured with surgery alone. Historically, the median survival time for subjects with Stage IV melanoma was short, at approximately 6 months with 26% of subjects alive at 1 year, and a median progression-free survival (PFS) of 1.7 months with 14.5% of subjects progression-free at 6 months (External references). With the advances in immune check-point inhibitor, such as the combination treatment of nivolumab and ipilimumab, the median PFS for metastatic melanoma patients can reach 11.5 months and response rate reached 57.6% (Larkin et al 2015). The mean age at baseline was 59 years old. On average, an individual loses 20.4 years of potential life as a result of melanoma mortality, compare to 16.6 years for all malignancies (NCCN 2016).

Unresectable, locally advanced melanoma (Stage IIIC) is often treated in the same manner as metastatic (Stage IV) melanoma (Webster and Hughes 2012). Based on SEER cancer registry data, for melanoma subjects diagnosed from 2004 to 2009, the 1-year and 5-year survival rates are approximately 81% and 35%, respectively, for Stage IIIC melanoma, and 39% and 13%, respectively, for Stage IV melanoma (National Cancer Institute Surveillance Research Program 2011). Using data from the Surveillance, Epidemiology, and End Results (SEER) database, patients diagnosed with unresectable stage IIIB/C and stage IV (M1a, M1b, M1c) melanoma between 2004 and 2009 were selected. Patients at stage IIIB/IIIC had a median overall survival (OS) of 24.3 months, with a survival rate of 67.2% at 1 year, 42.9% at 2 years, and 32.1% at 3 years. For patients at stage M1a, the median OS was 22.3 months, 1 year, 2 year, and 3 year survival rates were 64.5%, 40.4%, and 26.4%, respectively; for patients at stage M1b, median OS was 11.2 months, 1 year, 2 year, and 3 year survival rates were 43.8%, 23.4%, and 13.8%, respectively; for patients at stage M1c, median OS was 5.1 months, and 1 year, 2 year, and 3 year survival rates were 22.3%, 8.9%, and 4.7%, respectively (Song et al 2015).

Adverse events can occur in patients with unresectable or metastatic melanoma. Population-based studies or clinical trials in patients with placebo only arms evaluating untreated patients with unresectable or metastatic melanoma were not available. The following information is based on Phase III clinical trials in patients with unresectable or metastatic melanoma that included a comparator arm (dacarbazine or carboplatin/paclitaxel combination) with a placebo. In a Phase III trial on patients with previously untreated unresectable or metastatic melanoma, among patients in the control arm (treated with dacarbazine and placebo), 94% had an adverse

event with 27.5% reported to have a grade 3 or 4 adverse event. Grade3 or 4 nausea was reported in 1.2%, vomiting in 1.6%, abdominal pain in 2.8%, fatigue in 4.8%, asthenia in 2.4%, back pain in 1.2%, decreased appetite in 1.6%, increased aspartate aminotransferase in 1.2% and immune-related adverse events in 6% of patients in the control arm (Robert et al 2011, Robert et al 2011a). Similar information on patients' unresectable or metastatic melanoma treated with carboplatin and paclitaxel as first (Flaherty et al 2013) or second line therapy (Hauschild et al 2009) is included in Table 2-4.

Table 2-4 Adverse events reported in patients with unresected or metastatic melanoma (in a clinical trial control arm treated with placebo and carboplatin/paclitaxel)

Adverse Event (Grade 3 or higher)	Frequency
Total	**69%[2] – 78.2%[1]**
Blood/bone marrow	**60%[2]**
Neutrophils	46%[2]-49.1%[1]
Platelets	8.8%[1] -12%[2]
Hemoglobin	7.1%[1]- 13%[2]
Leukocytes	19%[2] – 22.9%[1]
Constitutional symptoms	**13%[2]**
Fatigue	10%[2] - 14.1%[1]
Anorexia	**2.3%[1]**
Gastrointestinal	**14%[2]**
Diarrhea	3.0%[2] - 3.8%[1*]
Infection	**15%[2]**
Febrile neutropenia	4.0%[1] – 7.0%[2]
Metabolic/laboratory	**11%[2]**
Lipase	2%[2]
Neurology	**20%[2]**
Neuropathy, sensory	13.0%[2] - 14.9%[1]
Pain	**18%[2]**
Pain, extremity	5.0%[2]
Muscle pain	**5.5%[1]**
Dermatology	**4%[2]**
Rash/desquamation	2.0%[1]
Hand-foot skin reaction	0.3%[1]
Hypertension	**1.3%[1]**
Allergic reaction	**2.8%[1]**
Lymphopenia	**4.3%[1]**
Dehydration	**4.8%[1]**
Hyponatremia	**2.3%[1]**
Hyperglycemia	**4.8%[1]**

Source: [1] Flaherty et al 2013; [2]Hauschild et al 2009; [*]without prior colostomy

Important co-morbidities:

To obtain background rates for the most commonly occurring co-morbidities in a real-world population of unresectable and metastatic melanoma subjects, a retrospective study was

conducted using the US SEER-Medicare Linked Databases. This study included 1746 subjects (aged 65+ years; male, 61%; primarily Whites, 95%) with initial diagnoses of Stage IIIC unresectable or Stage IV metastatic melanoma during 1992 to 2005 (cases) and 1746 age-, gender-, race-, and region-matched non-cancer controls, drawn from SEER-Medicare Linkage Databases. Of these unresectable/metastatic melanoma subjects, 89.8% subjects died during the follow-up and the median survival was 10 months (SEER-Medicare Study, Mekinist EU RMP V12-Annex 12.1).

During the 12 months prior to unresectable and metastatic melanoma diagnosis, the most prevalent co-morbidities, with prevalence >20%, included essential hypertension (53.1%), other skin disorders (38.7%), disorders of lipid metabolism (37.5%), cataract (32.9%), connective tissue disease (30.9%), lower respiratory disease (30.0%), non-traumatic joint disorders (26.8%), coronary atherosclerosis (23.3%), and diabetes mellitus without complication (21.0%). Compared with age-, gender, race-, and region-matched non-cancer controls, unresectable/metastatic melanoma subjects had more than 2-fold higher prevalence of neoplasms of unspecified nature or uncertain behavior (19% versus 9%), pleurisy and pleural effusion (4.8% versus 2.2%), other non-epithelial cancer of skin (17% versus 8%), and open wounds of extremities (5.5% versus 2.6%). Comparable databases with oncology information encompassing countries comprising the EU are not available. Therefore, US estimates of important co-morbidities are presented as a surrogate for the EU.

2.1.2 Indication: Adjuvant treatment of patients with stage III melanoma with a BRAF V600 mutation, following complete resection

Incidence:

According to the data from the 18 SEER (registries) in the US, among 102706 patients with melanoma diagnosed between 2010 and 2014, stage information (AJCC stage groups, 7th ed) was available on 93782 patients of whom 7.3% had stage III disease (including 1.5% with stage IIIA, 2.1% with stage IIIB, 1.6% with stage IIIC, and 2.1% listed as stage III or Stage III NOS) (SEER 2017b). Applying this percentage to the number of new patients expected to be diagnosed with melanoma in the US in 2017, it is estimated that 6359 new patients with stage III melanoma will be diagnosed in the US in 2017. Similar information on stage was not available in Europe. Applying the stage distribution from the SEER data to the incidence of melanoma in Europe in 2012, it is estimated that 7325 new patients are diagnosed with stage III melanoma in a year in Europe (EUCAN 2012d, SEER 2017b).

Prevalence:

Data on the prevalence of stage III melanoma are limited. Based on prevalence data from SEER and age-adjustment to the US population in 2016, it is estimated that there were 13322 patients who had been newly diagnosed to have melanoma with Stage III disease within the previous 3 years and were alive in 2016 in the US (SEER 2017a, CDC Wonder 2017). The corresponding estimate, age-adjusted to the European population in 2016, is 34,160 (SEER 2017a, United Nations 2017).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

According to data from the 18 SEER registries in the US, among 6868 patients diagnosed with stage III melanoma between 2010 and 2014, 4496 (65%) were male and 2372 (35%) were female. About 34% were younger than 55 years of age, 24% were between 55 and 64 years, 21% were between 65 and 74 years, 15% were between 75 and 84 years and 6% were over the age of 84 years (SEER 2017b). Most patients were white (97%), 1.2% were black and the remaining patients were of unknown or other races (SEER 2017b). Risk factors for melanoma are listed in Section 2.1.1.

Table 2-5 Age and gender distribution of patients with stage III melanoma

Age	Male	Female	Total
<55 years	1344 (30%)	994 (42%)	2338 (34%)
55-64 years	1141 (25%)	480 (20%)	1621 (24%)
65-74 years	1040 (23%)	415 (18%)	1455 (21%)
75-84 years	706 (16%)	332 (14%)	1038 (15%)
85+ years	265 (6%)	151 (6%)	416 (6%)
Total	4496 (100%)	2372 (100%)	6868 (100%)

*Data from SEER 18 registries, patients with Stage III melanoma (AJCC Stage group, 7th ed) diagnosed between 2010 and 2014, obtained using SEER*Stat version 8.3.4 (SEER 2017d)

The main existing treatment options:

Adjuvant therapy is indicated in patients with Stage III melanoma at high risk of recurrence following complete surgical resection with the intent of treating micrometastatic disease and reduce the risk of local and distant relapse (Kirkwood et al 2001, Van Akkooi et al 2009).

Different therapies have been explored in the adjuvant setting, including interferon, interleukin-2, and vaccines, bevacizumab (a vascular endothelial growth factor inhibitor), as well as ipilimumab (an immune checkpoint inhibitor) in the last decade. Specifically, high dose interferon alpha (HDI) and PEGylated interferon have been approved for adjuvant melanoma treatment based on relapse free survival (RFS) improvement, without significant survival benefit in the majority of the studies conducted; only one study (Kirkwood et al 2004) demonstrated initial survival benefit, although it was not confirmed in the analysis performed with additional follow up. The unfavorable safety profile, as shown by the significant treatment related toxicities, has limited use in clinical practice and patient adherence (Kirkwood 1996, Kirkwood 2000, Eggermont 2005). Iplimumab, an immune checkpoint inhibitor, used at a dosage of 10 mg/kg, has shown significant RFS improvement in high risk Stage III melanoma after complete resection (HR=0.76; 95% CI: 0.64, 0.89), and this has translated into a survival benefit (HR=0.72; 95% CI: 0.58, 0.88) after a median follow-up of 5.3 years; however, the treatment related toxicities are severe. Nearly half of the patients had toxicity equal to or greater than common terminology criteria for adverse events (CTCAE) grade 3. Five (1%) patients died due to drug related adverse event (AE) and all these events occurred within the first 12 weeks of treatment. A total of 52% patients discontinued treatment because of an AE. Only 7% of the patients completed the planned three year treatment (Eggermont et al 2015, Eggermont et al 2016). Iplimumab at a dosage of 10 mg/kg in the adjuvant setting was approved in the US in October 2015. In the AVAST-M Phase III study, bevacizumab treatment was assessed as

adjuvant treatment in patients with Stage IIB, IIC and III melanoma. The primary endpoint, overall survival was not met; survival rate at 5 years was 64% on bevacizumab versus 63% on observation arm (HR=0.99; 95% CI: 0.84, 1.18; p=0.96) (Corrie et al 2017).

The poor clinical outcome observed in patients with Stage III melanoma reflects the need for effective adjuvant treatments to prevent relapse.

Natural history of the indicated condition in the population, including mortality and morbidity:

Stage III melanoma accounts for approximately 10% of newly diagnosed melanomas, is treated with complete resection, however it is associated with a high risk of relapse. The risk of relapse and mortality is defined by independent predictive factors including, primary tumor thickness; ulceration; mitotic rate and lymph node burden (Balch et al 2009). The overall 5-year RFS observed for stage IIIA, IIIB, and IIIC patients was 63%, 32%, and 11%, respectively (Romano et al 2010). The estimated 5-year survivals for stages IIIA, IIIB, and IIIC from time of first relapse were 20%, 20%, and, 11%, respectively (Romano et al 2010).

Patients with stage III melanoma who are treated with surgical resection may experience recurrence and other adverse events. In a Phase III trial evaluating ipilimumab versus placebo in patients who had undergone complete resection of stage III melanoma, at a median follow-up of 5.3 years, the 5-year rate of recurrence-free survival was 30.3% in the placebo group (Eggermont et al 2016). The rate of overall survival was 54.4% and the rate of distant metastasis-free survival was 38.9% in the placebo group. Among the 474 patients who received placebo, 91.1% had an adverse event of any grade. Grade 3 or 4 events occurred in 26.2% of patients in the placebo group and included diarrhea (2.1%), abdominal pain (0.2%), vomiting (0.2%), colitis (0.2%), fatigue (1.5%), headache (0.2%), weight loss (0.4%), increased weight (0.4%), pyrexia (0.2%), and decreased appetite (0.2%).

Important co-morbidities:

Data on comorbidities specifically in patients with stage III melanoma specifically were not available from population-based studies. However, according to a nationwide cohort study in Denmark on patients diagnosed with melanoma (n=23476) between 1987 and 2009, 19% of patients with melanoma suffered from one or more comorbidities with 9.9% of patients having one comorbidity, 5.8% having two comorbidities, 1.8% having 3 comorbidities and 1.4% having 4 or more comorbidities. Any cancer (excluding melanoma and non-melanoma skin cancer) was the most common comorbidity (3.9%), followed by cerebrovascular disease (3.4%) and chronic pulmonary disease (2.4%), and diabetes (2.0%). Other comorbidities that occurred in over 1% of the melanoma patients included myocardial infarction (1.7%), congestive heart failure (1.7%), peripheral vascular disease (1.4%), ulcer disease (1.5%), and connective tissue disease (1.4%) (Grann et al 2013).

2.2 Indication: Treatment of patients with advanced non-small cell lung cancer with a BRAF V600 mutation

Incidence:

According to the Globocan (2012a) project of the World Health Organization and the International agency for Research on Cancer, lung cancer has been the most common cancer in the world for several decades, and in 2012, there were an estimated 1.8 million new cases worldwide, representing 12.9% of all new cancers. It was also the most common cause of death from cancer, with 1.59 million deaths worldwide in 2012 (19.4% of the total) (Globocan 2012b). The estimated number of patients diagnosed with lung cancer in 2012 was 409911 in Europe and 309589 in the 27 member states of EU (EUCAN 2012a, EUCAN 2012b, EUCAN 2012c).

Table 2-6 Incidence of lung cancer and NSCLC

	Incidence			
Country/Region	Annual rate of lung cancer (per 100000)	Number of lung cancer patients	Number of NSCLC patients with BRAF V600E mutation***	Source of data
Europe	41.9	409911	6968	EUCAN*/Ferlay et al (2013)
France	49.2	40043	681	EUCAN*/Ferlay et al (2013)
Germany	39.8	50813	864	EUCAN*/Ferlay et al (2013)
Italy	36.6	37238	633	EUCAN*/Ferlay et al (2013)
Spain	43.5	26715	454	EUCAN*/Ferlay et al (2013)
United Kingdom	45.1	40382	686	EUCAN*/Ferlay et al (2013)
US	55.8	222500	3783	SEER (2017)**

*EUCAN incidence rates are age-adjusted to the European standard population;**SEER incidence rates are age-adjusted to the 2000 US population; ***number of NSCLC patients with BRAF V600E mutation was estimated assuming that 85% of newly diagnosed lung cancer patients have NSCLC and that 2% of NSCLC patients harbor the V600E mutation.

NSCLC accounts for the majority of cases (~85%) of lung cancer. Pagano et al 2010 analyzed data on incident lung cancer cases in a regional cancer registry in Italy from 2000 through 2003. There were 2572 cases of NSCLC which represented 90% of all incident lung cancers. A Spanish study of 481 lung cancers diagnosed in a defined health area from February 1997 through December 1999 reported that approximately 80% were NSCLC (Prim et al 2010).

Prevalence:

The 5-year prevalence of lung cancer, including trachea and bronchus, was 442810 in Europe (40 countries) and 336143 (230842 men and 105301 women) in the EU (27 countries) in 2012 (EUCAN 2012a, EUCAN 2012b, EUCAN 2012c, Bray et al 2013). In the US, there were an estimated 527228 people living with lung and bronchus cancer in 2014 (SEER 2017).

Table 2-7 Prevalence of lung cancer

	Number of prevalent cases			
Country/Region	**1-year**	**3-year**	**5-year**	**Source of data/ reference**
Europe	184032	356582	442810	EUCAN 2012a
France	21863	43732	54811	EUCAN 2012a
Germany	21666	43554	55783	EUCAN 2012a
Italy	17866	35159	43960	EUCAN 2012a
Spain	11551	22532	28148	EUCAN 2012a
United Kingdom	13430	24826	30298	EUCAN 2012a
U.S.A.	103571	210138	268629	GLOBOCAN 2012d

BRAF mutations are observed in approximately 2% of NSCLC and occur most frequently in adenocarcinomas. Out of all the BRAF mutations, around half were BRAF V600 mutations. Out of the BRAF V600 mutations, almost all are V600E mutation (Chen et al 2014). Pratilas et al (2008) evaluated 916 patients from Japan, Taiwan, US and Australia with NSCLC and reported that 17 patients had BRAF mutations, including 11 patients with V600E mutation (1.2%). Similarly, in a study by Paik et al (2011), among 697 patients with lung adenocarcinoma, BRAF mutations were present in 18 patients. Out of these 18 patients, 9 patients were diagnosed with the BRAF V600E mutation, with a frequency of 1.3% (Paik et al 2011). Marchetti et al (2011) selected a cohort of 1046 patients in Italy with NSCLC of whom 739 patients had adenocarcinoma and 307 had squamous cell carcinoma. BRAF mutations were present in 37 patients among whom twenty-one patients were identified with BRAF V600E mutation leading to a frequency of 2 percent. A similar frequency of two percent of BRAF V600E mutation was reported by Cardarella et al (2013) when they evaluated 883 patients with NSCLC in the U.S. at a cancer institute among whom 36 tumors harbored the BRAF mutations (V600E in 18 and non-V600E in 18). According to a 1-year nationwide program of the French Cooperative Thoracic Intergroup (IFCT) on routine molecular profiling of patients with advanced NSCLC, BRAF mutations were reported in 262 (2%) of 13906 molecular analyses with available data among 17664 patients with NSCLC (Barlesi et al 2016).

Based on the above, the proportion of patients with BRAF V600E NSCLC among all lung cancer patients is expected to be small. Of the estimated 222500 new cases of lung cancer in the US in 2017 (SEER 2017), assuming that around 85% of lung cancer patients have non-small cell lung cancer (Pagano et al 2010) and up to 2% harbor the BRAF V600E mutation (Cardarella et al 2013), it is expected that up to 3783 patients have BRAF V600E mutant NSCLC. Similarly, of the estimated 409911 new cases of lung cancer in Europe in 2012 (EUCAN 2012$_a$), up to 6968 patients are expected to have BRAF V600E mutant NSCLC.

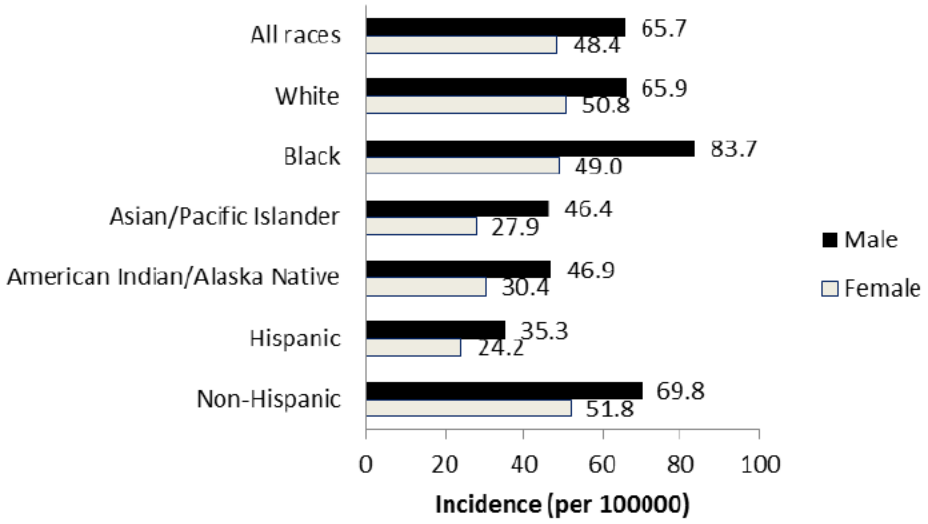
Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Lung cancer occurs in men more frequently than women. It is the most common cancer in men worldwide (1.2 million new cases worldwide in 2012, 16.7% of the total), with the highest estimated age-standardized incidence rates in Central and Eastern Europe, and Eastern Asia. In females, incidence rates are generally lower, (583000 cases and 491000 deaths worldwide in 2012) (Globocan 2012b). According to SEER data in the US, the overall incidence (per 100000) was 65.7 among men and 48.4 among women. The corresponding incidence rates across

different races/ethnicities (male and females) are shown in Figure 2-2 (SEER 2017). During 2005–2009, a total of 569366 invasive lung cancer cases among men and 485027 among women were reported in the US (Henley et al 2014).

Lung cancer is a disease of elderly population. From 2010-2014, the median age at diagnosis of cancer of the lung and bronchus was 70 years in the US. Approximately 21.5% were diagnosed between 55 and 64 years; 32.9% between 65 and 74; 27.1% between 75 and 84 years. About 9.4% were diagnosed over 84 years of age (SEER 2017).

Figure 2-2 Incidence of lung cancer by race/ethnicity and gender



SEER 18 registries (2010-2014), Age-adjusted rates
Based on SEER Cancer Stat Facts: Lung and Bronchus Cancer (SEER 2017)

There were no significant differences between the age and stage of the tumor at initial diagnosis between patients with BRAF mutations and wild type tumors (Cardarella et al 2013; Marchetti et al 2011). The gender difference of NSCLC with the BRAF V600 mutation is unclear. Some studies reported that it is more frequent in women than men (Li et al 2015, Marchetti et al 2011). However, other studies did not report a significant difference between males and females with respect to BRAF mutations (Luk et al 2015, Paik et al 2011, Schmid et al 2009). According to IFCT data, among 262 NSCLC patients with a BRAF mutation, 61% were male and 39% were female (compared to 65% males and 34% females in the wild type NSCLC group). The median age was 65.9 years among patients with the BRAF mutation and 64.7 years among those in the wild-type NSCLC group (Barlesi et al 2016).

Several risk factors contribute to the development of lung cancer, including cigarette, pipe, or cigar smoking; exposure to second-hand smoke, radon, arsenic, asbestos, chromates, chloromethyl ethers, nickel, polycyclic aromatic hydrocarbons, radon progeny, other agents, air pollution, and radiation therapy to the breast or chest (NCI 2016a). Smoking is considered the single most important risk factor for the development of lung cancer.

The BRAF V600E mutation can be diagnosed both in smokers and non-smokers. In a study by Litvak et al (2014), the majority of patients with BRAF mutations were smokers (92%),

although patients with V600 mutations were more likely to be light/never smokers compared to patients with non-V600 mutations (42% versus 11%). Marchetti et al (2011) reported that the V600E mutations were more frequent in patients who never smoked than in smokers or former smokers (10 of 197 patients [5.1%] versus 11 of 542 patients [2%]). Pratilas et al (2008) reported that the majority of NSCLC patients with BRAF mutations were current or former smokers, although information specifically on patients with BRAF V600 mutations was not available. In a study from France, the proportion of never, former, and current smokers was 25%, 38%, and 37% among NSCLC patients with the BRAF mutation and 18%, 42%, and 40% among those with wild-type NSCLC (Barlesi et al 2016).

The main existing treatment options:

There are different treatment options available for patients with NSCLC (NCI 2016b). These vary depending on the stage of the disease. According to the National Cancer Institute, results of standard treatment in NSCLC are poor except for the most localized cancers. Surgery is the most potentially curative therapeutic option for early stage disease. For advanced or metastatic NSCLC, systemic treatment is needed.

In advanced-stage and metastatic NSCLC, systemic chemotherapy with four to six cycles of a platinum-based doublet is widely used as the standard first-line therapy. In those NSCLC patients with good performance status who have experienced tumor regression or achieved at least disease stabilization, maintenance treatment with anticancer agents including pemetrexed or erlotinib has been validated as an effective treatment. Before programmed cell death (PD-1) antibodies were introduced in the clinic, for patients without an actionable mutation, further treatment options upon disease progression included single-agent chemotherapy such as pemetrexed or docetaxel or molecularly targeted therapy, such as erlotinib (Schiller et al 2002, Borghaei et al 2015, Mok et al 2009, Solomon et al 2014, Hanna et al 2004, Rosell et al 2012). The median progression-free survival (PFS) usually is about 4-6 months for patients receiving platinum doublet chemotherapy as first line, and 2-3 months for single agent chemotherapy as second line. The median overall survival (OS) is less than one year.

Major advances in the definition of the molecular pathology of NSCLC have led to the development of targeted agents attacking cancer-cell specific attributes essential for growth or survival, such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) or vascular endothelial growth factor receptor (VEGFR) tyrosine kinases, and antibodies that inhibit the immune checkpoint and restore antitumor immunity, while avoiding some of the severe side effects of conventional cytotoxic chemotherapy. The subgroup of non-squamous NSCLC patients who benefit most from systemic treatment are those who receive targeted therapies based on the presence of a specific actionable oncogenic driver mutation. For patients where this option is not available and who have progressed during or after platinum based chemotherapy, treatment using an immune checkpoint blocker (PD-1 antibody) is an option. However, the clinical benefit remains modest. Non-small cell lung carcinoma patients with non-squamous cancer histology treated with nivolumab as second line treatment had a PFS of 2.3 months, and response rate was 19% by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. The median survival time was 12.2 months (Borghaei et al 2015).

Recently pembrolizumab was approved as monotherapy for first line treatment in patients with ≥ 50% PD-L1 overexpression, based on data showing significantly improved survival vs

chemotherapy (HR: 0.60; 95% CI: 0.41, 0.89, P<0.005) (Reck NEJM 2016). A phase II study also reported pembrolizumab plus chemotherapy has better efficacy than chemotherapy alone in non-selected patients as first line treatment in NSCLC (Langer 2016). But this combination use is not yet approved in European region. Despite the advances in immune checkpoint inhibitors in NSCLC, data suggested patients with EGFR mutation may not benefit as much as those with wild type EGFR from these type of treatment (Rittmeyer 2017). Small molecule targeted therapy remains as the backbone treatment for NSCLC patients with an actionable mutation.

Natural history of the indicated condition in the population, including mortality and morbidity:

In the US, the mortality rates for cancer of the lung and bronchus were 55.9 per 100000 men and 36.3 per 100000 women. The mortality rates (per 100000) in men and women were 55.9 and 37.5 among Caucasians, 68.0 and 34.6 among Blacks, 31.7 and 18.0 among Asian/Pacific Islanders, 46.3 and 30.8 among American Indian/Alaska Natives, and 27.3 and 13.4 among Hispanics (SEER 2017).

From 2010-2014, the median age at death for cancer of the lung and bronchus was 72 years. Approximately 0.1% died between 20 and 34; 0.8% between 35 and 44; 7.0% between 45 and 54; 20.0% between 55 and 64; 31.3% between 65 and 74; 28.7% between 75 and 84; and 12.0% for those over 84 years of age (SEER 2017).

The age-adjusted death rate was 44.7 per 100000 men and women per year based on data from patients who died between 2010 and 2014 in the US. The overall 5-year relative survival for 2007-2013 from 18 SEER geographic areas was 18.1% (SEER 2017).

Litvak et al (2014) investigated the overall survival (OS) of patients who were diagnosed with BRAF mutant lung adenocarcinomas between 2009 and 2013. The study included 36 patients who had V600 mutation and 27 patients with non-V600 mutation. In patients with stage IIIb or IV BRAF mutant lung adenocarcinomas, those with V600 mutations had a longer 3-year overall survival as compared to patients with non-V600 mutations (24% versus 0%, p<0.001). The 3-year overall survival after resection of early stage lung cancer was similar for patients with V600 mutant tumors compared to non-V600 mutant tumors (67% vs 75%, p=0.42). Marchetti et al (2011) reported that in a series of 331 patients with lung adenocarcinoma including 21 patients with BRAF V600E mutation and 310 patients with wild type tumors, patients with V600E BRAF mutations had shorter median disease free survival (DFS) and overall survival (OS) than patients with wild type tumors (15.2 versus 52.1 months; p<0.001 and 29.3 versus 72.4 months; p<0.001, respectively). Cardarella et al (2013) reported no significant difference in overall survival between patients with advanced NSCLC who had BRAF mutations and those who had wild-type tumors. Barlesi et al (2016) reported the median overall survival for a group of 230 patients with mixed stage (mainly stage III and IV) NSCLC who had BRAF mutation was 13.8 months.

Various adverse events can occur in patients with advanced or metastatic NSCLC. Data on adverse events in untreated patients were not available from population-based studies. The following information on patients receiving placebo is based on completed Phase III clinical trials reported in Clinicaltrials.gov. In a randomized trial in patients with advanced or metastatic

non-small cell lung cancer that has not responded to standard therapy for advanced or metastatic cancer, serious adverse events occurred in 36.4% of patients in the placebo arm (NCT01000025). Such events with a frequency of over 1% included abdominal pain and vomiting (1.26% each), lung infection (5.02%), sepsis (1.26%), other neoplasms (17.99%), stroke (1.26%), bronchopulmonary hemorrhage (1.67%), dyspnea (5.86%), pleural effusion (1.26%), and thromboembolic event (1.26%).

In study NCT00556712, among patients with advanced, recurrent, or metastatic NSCLC with previous platinum-based chemotherapy who have not had disease progression or unacceptable toxicity during chemotherapy, serious adverse events were reported in 7.64% of patients in the placebo arm. No specific SAE were reported to occur in more than 1% of patients in the placebo arm. In Study NCT00404924 on patients with non-small cell lung cancer, whose disease has recurred after previous chemotherapy and an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR TKI), 20.79% of patients in the placebo arm experienced serious adverse events. Reported serious adverse events with a frequency of over 1% included dyspnea, pleural effusion and pulmonary embolism (1.65% of patients each) and pneumonia (1.98% of patients).

Important co-morbidities:

Islam et al (2015) evaluated 5683 newly diagnosed lung cancer patients in the U.S. and reported that the most common comorbidities were chronic pulmonary disease (52.5%), diabetes (15.7%), congestive heart failure (12.9%), peripheral vascular disease (8.8%), cerebrovascular disease (7%), myocardial infarction (6.8%) and renal disease (5.7%). Janssen-Heijnen et al (1998) evaluated 3864 lung cancer patients in the Netherlands between 1993 and 1995. The most frequent concomitant diseases reported were cardiovascular diseases (23%), chronic obstructive pulmonary diseases (COPD) (22%), other malignancies (15%), hypertension (12%) and diabetes (7%).

2.3 Indication: Treatment of Paediatric Gliomas with BRAF V600E mutation

Epidemiology data on paediatric gliomas, including grading (high grade vs. low grade glioma) and presence of BRAF v600E mutation, are limited. However, there is a greater degree of epidemiology data for paediatric central nervous system (CNS) tumors or for gliomas of specific histology. Therefore, many estimates reported in this review have been estimations based on either (1) the rates of paediatric CNS tumors and the proportion of these that are paediatric gliomas, or (2) the sums of data broken down by specific histologies that comprise all paediatric gliomas. All reported values that are based on estimations, are noted as such in the tables.

Methods

For population-based registry databases reporting the incidence of all paediatric CNS tumors, the incidence of paediatric gliomas was estimated from incidence of all brain and CNS tumors in children and the proportion of all paediatric CNS tumors that are gliomas in Europe and North America (range 45-65%, unweighted average of 56.2% used for estimations) (Ostrom et al 2021, Erdmann et al 2020, Desandes et al 2014, Rosychuk et al 2012).

The incidence of paediatric LGG and HGG are estimated from the proportion of all paediatric gliomas that are LGG and HGG in the US and Australia (range 61-72% LGG, 28-39% HGG, unweighted average 66.5% LGG and 33.5% HGG, used for estimations) (Ostrom et al 2021, Youlden et al 2021).

The estimation of the proportion of paediatric LGG and HGG that are BRAF v600E mutation positive was calculated as follows. The unweighted average of two estimates of the proportion of paediatric LGG that are BRAF v600E mutation positive is 10.5% (range 9-12%), and from this estimate and the proportion of BRAF v600E mutation paediatric gliomas that are HGG (16%), it is possible to estimate the proportion of paediatric HGG tumors that are BRAF v600E mutation positive (estimated to be 4%) (Nobre et al 2020, Gierke et al 2016, Horbinski et al 2012).

Incidence

Table 2-8 provides the incidence of paediatric gliomas by world region or country. Worldwide the age-adjusted incidence is 0.7 to 1.04 per 100,000 for all paediatric gliomas (0.5 to 0.7 for LGG, 0.2 to 0.34 for HGG, 0.05 to 0.07 for BRAF v600E mutation positive LGG, and 0.01 for BRAF v600E mutation positive HGG) (GBD 2022, Globocan 2022).

Estimates of the age-adjusted incidence of paediatric glioma for Europe range from 0.71 to 1.49 per 100,000 persons, and specifically, 0.47 to 0.99 per 100,000 persons for LGG and 0.24 to 0.50 per 100,000 persons for HGG, and 0.05 to 0.10 per 100,000 persons for BRAF v600E mutation positive LGG, and 0.01 to 0.02 per 100,000 persons for BRAF v600E mutation positive HGG (GBD 2022, Globocan 2022, Rarecarenet 2022). Within Europe, age-adjusted incidence per 100,000 persons is highest in Germany and the Nordic countries (2.4 to 2.7 for all paediatric gliomas, 1.6 to 1.8 for LGG, 0.8 to 0.9 for HGG, 0.17 to 0.19 for BRAF v600E mutation positive LGG, and 0.03 to 0.04 for BRAF v600E mutation positive HGG) and lowest in France (1.96 to 2.24 for all paediatric gliomas, 1.30 to 1.49 for LGG, 0.69 to 0.75 for HGG, 0.14 to 0.16 for BRAF v600E mutation positive LGG, and 0.03 for BRAF v600E mutation positive HGG) (Nordcan 2022, Erdmann et al 2020, Coll et al 2015, Desandes et al 2014).

The age-adjusted incidence of paediatric glioma in the US is 2.6 to 3.12 per 100,000 persons (1.7 to 2.07 for LGG and 0.9 to 1.05 for HGG, 0.18-0.22 for BRAF v600E mutation positive LGG, and 0.04 for BRAF v600E mutation positive HGG) (SEER 2022, Ostrom et al 2021).

Table 2-8 Incidence of paediatric CNS tumors, paediatric gliomas, LGG, HGG and BRAF v600E

	Incidence per 100,000 persons, age-standardized						
Setting	All paediatric CNS tumors	All paediatric gliomas	LGG	BRAF V600E+ LGG	HGG	BRAF V600E+ HGG	References
Europe (WHO region)	2.2-2.65	1.2-1.49*	0.80-0.99†	0.08-0.10‡	0.40-0.50**	0.02††	GBD (2022), Globocan (2022)
EU27	1.26	0.71*	0.47†	0.05‡	0.23**	0.01††	Rarecarenet (2022)

Setting	Incidence per 100,000 persons, age-standardized						References
	All paediatric CNS tumors	All paediatric gliomas	LGG	BRAF V600E+ LGG	HGG	BRAF V600E+ HGG	
Southern and Southeastern Europe	-	-	-	-	0.98-1.34**	0.04-0.05††	Papathoma et al (2015)
Nordic countries	4.3-4.8	2.4-2.7*	1.6-1.8†	0.17-0.19‡	0.8-0.9**	0.03-0.04††	Nordcan (2022)
France	-	1.96-2.24§	1.30-1.49†	0.14-0.16‡	0.66-0.75**	0.03††	Coll et al (2015), Desandes et al (2014)
Germany	-	2.49§	1.58-1.66†	0.17‡	0.83**	0.03††	Erdmann et al (2020), Gnekow et al (2021)
Netherlands	-	2.30§	1.53†	0.16‡	0.81**	0.03††	Reedijk et al (2020)
UK	-	2.29§	1.56†	0.16‡	0.77**	0.03††	Stiller et al (2019)
US and Canada	2.77-3.2	1.56-1.8*	1.04-1.2†	0.11-0.13‡	0.52-0.6**	0.02††	GBD (2022), Globocan (2022)
US	-	2.60-3.12§	1.73-2.07†	0.18-0.22‡	0.87-1.05**	0.03-0.04††	SEER (2022), Ostrom et al (2021)
Canada	4.3	2.88§	1.92†	0.20‡	0.96**	0.04††	Rosychuk et al (2012)
Worldwide	1.2-1.85	0.7-1.04*	0.5-0.69†	0.05-0.07‡	0.2-0.35**	0.01-0.02††	GBD (2022), Globocan (2022)

* All paediatric gliomas estimated as Incidence of all CNS tumors × 0.562, § All paediatric gliomas estimated as sum of astrocytomas, ependymomas oligodendrogliomas and other gliomas, † LGG estimated as Incidence of all paediatric gliomas × 0.665, ** HGG estimated as Incidence of all paediatric gliomas × 0.335, ‡ BRAF v600E mutation positive LGG estimated as Incidence of LGG × 0.105, †† BRAF v600E mutation positive HGG estimated as Incidence of HGG × 0.04, CNS: central nervous system, EU27: the 27 EU states in 2012 (including UK), GBD: global burden of disease, HGG: high grade glioma, LGG: low * grade glioma, SEER: Surveillance, Epidemiology and End Results, UK: United Kingdom, US: United States

Prevalence

For population-based registry databases reporting the prevalence of all paediatric central nervous system (CNS) tumors, the prevalence of paediatric gliomas was estimated from prevalence of all brain and CNS tumors in children and the proportion of all incident paediatric CNS tumors that are gliomas in Europe and North America (range 45-65%, unweighted average of 56.2% used for estimations) (Ostrom et al 2021, Erdmann et al 2020, Desandes et al 2014, Rosychuk et al 2012). Where each type of glioma is reported separately, the prevalence for all gliomas is summed across histological subtypes. The prevalence of paediatric LGG and HGG are estimated from the proportion of all incident paediatric gliomas that are LGG and HGG in

the US and Australia (range 61-72% LGG, 28-39% HGG, unweighted average 66.5% LGG and 33.5% HGG, used for estimations) (Ostrom et al 2021, Youlden et al 2021). This method of estimation may overestimate the prevalence of HGG and underestimate the prevalence of LGG, due to differences in survival between LGG and HGG. The estimation of the proportion of paediatric LGG and HGG that are BRAF v600E mutation positive is described in "incidence section" above.

For Europe, the estimated prevalence of LGG in children in 2019 was 5.81 per 100,000 persons, and the estimated prevalence of HGG in children in 2019 was 2.93 per 100,000 persons (GBD 2022). The estimated 10-year period prevalence in children in Nordic countries is 6.5 to 7.5 per 100,000 persons for LGG and 3.2 to 3.9 per 100,000 persons for HGG (Nordcan 2022). In Europe, the estimated prevalence of BRAF v600E mutation positive LGG in children in 2019 was 0.61 per 100,000 persons and the estimated prevalence of BRAF v600E mutation positive HGG in children in 2019 was 0.12 per 100,000 persons (GBD 2022). For the Nordic countries, the estimated 10-year period prevalence in children is 0.7 to 0.8 per 100,000 for BRAF v600E mutation positive LGG and 0.1 to 0.2 per 100,000 for BRAF v600E mutation positive HGG (Nordcan 2022).

For the US and Canada, the estimated prevalence of LGG in children in 2019 was 7.09 per 100,000 persons, and for HGG it was 3.57 per 100,000 persons (GBD 2022). In the US, the 26-year period prevalence in children is estimated to be 10 per 100,000 persons for LGG and 5 per 100,000 persons for HGG (SEER 2022). The 26-year period prevalence of BRAF v600E mutation positive LGG in US children is estimated to be 0.74 per 100,000 persons, and the 26-year period prevalence of BRAF v600E mutation positive HGG in US children is estimated to be 0.14 per 100,000 persons (SEER 2022).Table 2-9 provides the prevalence of paediatric gliomas by region or country.

Table 2-9 Prevalence of paediatric CNS tumors, LGG, HGG and BRAF v600E

Setting	Outcome definition	5-y period prevalence (per 100,000)	10-y period prevalence (per 100,000)	26-y period prevalence (per 100,000)	Prevalence in 2019 (per 100,000)	References
Europe (WHO region)	All CNS tumors	7.0	-	-	15.56	GBD (2022), Globocan (2022)
Europe (WHO region)	LGG	2.6†	-	-	5.81†	GBD (2022), Globocan (2022)
Europe (WHO region)	HGG	1.3**	-	-	2.93**	GBD (2022), Globocan (2022)
Europe (WHO region)	BRAFv600E mutation+ LGG	0.3‡	-	-	0.61‡	GBD (2022), Globocan (2022)
Europe (WHO region)	BRAFv600E mutation+ HGG	0.05††	-	-	0.12††	GBD (2022), Globocan (2022)
Nordic countries	All CNS tumors	17.2-20.1	33.7-39.2	-	-	Nordcan (2022)
Nordic countries	LGG	6.5-7.5†	12.6-14.6†	-	-	Nordcan (2022)

Setting	Outcome definition	5-y period prevalence (per 100,000)	10-y period prevalence (per 100,000)	26-y period prevalence (per 100,000)	Prevalence in 2019 (per 100,000)	References
Nordic countries	HGG	3.2-3.9**	6.3-7.4**	-	-	Nordcan (2022)
Nordic countries	BRAFv600E mutation+ LGG	0.7-0.8‡	1.3-1.5‡	-	-	Nordcan (2022)
Nordic countries	BRAFv600E mutation+ HGG	0.1-0.2††	0.3††	-	-	Nordcan (2022)
US and Canada	All CNS tumors	11.3	-	-	18.96	GBD (2022), Globocan (2022)
US and Canada	LGG	4.3†	-	-	7.09†	GBD (2022), Globocan (2022)
US and Canada	HGG	2.1**	-	-	3.57**	GBD (2022), Globocan (2022)
US and Canada	BRAFv600E mutation+ LGG	0.5‡	-	-	0.75‡	GBD (2022), Globocan (2022)
US and Canada	BRAFv600E mutation+ HGG	0.1††	-	-	0.14††	GBD (2022), Globocan (2022)
US	LGG	-	-	10*	-	SEER (2022)
US	HGG	-	-	5***	-	SEER (2022)
US	BRAFv600E mutation+ LGG	-	-	1.1‡	-	SEER (2022)
US	BRAFv600E mutation+ HGG	-	-	0.2††	-	SEER (2022)
Worldwide	All CNS tumors	3.3	-	-	8.24	GBD (2022), Globocan (2022)
Worldwide	LGG	1.2†	-	-	3.08†	GBD (2022), Globocan (2022)
Worldwide	HGG	0.6**	-	-	1.56**	GBD (2022), Globocan (2022)
Worldwide	BRAFv600E mutation+ LGG	0.1‡	-	-	0.32‡	GBD (2022), Globocan (2022)
Worldwide	BRAFv600E mutation+ HGG	0.02††	-	-	0.06††	GBD (2022), Globocan (2022)

†LGG estimated as Prevalence of all CNS tumors × 0.562 × 0.665, * LGG estimated as sum of all paediatric gliomas × 0.665, ** HGG estimated as Prevalence of all CNS tumors × 0.562 × 0.335, *** HGG estimated as sum of all paediatric gliomas × 0.335, ‡ BRAF v600E mutation positive LGG estimated as Prevalence of LGG × 0.105, †† BRAF v600E mutation positive HGG estimated as

Prevalence of HGG × 0.04, CNS: central nervous system, GBD: global burden of disease, HGG: high grade glioma, LGG: low grade glioma, SEER: Surveillance, Epidemiology and End Results, US: United States, y: year

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease

Globally, between 30% and 40% of paediatric gliomas are diagnosed before age five years, and there is a slight male preponderance (51-57% males) (Youlden et al 2021, Erdmann et al 2020, Rosychuk et al 2012). In the US, 57-81% of paediatric gliomas are in Non-Hispanic whites or whites including white Hispanics, 18-24% are in Hispanics (white and non-white), 13-14% are in blacks, 5-6% are in Asians or Pacific Islanders, and 1-2% are in American Indians and Alaska Natives (Ostrom et al 2021, Jiang et al 2020). Table 2-10 Demographic characteristics of paediatric gliomas provides the demographic characteristics of paediatric glioma patients in Europe and the US and Canada.

Table 2-10 Demographic characteristics of paediatric gliomas

Setting	Outcome definition	Age (%)	Sex (%)	Race (%)	References
Germany	All gliomas	Age < 1 y: 6%* Age 1-4 y: 27%* Age 5-9 y: 28%* Age 10-14 y: 27%* Age 15-17 y: 12%*	Males: 54%* Females: 46%*	-	Erdmann et al (2020)
US	All gliomas	Age 0-4 y: 29%* Age 5-9 y: 27%* Age 10-14 y: 24%* Age 15-19 y: 20%*	-	White: 81%* Black: 13%* Asian or Pacific Islander: 5%* American Indian or Alaska Native: 1%* Non-Hispanic: 82%* Hispanic: 18%*	Ostrom et al (2021)
US	All gliomas and medulloblastomas	-	-	57% Non-Hispanic Whites 24% Hispanic whites 12% Blacks 6% Asians or Pacific Islanders 2% American Indians or Alaska Natives	Jiang et al (2020)
Canada	All brain and CNS tumors	Age < 1 y: 6% Age 1-4 y: 24% Age 5-9 y: 28% Age 10-14 y: 21% Age 15-19 y: 21%	Male: 57% Female: 43%	-	Rosychuk et al (2012)
Australia	All gliomas	Age 0-4 y: 40%* Age 5-9 y: 32%* Age 10-14 y: 27%*	Male: 51%* Female: 49%*	-	Youlden et al (2021)

* Proportions are taken for all paediatric gliomas, which are summed across the histologies that comprise gliomas, CNS: central nervous system, US: United States, y: year

In the US, the incidence of malignant brainstem gliomas among children is significantly higher in Hispanics than in non-Hispanic whites (Patil et al 2021). Non-white race is associated with reduced risk of incident ependymal tumors in US children (Zhang et al 2020). Prenatal pesticide and diesel exhaust exposures are associated with an increased risk of incident astrocytomas and ependymomas (Lombardi et al 2021, Volk et al 2019). For instance, Danish children whose mothers are employed in industries with diesel exhaust exposure have and increased risk of incident astrocytomas with an odds ratio (OR) of 1.5, with a 95% Confidence Interval (CI) of 1.0-2.1 (Volk et al 2019).

Natural history of the indicated condition in the population, including mortality and morbidity:

Survival is closely linked to histology, tumor site, age at diagnosis and tumor grade. Overall survival (OS) in paediatric gliomas ranges from 1-year OS of 91-99% in LGG to a 1-year OS of 50 to 60% in HGG (Youlden et al 2021, Tabash et al 2019, Ostrom et al 2021), and a 5-year OS of 78 to 98% in LGG and 16 to 70% in HGG (SEER 2022, Gnekow et al 2021, Ostrom et al 2021, Youlden et al 2021, Napieralska et al 2021a, Tabash et al 2019). Long-term survival is good for paediatric LGG with a 10-year OS of 75 to 98% (Gnekow et al 2021, Ostrom et al 2021, Youlden et al 2021), but poor for paediatric HGG with a 10-year OS of 14 to 69% (SEER 2022, Napieralska et al 2021a, Ostrom et al 2021, Youlden et al 2021). Table 2-11 provides the 1-year, 2-year, 5-year and 10-year OS or relative survival (RS) of paediatric glioma patients by country and histological subtype. Only the Surveillance, Epidemiology and End Results (SEER) data report RS, all other sources in Table 2-11 report OS.

Table 2-11 Survival in paediatric gliomas

Setting	Grade	Glioma histology	1-y OS or RS	2-y OS	5-y OS or RS	10-y OS	References
Germany	LGG	All LGG	--	--	98%	98%	Gnekow et al (2021)
Poland	HGG	Primary HGG	78%	48%	30%	17%	Napieralska et al (2021a)
Poland	Both	Ependymomas	98%	95%	83%	73%	Napieralska et al (2021b)
US	HGG	Glioblastomas	57-58%*	-	15-19%*	16%	SEER (2022), Ostrom et al (2021)
US	Both	Brainstem gliomas	91%-	87%-	86%	--	Khalid et al (2019)
US	Both	Ependymal tumors	96%-	--	80%	72%-	Ostrom et al (2021)
US	LGG	Pilocytic astrocytomas	99%	--	95-97%	96%	Tabash et al (2019), Ostrom et al (2021)
US	HGG	Anaplastic astrocytomas	66%	-	25%	19%	Ostrom et al (2021)
US	Both	Diffuse and anaplastic astrocytomas	83%*	-	45%*	-	SEER (2022)
US	Both	Diffuse astrocytomas	92%-	--	82%	80%-	Ostrom et al (2021)
US	Both	Oligodendrogliomas	97%	-	94%	92%	Ostrom et al (2021)
US	Both	Malignant gliomas, NOS	82%	-	70%	69%	Ostrom et al (2021)
US	Both	Other gliomas	92%*	-	86%*		SEER (2022)

Setting	Grade	Glioma histology	1-y OS or RS	2-y OS	5-y OS or RS	10-y OS	References
Australia	LGG	Grade I astrocytomas	98%	-	96%	94%	Youlden et al (2021)
Australia	LGG	Grade II gliomas	91%	-	78%	75%	Youlden et al (2021)
Australia	HGG	Grade III ependymomas	90%	-	56%	51%	Youlden et al (2021)
Australia	HGG	Grade III astrocytomas	59%	-	30%	25%	Youlden et al (2021)
Australia	HGG	Grade IV astrocytomas	50%	-	16%	14%	Youlden et al (2021)
Australia	HGG	Grade III/IV gliomas, NOS	60%	-	44%	42%	Youlden et al (2021)

*SEER data are relative survival, all other data are overall survival, CNS: central nervous system, OS: overall survival, RS: relative survival, SEER: Surveillance, Epidemiology and End Results, US: United States, y: year

After adjusting for confounding factors, histology is strongly associated with overall survival or mortality risk in paediatric gliomas. The adjusted odds ratio (AOR) and adjusted hazard ratios (AHR) are as follows (if the histological type in the following list is always HGG or always LGG, this is noted in parentheses): for ependymoma (both LGG and HGG) vs. astrocytoma (both LGG and HGG) the AHR is 0.6 (95% CI 0.5-0.8), for anaplastic glioma (HGG) vs. pilocytic astrocytoma (LGG) the AOR is 7.8 (95% CI 3.2-19.2), for glioblastoma (HGG) vs. pilocytic astrocytoma (LGG) the AOR is 36.5 (95% CI 18.3-72.7), for oligodendroglioma (both LGG and HGG) vs. pilocytic astrocytoma (LGG) the AOR is 3.8 (95% CI 1.4-9.8), for glioma not otherwise specified (NOS) (both LGG and HGG) vs. ependymomas (both LGG and HGG) the AHR is 13.0 (95% CI 2.5-67.5), and for astrocytoma (both LGG and HGG) NOS vs. ependymomas (both LGG and HGG) the AHR is 12.5 (95% CI 1.9-80.9) (Jiang et al 2020, Zhou et al 2020, Khalid et al 2019).

In LGGs, no survival difference was found between paediatric patients with and without BRAF v600E mutations (Horbinski et al 2012). In HGGs, no observational studies reported differences in survival by BRAF v600E mutation status, but one study reported 1-y progression free survival (PFS) for BRAF v600E mutation positive paediatric HGGs (n=11) to be 27% (95% CI 10-72%) (Nobre et al 2020, Youlden et al 2021). In this same small study, the 1-y PFS for BRAF v600e mutation positive paediatric LGGs (n=56) was 86% (95% CI 78-96%) (Nobre et al 2020). Table 2-12 shows frequency of BRAF v600E mutations in paediatric gliomas and survival outcomes.

Neurocognitive impairments are common in paediatric gliomas, with a 25-y cumulative incidence of 26% for at least one grade 3-5 neurological condition in survivors of paediatric astrocytomas in the US and Canada, and a 25-y cumulative incidence of 7% for paralysis (Effinger et al 2019). Other common complications in paediatric gliomas include visual acuity deficits (68% of neurofibromatosis-associated optic pathway gliomas, 25-y cumulative incidence of 19% in astrocytomas), auditory impairments (25-y cumulative incidence of 17% in astrocytomas), post-operative speech impairment (30% of posterior fossa tumors), subsequent neoplasms (25-y cumulative incidence of 7% in astrocytomas), cardiac conditions (25-y CuI of 8% in astrocytomas), endocrine conditions (25-y cumulative incidence of 6% in astrocytomas) and stroke (25-y cumulative incidence of 13% in astrocytomas) (Kotch et al 2022, Gronbaek et al 2021, Effinger et al 2019).

Neurofibromatosis type 1 (NF1) is associated with increased risk of subsequent neoplasms in survivors of paediatric glioma with a relative risk (RR) of 4.0 (95% CI 2.1-7.6) (De Blank et al 2020). Familial NF1 inheritance is associated with increased risk of relapsed/refractory optic-pathway paediatric gliomas with an adjusted risk ratio (ARR) of 2.2 (95% CI 1.2-3.9). Other risk factors for relapsed/refractory optic pathway paediatric gliomas include age < 2 y at initial therapy (ARR 3.2, 95% CI 1.2-5.2) and posterior tumor location (ARR 2.2, 95% CI 1.1-4.1) (Kotch et al 2022).

Some tumor locations are associated with a reduced risk of post-operative speech impairments in paediatric posterior fossa gliomas: cerebellar vermis vs. fourth ventricle AOR 0.3 (95% CI 0.1-0.8), and hemispheric vs fourth ventricle AOR 0.2 (95% CI 0.1-0.7) (Gronbaek et al 2021). Survivors of paediatric ependymomas who become mothers are at increased risk of preterm birth, with an AOR of 2.8 (95% CI 1.2-6.5) (Huang et al 2020).

Table 2-12 Frequency of BRAF v600E mutations in paediatric gliomas and survival outcomes

Reference	Setting and study period	Design and data source	Study population (N)	Glioma grade and histology (n)	Frequency (%) BRAF v600E mutation positive	PFS (95% CI) or HR for PFS (95% CI)	FU / comments
Nobre et al (2020)	International, study period NR	Case series, chart review from 29 institutions	Age < 25 y, BRAF v600E mutation positive gliomas (N=67) treated with BRAF inhibitors, excluding those w/missing data or < 6 months FU, median age 4.8 y (range 0.1-22.3 y), 55%* male (37/67)	HGG (n=11)	100%	1-y PFS: 27% (10-72%)	FU ≥ 0.5 y (6/12) *% male: (37/67)
				LGG (n=56)	100%	1-y PFS: 86% (78-96%)	
Gierke et al (2016)	Germany, study period NR	Retrospective observational, data source NR	Age 0-18 paediatric brain tumors (N=170), mean age NR, 56%* male (431/765)	Grade IV glioblastoma (n=10)	0%	NR	*% male: (431/765)
				Grade III anaplastic astrocytoma (n=3)	0%	NR	
				Grade III anaplastic ependymoma (n=4)	0%	NR	
				Grade II diffuse astrocytoma (n=6)	34%	NR	
				Grade II ependymoma (n=3)	0%	NR	

Reference	Setting and study period	Design and data source	Study population (N)	Glioma grade and histology (n)	Frequency (%) BRAF v600E mutation positive	PFS (95% CI) or HR for PFS (95% CI)	FU / comments
				Grade I pilocytic astrocytoma- (n=45)	2%	NR	
				Grade II pilomyxoid astrocytoma (n=3)	0%	NR	
				Grade II pleomorphic xanthoastrocytoma (n=5)	60%	NR	
				Grade I ganglioglioma / gangliocytoma (n=22)	55%	NR	
				All HGG	0%	NR	
				All LGG	9%* (16/170)	NR	
Koelsche et al (2014)	Germany and Italy, study period NR	Case series, archives of three institutions	Desmoplastic infantile gangliogliomas (N=16), Age < 24 months at diagnosis, Median age at surgery 10.5 months (range 1-60 months), Female to male ratio 0.8	Grade I desmoplastic infantile gangliogliomas	13%* (2/16)	NR	FU NR
Horbinski et al (2012)	US, study period NR	Retrospective cohort study	Paediatric non-NF1-related LGGs (N=198) (157	Grade I/II Pilocytic astrocytomas (n=110)	9%	NR	Median FU 6.3 y

Reference	Setting and study period	Design and data source	Study population (N)	Glioma grade and histology (n)	Frequency (%) BRAF v600E mutation positive	PFS (95% CI) or HR for PFS (95% CI)	FU / comments
			successfully analyzed for BRAF v600E mutation), median age 8.2 y, 56^* male (111/198)	Grade I/II gangliogliomas (n=22)	23%	NR	*% male: (111/198)
				Grade I/II pilomyxoid astrocytomas (n=5)	20%	NR	
				Grade I/II pleomorphic xanthoastrocytomas (n=5)	40%	NR	
				Other LGG (n=12)	8%	NR	
				All LGG (n=154)	12%* (19/154)	HR 2.4 (0.9-6.2) for BRAF v600E vs no BRAF v600E mutation	

CI: confidence interval, FU: follow up, HGG: high grade glioma, HR: hazard ratio, LGG: low grade glioma, N: sample size, n: number of patients per histology/grade group, NF1: neurofibromatosis type 1, NR: not reported, PFS: progression free survival, y: years

Important comorbidities

The prevalence of any comorbidity in paediatric glioma patients ranges from 7% in posterior fossa tumors to 37% in astrocytomas (Gronbaek et al 2021, Effinger 2019). Common comorbidities include neurological, psychiatric or speech problems (12% of posterior fossa tumors) (Gronbaek et al 2021). Compared to matched siblings, paediatric astrocytoma patients are more likely to experience poor general health (ARR 2.3, 95% CI 1.9-2.7), poor mental health (ARR 1.6, 95% CI 1.4-1.8), functional impairments (ARR 5.3, 95% CI 4.4-6.4) and activity limitations (ARR 1.9, 95% CI 1.6-2.3) (Effinger et al 2019).

In paediatric patients with low-grade gliomas, the prevalence of NF1 is 17% (Gnekow et al 2021). Among paediatric patients with NF1-associated optic pathway gliomas, common comorbidities include central precocious puberty (72%), growth hormone deficiency (9%), diencephalic syndrome (12%), and growth hormone hyper-secretion (6%) (Santoro et al 2020). For more details on comorbidities in paediatric gliomas, see Table 2-13.

Table 2-13 Morbidity and complications in paediatric glioma

Reference	Setting and study period	Design and data source	Study population (N)	Glioma definition	Complications and AEs: frequency (%), CuI or OR	FU / comments
Kotch et al (2022)	US, 2005-2014	Retrospective cohort, chart review at 7 hospitals	Age ≤ 18 y, NF1-associated optic pathway gliomas (N=103), excluding those who received CT before 2005 or received radiation therapy as initial treatment, median age at diagnosis 2.1* y (25/12)	NF1-associated optic pathway gliomas	Visual acuity deficit at initiation of therapy: 68% Worsened visual acuity at last FU: 35% Relapsed/refractory OPG: 44%	Median FU 7.9* y (range 1.1* -15.4* y) * FU: (95/12), (13/12 and 185/12)
Gronbaek et al (2021)	Europe, 2014-2020	Prospective observational, 26 centers in 9 countries	Age < 18 y, posterior fossa tumors undergoing primary surgery (N=426), 55% male	Posterior fossa tumors	Post-operative speech impairment: 30% Post-operative mutism: 14% Post-operative reduced speech: 16%	Maximum FU 1 year
Huang et al (2020)	Sweden, 1973-2014	Population-based cohort study, linked Swedish Medical Birth Register and Swedish Cancer Registry	Singleton live births to parents w/CNS tumor (N=1,369), excluding those born within 1 y of parental diagnosis, and 5:1 matched controls (N=6,845)	Any CNS tumor	Adjusted OR for preterm birth: Reference: matched controls Ependymoma: 2.8 (1.2-6.5)	FU NR Controls matched on birth year, gender, maternal and paternal age at birth, and region of birth Adjusted OR: adjusted for year of childbirth, gender, maternal and paternal age at birth, region at birth, parity, maternal birth country, maternal highest education, maternal pregnancy BMI, maternal smoking, gestational hypertensive disorder and gestational diabetes

Reference	Setting and study period	Design and data source	Study population (N)	Glioma definition	Complications and AEs: frequency (%), CuI or OR	FU / comments
Effinger et al (2019)	US and Canada, 1970-1986	Retrospective cohort, Childhood Cancer Survivor Study	Astrocytoma patients diagnosed before age 21 who survived > 5 y (N=1,182), 54% male	Astrocytoma	25-y CuI for at least one grade 3-5 chronic condition: 57%	Median FU 23.4 y (range 7.3-38.9 y)
					25-y CuI for at least one grade 3-5 neurological condition: 26% Neurologic conditions include paralysis CuI 7%*	*CuI paralysis: (83/1,182)
					25-y CuI for at least one grade 3-5 visual condition: 19%, including legally blind in one or both eyes or loss of an eye CuI 3%*	* CuI for legally blind in one or both eyes or loss of an eye: (33/1,182)
					25-y CuI for at least one grade 3-5 auditory condition: 17%, including hearing loss requiring a hearing aid CuI 8%*	* CuI for hearing loss requiring a hearing aid: (100/1,182)
					25-y CuI for stroke: 13%	
					25-y CuI for at least one grade 3-5 cardiac condition: 8%	
					25-y CuI for subsequent neoplasm: 7%	
					25-y CuI for at least one grade 3-5 endocrine condition: 6%, including ovarian failure CuI 3%*	* CuI for ovarian failure: (30/1,182)

2.3.1 Low-grade Glioma with BRAF V600E mutation

In LGGs, the frequency of BRAF v600E mutations ranges from 0% in ependymomas, pilomyxoid astrocytomas, and choroid plexus tumors to 2 to 9% in pilocytic astrocytomas, 13 to 55% in gangliogliomas and gangliocytomas, and 40 to 60% in pleomorphic xanthroastrocytomas (Gierke et al 2016, Koelsche et al 2014, Horbinski et al 2012).

Main existing treatment options

Regardless of the molecular profile, surgical removal is often the treatment of choice, if practical. The extent of resection is predictive of PFS. Only those patients with LGGs that can be completely resected can anticipate a median PFS of 10 years or more. Most patients will eventually experience progression of their disease and require post-surgical therapy with focal irradiation to the tumor bed plus additional chemotherapy.

For paediatric patients with molecularly unselected LGG, who could not be cured by surgical resection and were enrolled into studies of cytotoxic chemotherapy with carboplatin plus vincristine regimens, the ORR at 6 months was 29% (CR+PR), the 5-year PFS rate was 46% and 5-year OS was 89% (Gnekow et al 2017). In another large study, the ORR (CR+PR) by central review was 35% in paediatric patients with molecularly unselected LGG requiring postoperative systemic therapy with carboplatin and vincristine; 5-year OS was 86% (Ater et al 2012). In this setting of disease requiring systemic therapy after optimal surgical resection, the treatment goals generally are to prolong OS and PFS while minimizing morbidity of disease and treatment. Because of the typical young age of paediatric LGG patients and the potential for long term neurocognitive effects of radiotherapy, this modality is often avoided where possible.

An analysis revealed that patients with paediatric LGG harboring the BRAF V600E mutation had worse PFS and OS (Lassaletta et al 2017, Ryall et al 2020) than BRAF V600 wild type patients. In paediatric LGG patients with a BRAF V600E mutation, the 10-year OS was 89% and the 10-year PFS rate was 30% (Ryall et al 2020). In Lassaleta et al (2017), the 10-year PFS rate for BRAF V600E-mutant LGG was 27% (95% CI: 12.1, 41.9) compared to 60.2% (95% CI, 53.3% to 67.1%) for wild type. The Lassaletta work suggests a lower ORR of 11% (PR+CR) for these patients when treated with chemotherapy (Lassaletta et al 2017) versus 35% for the molecularly unselected population treated with chemotherapy (Ater et al 2012). There is evidence of poorer outcomes when deletion of CDKN2A is coupled with the BRAF V600E mutation (Mistry et al 2015, Lassaletta et al 2017, Ryall et al 2020). Patients with LGG who have progressed to secondary HGG (sHGG) are more likely to have had BRAF V600E mutation in their LGG at initial diagnosis (Mistry et al 2015), contributing to the poor prognosis upon initial diagnosis of BRAF V600 mutant paediatric LGG.

The survival outcomes have changed little over the past several decades, and thus improved treatment options are needed in the majority of patients with paediatric gliomas.

2.3.2 High-grade glioma with BRAF V600E mutation

Main existing treatment options

Current therapies for paediatric patients with HGGs are limited. Agents that have demonstrated activity in adult patients with HGG have not demonstrated similar benefit to paediatric patients with HGG (Sturm et al 2017). Current standard of care for newly diagnosed paediatric patients with HGGs include:

- Gross total surgical resection
- followed by focal irradiation to the tumor bed
- plus additional chemotherapy (MacDonald et al 2011)

The majority of patients develop recurrent disease and in these cases there are no effective systemic treatment options. Chemotherapy regimens have been used, but they often have burdensome toxicity and provide limited benefit. Temozolomide is currently the only anticancer substance authorized specifically for HGG; it is most often used in the recurrent disease setting in adults but has proven to be of limited benefit for paediatric patients. In 5 trials evaluating temozolomide monotherapy or temozolomide-based combinations, the ORR in recurrent or refractory, paediatric molecularly unselected HGGs ranged from 0-12% (Hummel et al 2013, Lashford et al 2002, Ruggiero et al 2006, Nicholson et al 2007, Warren et al 2012). An OS of 4.7 months was estimated in Lashford et al (2002) and a 6-month PFS rate of 16% was estimated in Warren et al (2012). Treatment of relapsed, refractory paediatric molecularly unselected HGG with several other chemotherapies and/or targeted agents has shown a similar lack of benefit.

For paediatric HGG, the BRAF V600E mutation is more frequently found in favorable prognosis subgroups of this disease, such as those lacking H3K27 mutations, and is not found in some of the worst prognostic subgroups, such as those arising from the brainstem (Mackay et al 2017). Thus, a paediatric patient diagnosed with a BRAF V600E mutation positive HGG may expect an improved OS versus those paediatric HGG that are wild type at BRAF V600. It is not known if this improvement in outcome would also be seen in those same patients at the time their disease has relapsed or become refractory to their initial treatment.

Overall, the treatment of children with HGG reflects a significant unmet need, with almost no improvement in survival outcomes in recent years.

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Key safety findings from non-clinical studies that are associated with combination therapy with dabrafenib are also described in the trametinib EU RMP.

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Effects on embryofetal development: Dabrafenib was assessed in reproductive and developmental toxicity studies in rats. At maternally toxic doses (≥0.5 times clinical exposure), fetal effects, including embryo lethality, reduced body weight, cardiac ventricular septal defects, delayed skeletal development, and variations in thymic shape were observed. **Male Fertility** Testicular toxicity in rats, dogs and mice, characterized by seminiferous tubule degeneration, depletion and/or spermatid retention, was observed below human clinical exposure to dabrafenib monotherapy (≥0.2 times clinical exposure) in studies up to 13 weeks duration without clear evidence of reversibility following recovery periods of up to 4 weeks. Effects on male fertility in non-clinical studies with dabrafenib monotherapy have not been investigated. Testicular effects, consisting of degeneration and secondary epididymal oligospermia, were observed in dogs given dabrafenib + trametinib in combination and were consistent with dogs given dabrafenib alone at comparable doses.	**Dabrafenib monotherapy** The embryofoetal developmental and testicular toxicity findings observed in non-clinical studies indicated risk for maternal toxicity, teratogenicity and impaired spermatogenesis in males, which may be irreversible. Sperm cryopreservation is an option for male patients who wish to mitigate this concern. Dabrafenib should not be used during pregnancy. Women of childbearing potential should use effective methods of contraception during therapy and for 4 weeks following discontinuation. Hormonal contraceptives are not considered adequate and an alternate method of contraception should be used. If dabrafenib is used during pregnancy, or if the patient becomes pregnant while taking dabrafenib, the patient should be informed of the potential hazard to the fetus. **Dabrafenib + trametinib combination therapy** The testicular toxicity findings observed in non-clinical studies with dabrafenib + trametinib in combination indicate a risk for impaired spermatogenesis in males. As of 12-Jan-2015, no pregnancies were reported in MEK115306 (CDRB436B2301). Two pregnancies have been reported in subjects receiving combination therapy with dabrafenib and trametinib in MEK116513 (CDRB436B2302); both subjects chose to have an elected abortion.
Bone effects Reduced long bone length was observed in juvenile rat study at dose of 10/20 and 0/200 mg/kg/day (the first value was given from postnatal Day or PND 7 to 21 and the second value was given from PND 22 to 35), at systemic exposure similar to that in humans at therapeutic dose of 150 mg bid. No bone findings were observed in studies with adult rats or dogs.	**Dabrafenib+ trametinib combination therapy** There have been no bone effects observed in adult patients taking dabrafenib or dabrafenib + trametinib in combination. Bone effects in rats occur in actively growing bones and therefore would not pose a risk to adult human patients with closed physes. The effects on bone growth are likely relevant for paediatric population, and growth is monitored in clinical trials with paediatric patients during treatment.
Epithelial Effects: In dabrafenib monotherapy toxicity studies of up to 26 weeks duration, epithelial lesions, characterized primarily by epithelial degeneration, hyperplasia and/or hyperkeratosis, have been observed (in skin of rats and dogs, oesophagus and tongue of mice and non-glandular forestomach of rats and mice [≥0.7 times clinical exposure for rats; ≥0.6 times clinical exposure for mice; 1.5 times clinical exposure for dogs]). No gastric pathology was observed in dogs. In a 13 week toxicity study in rats, epithelial hyperplasia with associated mucosal epithelial down growth of the non-	**Dabrafenib monotherapy** Proliferative and hyperkeratotic skin lesions, including squamous cell carcinoma (SCC), keratoacanthoma, papilloma, palmar-plantar erythrodysaesthesia syndrome (PPES) and hyperkeratosis have been observed in human clinical studies with dabrafenib. **Dabrafenib + trametinib combination therapy** Skin-related toxicities were observed in approximately one-half of subjects in Phase III human clinical studies with dabrafenib + trametinib combination therapy; the most frequently reported were rash, dermatitis acneiform and erythema.

Key Safety findings (from non-clinical studies)	Relevance to human usage
glandular forestomach was observed in rats given ≥20 mg/kg/day (≥0.7 times clinical exposure). Epithelial down growth was not evident in rats following the 4-week recovery period. Epithelial hyperplasia persisted, albeit of lesser overall severity, suggesting partial recovery.	Proliferative and hyperkeratotic skin lesions including squamous cell carcinoma (including keratoacanthoma), papilloma and hyperkeratosis, which are known adverse effects of BRAF inhibitors, were seen in human clinical studies with dabrafenib + trametinib combination therapy at frequencies lower than those observed with monotherapy comparator arms with BRAF inhibitors.
Cardiovascular Toxicity: Cardiovascular toxicity has been observed in dogs and rats given dabrafenib monotherapy in studies of up to 13 weeks duration. In dogs, marked coronary arterial degeneration/necrosis with secondary localized myocardial degeneration/necrosis and/or inflammation) was observed at a non-tolerated dose (≥18 times clinical exposure). Additional findings at tolerated doses included localized myocardial inflammation and haemorrhage, and minimal coronary arterial haemorrhage (≥2 times clinical exposure). In the 4-week toxicity study in dogs, a valvular lesion, characterized by hypertrophy and haemorrhage of the right atrioventricular valve, was observed in one of 22 dogs given dabrafenib (5 times clinical exposure). Valvular lesions were not reproduced in the subsequent 13-week study despite longer dosing duration and generally higher exposures. Fibrovascular proliferation of the right atrium/atrial appendage was observed (≥9 times clinical exposure) in two of 30 dogs in a 13-week study. Cardiovascular effects in rats, consisting primarily of an increased incidence of arterial degeneration and spontaneous cardiomyopathy in a 10-day and 28-day dabrafenib repeat dose study, respectively, occurred at exposures at or below human clinical exposures (>0.5 times clinical exposure) and were not observed in subsequent studies of longer dosing duration. In a 26-week study in mice, vascular and perivascular inflammation, with or without vascular wall necrosis was observed (≥0.6 times clinical exposure). In a 4-week toxicity study in dogs given dabrafenib + trametinib in combination, coronary arterial degeneration/necrosis with inflammation was observed within the epicardium of one dog killed after 10 days of dosing due to poor clinical condition.	**Dabrafenib monotherapy** Subjects were monitored for cardiovascular effects with echocardiogram/ electrocardiogram monitoring during BREAK-2 and BREAK-3 clinical trials. Of note, the BREAK-3 study included unbalanced randomization (3-fold dabrafenib treated to dacarbazine, DTIC), with significantly longer exposure to therapy in dabrafenib-treated subjects as compared to DTIC (4.9 vs. 2.8 months). Valvular toxicity was investigated as an adverse event of special interest in dabrafenib clinical studies. Subjects with abnormal cardiac valve morphology at screening (≥grade 2) documented by echocardiogram, and those with moderate valvular thickening, were excluded from clinical studies. Subjects were routinely evaluated throughout treatment by serial echocardiography. The incidence of valvular abnormalities in clinical studies was lower than expected from epidemiological studies. A single non-serious case of worsening of pre-existing valve disease to grade 2, and 2 non-serious cases of grade 1 mitral valve incompetence were identified in the randomized Phase 3 study. Blinded independent review of echocardiograms in BREAK-2 did not identify a pattern of valvular abnormalities consistent with a potential drug induced effect. LVEF: Compared with DTIC in the randomized BREAK-3 study there were more reports of decreased LVEF (3 subjects vs. 0). Decreased left ventricular ejection fraction appears to be an infrequent, largely asymptomatic, and a reversible event. Atrial/conduction effects: In the pivotal phase III study BREAK-3 the overall frequency of atrioventricular (AV) block was 4% for subjects on the dabrafenib arm and 7% for the DTIC comparator arm at baseline. First degree AV block is seen in 5-10% of healthy Caucasians (Upshaw 2004) and thus the rate in dabrafenib treated subjects does not exceed the expected background rate or that of the comparator (DTIC) population and a relationship to treatment is not apparent. In the randomized BREAK-3 study there were 2 reports of atrial fibrillation and 1 report of supraventricular tachycardia in subjects receiving dabrafenib. Neither atrial fibrillation nor supraventricular tachycardia were reported in subjects receiving DTIC. Tachycardia: In the ISP, the majority of subjects (71%) maintained a heart rate within the normal range (i.e., 60 to 100 beats per minute) while on study (Data Source: ISS Table 8.4001). No consistent changes from baseline were noted (baseline shift to worse-case on-

Key Safety findings (from non-clinical studies)	Relevance to human usage
	therapy). These results were consistent with those observed in dabrafenib-treated subjects in BREAK-3. Coronary vascular effects: Dabrafenib clinical protocols did not exclude subjects with risk factors for or known atherosclerotic coronary artery disease if cardiac function was stable, thus these conditions were frequently present at study entry, consistent with the expected incidence in the general population. In the randomized BREAK-3 study, myocardial infarction occurred in 1 subject receiving dabrafenib compared with none in subjects receiving DTIC. Overall, none of the individual cardiac AEs of concern including decreased LVEF, valvular abnormalities, conduction abnormalities, nor myocardial effects is seen at a higher incidence relative to DTIC than expected, when viewed in context of the 3:1 randomization and the longer exposure of dabrafenib treated patients. Therefore, GSK/Novartis does not believe there is sufficient evidence to consider these cardiovascular events to be treatment-related. **Dabrafenib + trametinib combination therapy** Subjects receiving dabrafenib + trametinib combination therapy were monitored for cardiovascular effects with echocardiogram/electrocardiogram monitoring. Cardiovascular effects including decreases in ejection fraction and hypertension were seen in human clinical studies with dabrafenib + trametinib combination therapy.
Potential Respiratory Effects: In a 13-week dabrafenib monotherapy study in dogs, lobar bronchoalveolar inflammation of the lungs, with correlating clinical signs of shallow and/or laboured breathing was observed (≥9 times clinical exposure). In a 26–week study in mice, increased intra-epithelial eosinophilic globules and/or bronchiolar epithelial hypertrophy was observed within the respiratory tract.	**Dabrafenib monotherapy** The majority of these events were low grade and a consistent relationship to treatment was not observed. No pattern of specific events was observed; all adverse events in the integrated safety population (ISP) occurred at a frequency of <1% with the exceptions of cough (11%), dyspnoea (5%), oropharyngeal pain and productive cough (1% each). **Dabrafenib + trametinib combination therapy** Respiratory toxicity findings observed in non-clinical studies to date have not translated into clinically relevant observations in humans. Adverse events classified as respiratory, thoracic or mediastinal disorders have been reported in studies of dabrafenib and dabrafenib + trametinib combination therapy in subjects both with and without pulmonary metastases. The frequency of events was similar between the combination therapy and dabrafenib monotherapy arms in MEK115306. No pattern of specific events was observed; all adverse events in the combination therapy arm of MEK115306 occurred at a frequency of ≤3% with the exceptions of cough (21%), oropharyngeal pain (11%), epistaxis (9%) and dyspnoea (6%).
Potential Haematological Effects: In repeat dose toxicity studies of up to 26 weeks duration with dabrafenib monotherapy, decreases in reticulocyte counts and/or red cell mass (total red blood cell count, haemoglobin and/or haematocrit) were observed in dogs (≥10 times clinical exposure) and rats	**Dabrafenib monotherapy** Haematological findings observed in non-clinical studies have not translated into significant clinical observations in humans. Elevations in white blood cell parameters noted in animal studies are likely in response to inflammatory changes observed

Key Safety findings (from non-clinical studies)	Relevance to human usage
(≥1.4 times clinical exposure). Increases in white blood cells (neutrophils, lymphocytes, eosinophils and/or monocytes) have also been observed (≥9 times clinical exposure for dogs, ≥0.7 times clinical exposure for rats and ≥0.6 times clinical exposure for mice). In a 4-week toxicity study in dogs given dabrafenib + trametinib in combination, there was no exacerbation of hematologic effects versus either trametinib or dabrafenib monotherapy.	microscopically in skin, lung and/or forestomach. The majority of clinical haematology observations in humans have been cytopenias (neutropenia [2%], leukopenias [2%], lymphopenia [3%], thrombocytopenia [2%], and anaemia [8%]) rather than elevations; the effects are considered manageable (Source: m3.5.3.5.Table 8.1002, 8.1008). **Dabrafenib + trametinib combination therapy** Hematologic effects of the combination therapy were observed in human clinical trials. In MEK115306 hematologic effects including neutropenia (10%) anemia (9%), thrombocytopenia (4%), and lymphopenia (2%) were observed with dabrafenib + trametinib combination therapy. Similar results were observed on combination therapy in MEK116513 study. With the exception of neutropenia the frequencies of these events are similar to those reported with monotherapy and did not require dose modifications. Therefore these hematologic effects for the combination of dabrafenib + trametinib are considered manageable. Effects including neutropenia (10%) anaemia (9%), thrombocytopenia (4%), and lymphopenia (2%) were observed with dabrafenib + trametinib combination therapy. Similar results were observed on combination therapy in MEK116513 study. With the exception of neutropenia the frequencies of these events are similar to those reported with monotherapy and did not require dose modifications. Therefore these hematologic effects for the combination of dabrafenib + trametinib are considered manageable. Neutropenia (listed as an ADR) is also considered manageable.
Potential for Phototoxicity: Evaluation of phototoxicity was performed *in vitro* on Balb/c 3T3 fibroblasts using a neutral red uptake assay. Dabrafenib was positive in the assay. Additionally dabrafenib was phototoxic at doses ≥ 100 mg/kg (> 44 times clinical exposure based on C_{max}) in an oral phototoxicity study in hairless mice.	**Dabrafenib monotherapy** There have been very few reports of photosensitivity reactions (2%, all <grade 3) with dabrafenib and no events of Steven's Johnson Syndrome or toxic epidermal necrolysis. In comparison with DTIC in the Phase III study, BRF113683 (CDRB436A2301), dabrafenib had less photosensitivity (5% vs. 2%, respectively) reported as an adverse event. **Dabrafenib + trametinib combination therapy** Although pre-clinical in-vitro and in vivo data suggest potential for phototoxicity based on clinical safety data available to date, there is low risk for phototoxicity in humans. No restrictions on sun exposure or instructions for prophylaxis (e.g. use of sunscreen) were imposed in clinical studies with dabrafenib or dabrafenib + trametinib combination therapy. Photosensitivity reactions have been reported in 2% and 4% of subjects treated with dabrafenib + trametinib combination therapy in MEK115306 and MEK116513, respectively with 3% in the dabrafenib monotherapy arm. In comparison, photosensitivity was reported in 22% of subjects treated with vemurafenib in MEK116513. In MEK116513 no dose modification was required for photosensitivity events in the combination therapy arm, while 3% of subjects in the vemurafenib monotherapy

Key Safety findings (from non-clinical studies)	Relevance to human usage
	arm required dose interruption and/or dose reduction. In addition, the incidence of sunburn was higher in the vemurafenib monotherapy arm (14%) compared with the combination therapy arm (<1%). Adverse events sorted by risk difference indicate a higher risk of sunburn and photosensitivity in the vemurafenib monotherapy arm as compared to the combination therapy arm. Photosensitivity is included in Section 4.4, Warnings and Precautions, in the vemurafenib SmPC. Based on the clinical data available to date there is low risk for phototoxicity with dabrafenib monotherapy or combination therapy. Photosensitivity is not considered to be a BRAF inhibitor class effect and is not included as an important potential risk for either dabrafenib monotherapy or dabrafenib + trametinib combination therapy.
Potential for Hepatotoxicity: Hepatic effects (hepatocellular necrosis/inflammation, hepatocellular hypertrophy, Kupffer cell hypertrophy/hyperplasia, peribiliary inflammation, pigment deposit and/or increased hepatocellular mitotic figures) were observed in a 26-week study of dabrafenib in mice (≥0.6 times clinical exposure). Similar liver findings have not been observed in studies to date in rats and dogs (studies of up to 13 weeks duration). Hepatic effects have not been observed in dogs given dabrafenib + trametinib in combination.	**Dabrafenib monotherapy** Hepatotoxicity findings observed in non-clinical studies have not been observed in humans to date. **Dabrafenib + trametinib combination therapy** Hepatic effects including increases in ALT and AST were seen in human clinical studies with dabrafenib + trametinib combination therapy.
Paediatric Effects: In juvenile rat toxicity studies with dabrafenib, there were dose-related decreases on body weight, food consumption and growth. Toxicities that were only observed in juvenile rats (had not been observed in studies in adult animals) included partially reversible effects on kidneys (primary findings of tubular deposits, increased incidence of cortical cysts and tubular basophilia, increases in urea and/or creatinine concentrations). There were similar effects in juvenile rats as seen in adults in the testes, forestomach and thymus.	**Dabrafenib monotherapy** The safety of dabrafenib in children below 1 year of age has not been established **Dabrafenib + trametinib combination therapy** The safety of dabrafenib + trametinib combination therapy in children below 1 year of age has not been established.

4 Part II Safety specification Module SIII Clinical trial exposure

Dabrafenib is an orally administered, potent and highly selective inhibitor of the B- and C-RAF kinases which has demonstrated activity in BRAF V600-mutation positive melanoma in a randomized Phase III study.

Trametinib development is discussed in the trametinib EU RMP.

BRAF V600 mutations in melanoma lead to a constitutive activation of the RAS/RAF/MEK/ERK (MAP-kinase) signal transduction pathway.

In combination, dabrafenib and trametinib inhibit two critical kinases and provide a more pronounced inhibition of the MAP-kinase pathway. The combination of dabrafenib with trametinib is synergistic in BRAF V600 mutation positive melanoma cell lines in vitro and delays the emergence of resistance to dabrafenib monotherapy in BRAF V600 mutation positive melanoma xenografts in vivo. The combination also synergistically inhibits phosphorylation of ERK and induces apoptosis in the MV522 NSCLC cell line in vitro that harbors the BRAF V600E mutation.

Dabrafenib Monotherapy

Advanced/ Metastatic Melanoma

The integrated safety population (ISP, n=578 subjects) for the RMP included subjects with melanoma who received at least one dose of dabrafenib at the dose proposed for labelling (150 mg BID) during study participation. Data was integrated from 5 clinical studies, including one pivotal Phase III study BRF113683 (BREAK-3) and 4 supportive studies, listed below. In these studies adverse event severity was assessed by the investigator using the National Cancer Institute (NCI) CTCAE Version 4.0, with the exception of Study BRF112680 (n=47 subjects included in the ISP), which used CTCAE Version 3.0.

Phase I Study with Dabrafenib

BRF112680 was a first time in human, multiple-dose, open-label study to determine the recommended dose and regimen for dabrafenib in subjects with solid tumors. This study was comprised of 2 parts. Part 1 identified the maximum tolerated dose and regimen using a dose-escalation procedure that began with an accelerated titration phase and switched to a standard dose escalation scheme. A total of 10 dose escalation cohorts, including doses ranging from 12 mg once daily to 300 mg bid were assessed in Part 1. Part 2 further explored the safety, tolerability, and clinical activity of dabrafenib in subjects with solid tumors in 3 cohorts:

- Cohort A: subjects with metastatic melanoma (150 mg BID)
- Cohort B: subjects with other BRAF V600 mutation-positive tumours (150 mg BID)
- Cohort C: subjects with metastatic melanoma (50 mg BID)

The recommended dose and regimens investigated in Part 2 were selected based on the safety, pharmacokinetic, and pharmacodynamic profiles of subjects with solid tumors treated with dabrafenib in Part 1. Subjects continued to receive dabrafenib in this study until disease progression or unacceptable toxicity.

In this study 47 subjects with melanoma received at least one dose of dabrafenib 150 mg bid in either Part 1 or Part 2; these subjects were included in the dabrafenib ISP. This study was completed.

Phase II Study with Dabrafenib (CDRB436A2201; BRF113710, BREAK-2)

BREAK-2 was an open-label single arm study to determine the ORR of dabrafenib in subjects with BRAF V600E mutation-positive metastatic melanoma. Secondary objectives included ORR in subjects with BRAF V600K mutation-positive melanoma, PFS, duration of response, overall survival (OS), and the incidence and severity of AEs. Eligible subjects were treatment naïve or may have received prior treatment for metastatic disease (e.g., chemotherapy, immunotherapy, prior targeted therapy).

A total of 92 subjects were enrolled at 21 centers in 5 countries to receive dabrafenib 150 mg BID; all 92 subjects received at least 1 dose of dabrafenib. Study treatment continued until disease progression, unacceptable toxicity, or death. After discontinuation of the study treatment, subjects remained on the study for follow-up assessments and updates on anti-cancer treatments until death.

Phase II Study with Dabrafenib (BRF113929; BREAK-MB)

BREAK-MB was designed to assess the efficacy, pharmacokinetics, safety, and tolerability of open-label dabrafenib 150 mg bid administered to subjects with BRAF V600E or V600K mutation-positive melanoma metastatic to the brain. Subjects who were treatment-naive for brain metastases were enrolled into Cohort A, and those who had previously received local therapy for brain metastases were enrolled into Cohort B. The primary objective of the study was to assess the overall intracranial response rate (OIRR) in BRAF V600E mutation-positive subjects in each of the two cohorts. Secondary objectives included: an estimation of the ORR and duration of intracranial and overall response in V600E mutation-positive subjects; PFS and OS in V600E mutation-positive subjects; and OIRR, ORR, duration of intracranial and overall response, PFS, and OS in BRAF V600K mutation-positive subjects.

A total of 172 subjects were enrolled at 24 centers in 6 countries; all 172 subjects received at least 1 dose of dabrafenib. All subjects who permanently discontinued study treatment continued to be followed for survival and new anti-cancer therapy.

Phase III Study with Dabrafenib (BRF113683)

BREAK-3 was a randomized, multi-center, open-label Phase III study to evaluate the safety and efficacy of dabrafenib compared with treatment with DTIC in subjects with unresectable or metastatic BRAF V600E mutation-positive melanoma. Eligible subjects were required to be treatment-naïve for metastatic disease, with the exception of interleukin-2, surgery, and radiotherapy, which were allowed. The primary objective of the study was to establish the superiority of dabrafenib over DTIC with respect to PFS. Secondary objectives included OS, ORR, duration of response, and the incidence and severity of AEs. Study treatment continued in BREAK-3 until disease progression, unacceptable toxicity, or death. Following radiologically-confirmed disease progression, subjects randomized to DTIC were offered crossover therapy with dabrafenib.

A total of 250 subjects were centrally randomized at 70 centers in 12 countries to dabrafenib 150 mg bid or DTIC 1000 mg/m^2 every 3 weeks in a 3:1 ratio, respectively. Of these 250 subjects, 215 received at least 1 dose of dabrafenib, either in the randomized phase (N=187) or following crossover from DTIC (N=28). Prior to randomization, eligible subjects were stratified by disease staging at study entry (unresectable IIIC +IVM1a+IVb vs. IVM1c). All subjects who permanently discontinued study treatment were followed for survival and additional anti-cancer therapies (including radiotherapy) every 12 weeks until death.

Integrated safety data from the above-mentioned dabrafenib clinical trials provides comprehensive evaluation of the incidence of adverse events as well as the dabrafenib safety profile.

In addition, the safety profile identified at the time of the initial MAA based on the ISP (data cut-off March – December, 2011) was confirmed at the 120 day update (data cut-off March – June, 2012) demonstrating long-term exposure (≥12 months) in 15% of dabrafenib treated subjects. The final CSR was updated with the longer follow-up data.

Dabrafenib + Trametinib Combination Therapy

Advanced / Metastatic Melanoma

Dabrafenib + trametinib combination therapy is under evaluation in 3 clinical trials listed below. The overall survival analyses from MEK115306 and MEK116513 provides data for the combination indication, supported by data from BRF113220 (CDRB436B2201) Part C.

Study BRF113220 is a Phase IB/II, open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical efficacy of dabrafenib + trametinib combination treatment. This study comprised 4 parts: designated as Parts A, B, C, and D. Parts A, B, and D were Phase I evaluations to investigate if repeat doses of trametinib had an effect on the pharmacokinetics of single-dose dabrafenib (Part A); identify appropriate doses for combination-therapy using a dose-escalation procedure, and assess whether concomitant repeat dosing of dabrafenib and trametinib affected the pharmacokinetics of either investigational product (Part B); and evaluate the pharmacokinetics and safety of dabrafenib administered in hydroxypropyl methylcellulose (HPMC) capsules alone and in combination with trametinib (Part D).

Part C was a randomized open-label Phase II portion of the study in subjects with BRAF mutation-positive metastatic melanoma. Subjects were randomized to receive either one of 2 combination dosing regimens (dabrafenib 150 mg bid and trametinib 1 mg once daily or dabrafenib 150 mg bid and trametinib 2 mg once daily) or dabrafenib 150 mg bid as monotherapy.

Study MEK115306 is a Phase III, two arm, double blinded, randomized study comparing dabrafenib + trametinib as first line combination therapy (150 mg bid dabrafenib + 2 mg once daily trametinib) to dabrafenib monotherapy (dabrafenib 150 mg bid + trametinib placebo) in subjects with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. Primary analysis of PFS and final comparative analysis of OS have both completed. This study is ongoing to assess long-term OS and safety.

Study MEK116513 is a Phase III, two-arm, open label, randomized study comparing dabrafenib + trametinib combination therapy (150 mg bid dabrafenib + 2 mg once daily trametinib) to vemurafenib (960 mg BID) in subjects with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. The final comparative analysis of the primary endpoint of OS is complete. This study is ongoing to assess long-term OS and safety.

Adjuvant treatment of patients with stage III melanoma with a BRAF V600 mutation, following complete resection

Study BRF115532: a randomized, double-blind study of dabrafenib in combination with trametinib versus 2 placebos as adjuvant treatment of high risk BRAF V600 E/K mutant melanoma after surgical resection. Subjects with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high-risk [Stage IIIA (lymph node metastasis >1 mm), IIIB or IIIC] cutaneous melanoma were screened for eligibility. Approximately 852 subjects were planned to be randomized at 1:1 ratio, stratified by BRAF mutation status (V600E, V600K) and stage of disease (Stage IIIA, IIIB, IIIC). The primary endpoint of the study is relapse-free survival (RFS); overall survival is defined as key secondary endpoint. Other secondary endpoints include distant metastasis-free survival (DMFS) and freedom from relapse (FFR). The primary analysis has been conducted with a cut-off date of 30-Jun-2017. The study is currently ongoing with overall survival follow up ongoing. The next interim analysis for OS is planned for when approximately 50% of events are reached. A final OS analysis is planned to be conducted when the required 597 OS events have occurred.

Adult patients with advanced NSCLC with BRAF V600E mutation

Study BRF113928 (CDRB436E2201), is a Phase II study of the BRAF inhibitor dabrafenib as a single agent or in combination with the MEK inhibitor trametinib in subjects with BRAF V600E mutation positive metastatic (stage IV) non-small cell lung cancer. This study consists of 3 patient cohorts with metastatic Non-Small Cell Lung Cancer that had BRAF V600E mutation tested from a certified local laboratory:

- Cohort A (dabrafenib monotherapy)—dabrafenib 150 mg twice daily for patients as second- or later line treatments
- Cohort B (combination therapy for second-, third-, or fourth-line) —dabrafenib 150 mg twice daily and trametinib 2 mg once daily for patients as second-, third-, or fourth-line treatment
- Cohort C (combination therapy for first-line) —dabrafenib 150 mg twice daily and trametinib 2 mg once daily for patients as first-line treatment for the metastatic disease

The primary endpoint was objective response rate by Investigator assessment, which was completed for Cohorts A and B. This study is ongoing to assess the investigator-assessed overall response rate for Cohort C, long-term time-to-event data for Cohorts A-C, and long-term safety.

Patients with locally advanced or metastatic anaplastic thyroid cancer with BRAF V600E mutation

Study BRF117019 is an ongoing Phase II, open-label, non-randomized study designed to assess the clinical efficacy and safety of dabrafenib in combination with trametinib in subjects with BRAF V600E-mutant rare cancers, demonstrating a high unmet medical need. The study can

enroll up to 25 subjects with a confirmed BRAF V600E mutation in each of the following 9 histologies: anaplastic thyroid cancer (ATC), biliary tract cancer (BTC), gastrointestinal stromal tumor (GIST), WHO grade 1 or 2 glioma, WHO grade 3 or 4 glioma, non-seminomatous/non-germinomatous germ cell tumors (NSGCT/NGGCT), adenocarcinoma of small intestine (ASI), hairy cell leukemia (HCL), and multiple myeloma (MM). The primary objective of this study is to determine the overall response rate (ORR) by investigator assessment for each histologic cohort. Further supporting secondary objectives include the evaluation of duration of response (DoR), progression-free survival (PFS), overall survival (OS), and the safety of the combination treatment. To address the small sample sizes per histologic cohort, Study BRF117019 uses an adaptive design utilizing a Bayesian hierarchical model that increases the power to detect clinically meaningful differences in the ORR by borrowing information across histology cohorts while controlling the Type I error rate. The adaptive design allows for multiple interim evaluations of the accumulating data to determine if one or more histologic cohorts should stop enrollment early due to either success or futility. This study is continuing to enroll patients.

Paediatric gliomas

CDRB436G2201 study: Phase II open-label multi-center study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive Low Grade Glioma (LGG) or relapsed or refractory High Grade Glioma (HGG). Paediatric patients (≥ 12 months and < 18 years of age) with BRAF V600 mutation-positive LGG or relapsed or refractory HGG were enrolled. LGG cohort is a randomized, open label part in children and adolescent patients with BRAF V600 mutation. HGG cohort is a single arm, open label part in which children and adolescent patients with BRAF V600 mutation-positive, refractory or relapsed HGG tumors received dabrafenib+trametinib. A total of 151 patients were enrolled in the study; 110 in the LGG cohort and 41 in the HGG cohort. Of the 110 patients in LGG cohort 73 patients were randomized to dabrafenib+trametinib combination therapy arm and 37 patients were randomized to chemotherapy arm (carboplatin+vincristine). Four patients in chemotherapy arm discontinued prior to first dose and were not treated in this study. A total of 9 patients initially randomized to the chemotherapy arm and treated with chemotherapy later crossed-over to receive dabrafenib+trametinib combination therapy. The HGG part of the study was single-arm and enrolled 41 patients who received targeted therapy (D+T). A total of 123 patients (LGG: 73, LGG crossover: 9, and HGG: 41) received dabrafenib+trametinib combination therapy.

CTMT212X2101 study: This study was a Phase I/IIa, multi center, open-label clinical study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity trametinib and dabrafenib + trametinib in paediatric patients with refractory or recurrent solid tumors with presumed MAPK pathway activation. This study had 4 parts:

Part A (≥ 1 month and <18 years) was a trametinib monotherapy dose escalation phase (0.0125, 0.025, 0.032, and 0.04 mg/kg/day).

Part B (≥ 1 month and <18 years) was monotherapy disease cohort expansion phase (age <6 years: 0.032 mg/kg/d; age ≥ 6 years: 0.025 mg/kg/day).

Part C (≥12 months and <18 years) was a limited dose escalation phase of dabrafenib + trametinib in BRAF V600 mutant tumors while (trametinib 0.025 mg/kg/day + 50% dabrafenib RP2D; trametinib 0.025 mg/kg/day + 100% dabrafenib RP2D; trametinib 0.032 mg/kg/day + 100% dabrafenib RP2D).

Part D (≥12 months and <18 years) was a cohort expansion phase of dabrafenib + trametinib in children and adolescents with BRAF V600 mutated tumors (LGG and LCH) (trametinib 0.032 mg/kg/day + 100% dabrafenib RP2D for patients < 6 years old and trametinib 0.025 mg/kg/day + 100% dabrafenib RP2D for patients ≥ 6 years to <18 years).

A total of 139 paediatric patients were enrolled into this study: 91 patients in trametinib monotherapy arms (A and B) and 48 patients in dabrafenib + trametinib combination therapy arms. This study is completed.

4.1 Part II Module SIII Clinical trial exposure

4.1.1 Dabrafenib Monotherapy

There were no randomized blinded clinical trials conducted with dabrafenib monotherapy.

Table 4-1 Summary of Duration of Exposure to Dabrafenib (Monotherapy ISS Population)

Indication: Treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma
Treatment: Total Dabrafenib Monotherapy ISS population (N=578)

Duration of exposure (months)[a]	Persons	Person time (PY)
<3	146 (25%)	24.9
3-6	272 (47%)	102.3
>6-12	156 (27%)	99.0
>12	4 (1%)	4.6
Total person time	578 (100%)	230.8

a. Duration in months is calculated by (treatment end date - treatment start date +1) / 40.4375.
Source: RMP v8.3 Annex 7 – Dab Mono Table 6.3001

All subjects in the ISP received dabrafenib 150 mg bid.

Table 4-2 Summary of Exposure to Dabrafenib by age and gender (Monotherapy ISS Population)

Indication: Treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma
Treatment: Total Dabrafenib Monotherapy ISS population (N=578)

	Persons		Person time	
Age group	M	F	M	F
<65	265 (46%)	188 (33%)	104.3	74.3
65-74	64 (11%)	29 (5%)	26.2	12.5
75-84	20 (3%)	9 (2%)	9.3	3.2
≥75	23 (4%)	9 (2%)	10.2	3.2
≥85	3 (1%)	0	0.9	0
Total	352 (61%)	226 (39%)	140.7	90.0

Source; RMP v8.3 Annex 7 - Dab Mono Table 6.3002

4.1.2 Dabrafenib + Trametinib Combination Therapy

Treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (Study MEK115306 and Study MEK116513)

Duration	Dabrafenib N=420 n (%)	Trametinib N= 209 n (%)	Trametinib + dabrafenib N= 209 n (%)
Less than 1 month	11 (2.6)	4 (1.9)	4 (1.9)
At least 1 month	409 (97.4)	205 (98.1)	205 (98.1)
At least 3 months	371 (88.3)	193 (92.3)	193 (92.3)
At least 6 months	287 (68.3)	156 (74.6)	156 (74.6)
At least 9 months	226 (53.8)	124 (59.3)	124 (59.3)
At least 12 months	183 (43.6)	103 (49.3)	103 (49.3)
At least 15 months	156 (37.1)	91 (43.5)	91 (43.5)
At least 18 months	137 (32.6)	84 (40.2)	84 (40.2)
At least 21 months	123 (29.3)	78 (37.3)	78 (37.3)
At least 24 months	111 (26.4)	73 (34.9)	73 (34.9)
At least 27 months	47 (11.2)	29 (13.9)	29 (13.9)
At least 30 months	8 (1.9)	4 (1.9)	4 (1.9)
Subject-time (months)	**5332**	**3012**	**3012**

Source: RMP version 8.3 Attachment to Annex 12 MEK115306 Table 3.702

Table 4-3 Duration of exposure – Study MEK116513

Duration	Dabrafenib N=350 n (%)	Trametinib N=350 n (%)	Trametinib + dabrafenib N=350 n (%)	Vemurafenib N=349 n (%)
Less than 1 month	7 (2.0)	6 (1.7)	7 (2.0)	27 (7.7)
At least 1 month	343 (98.0)	344 (98.3)	343 (98.0)	322 (92.3)
At least 3 months	318 (90.9)	317 (90.6)	317 (90.6)	268 (76.8)
At least 6 months	245 (70.0)	247 (70.6)	248 (70.9)	184 (52.7)
At least 9 months	199 (56.9)	199 (56.9)	200 (57.1)	132 (37.8)
At least 12 months	120 (34.3)	118 (33.7)	120 (34.3)	68 (19.5)
At least 15 months	48 (13.7)	46 (13.1)	48 (13.7)	21 (6.0)
At least 18 months	13 (3.7)	13 (3.7)	13 (3.7)	1 (0.3)
At least 21 months	1 (0.3)	1 (0.3)	1 (0.3	0
At least 24 months	0	0	0	0
Subject-time (months)	**3183**	**3171**	**3186**	**2368**

Source: RMP v8.3 Attachment to Annex 12 MEK116513 Table 3.702

Table 4-4 Exposure by age group and gender – Study MEK115306

		Dabrafenib N=420		Trametinib N=209		Trametinib + dabrafenib N=209	
Age	Sex	Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)
Total	**Total**	**420 (100.0)**	**5332**	**209 (100.0)**	**3012**	**209 (100.0)**	**3012**

		Dabrafenib N=420		Trametinib N=209		Trametinib + dabrafenib N=209	
Age	**Sex**	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**
	Male	225 (53.6)	2653	111 (53.1)	1435	111 (53.9)	1435
	Female	195 (46.4)	2679	98 (46.9)	1577	98 (46.9)	1577
<65	**Total**	**304 (72.4)**	**3916**	**153 (73.2)**	**2249**	**153 (73.2)**	**2249**
65-74	**Total**	**88 (21.0)**	**1205**	**45 (21.5)**	**701**	**45 (21.5)**	**702**
75-84	**Total**	**26 (6.2)**	**204**	**10 (4.8)**	**59**	**10 (4.8)**	**58**
At least 75	**Total**	**28 (6.7)**	**211**	**11 (5.3)**	**62**	**11 (5.3)**	**61**
At least 85	**Total**	**2 (0.5)**	**7**	**1 (0.5)**	**3**	**1 (0.5)**	**3**

Source: RMP v8.3 Attachment to Annex 12 MEK115306 Table 3.703

Table 4-5 Exposure by age group and gender – Study MEK116513

		Dabrafenib N=350		Trametinib N=350		Trametinib + dabrafenib N=350		Vemurafenib N=349	
Age	**Sex**	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**
Total	**Total**	**350 (100.0)**	**3183**	**350 (100.0)**	**3171**	**350 (100.0)**	**3186**	**349 (100.0)**	**2368**
	Male	207 (59.1)	1821	207 (59.1)	1795	207 (59.1)	1816	179 (51.3)	1215
	Female	143 (40.9)	1362	143 (40.9)	1376	143 (40.9)	1370	170 (48.7)	1153
<65	**Total**	**273 (78.0)**	**2511**	**273 (78.0)**	**2520**	**273 (78.0)**	**2524**	**262 (75.1)**	**1755**
65-74	**Total**	**56 (16.0)**	**511**	**56 (16.0)**	**486**	**56 (16.0)**	**497**	**61 (17.5)**	**485**
75-84	**Total**	**18 (5.1)**	**159**	**18 (5.1)**	**163**	**18 (5.1)**	**163**	**25 (7.2)**	**128**
At least 75	**Total**	**21 (6.0)**	**161**	**21 (6.0)**	**165**	**21 (6.0)**	**165**	**26 (7.4)**	**128**
At least 85	**Total**	**3 (0.9)**	**2**	**3 (0.9)**	**2**	**3 (0.9)**	**2**	**1 (0.3)**	**0**

Source: RMP v8.3 Attachment to Annex 12 MEK116513 Table 3.703

Adjuvant treatment of patients with stage III melanoma with a BRAF V600 mutation, following complete resection (Study BRF115532)

Table 4-6 Duration of exposure – Study BRF115532

Duration	Dabrafenib N=435 n(%)	Trametinib N=435 n(%)	Trametinib + dabrafenib N=435 n(%)
Less than 1 month	25 (6.0%)	25 (6%)	26 (6%)
At least 1 month	410 (94.0%)	410 (94%)	409 (94%)
At least 3 months	363 (83.0%)	363 (83%)	360 (83%)
At least 6 months	319 (73.0%)	324 (74%)	316 (73%)
At least 9 months	296 (68.0%)	299 (69%)	293 (67%)
Subject-time (months)	**3567**	**3601**	**3540**

Note: For 'Dabrafenib + Trametinib', when deriving person time, duration of exposure for each subject is calculated as: Min(Last Dose of Dabrafenib, Last Dose of Trametinib) - Max(First Dose of Dabrafenib, First Dose of Trametinib)+1
Source: Annex 7 Table 14.3-1.3

Table 4-7 Exposure by age group and gender – Study BRF11532

		Dabrafenib N=435		Trametinib N=435		Trametinib + dabrafenib N=435	
Age	**Sex**	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**
Total	**Total**	**435 (100.0)**		**435 (100.0)**		**435 (100.0)**	
	Male	242 (56.0)	2054	242 (56.0)	2059	242 (56.0)	2047
	Female	193 (42.0)	1513	193 (42.0)	1542	193 (42.0)	1493
<65	**Total**	**350**		**350**		**350**	
	Male	191 (44.0)	1663	191 (44.0)	1676	191 (44.0)	1666
	Female	159 (37.0)	1267	159 (37.0)	1299	159 (37.0)	1250
65-74	**Total**	**73**		**73**		**73**	
	Male	46 (11.0)	343	46 (11.0)	336	46 (11.0)	333
	Female	27 (6.0)	201	27 (6.0)	200	27 (6.0)	200
75-84	**Total**	**11**		**11**		**11**	
	Male	4 (<1.0)	37	4 (<1.0)	36	4 (<1.0)	37
	Female	7 (2.0)	45	7 (2.0)	43	7 (2.0)	43
At least 75	**Total**	**12**		**12**		**12**	
	Male	5 (1.0)	48	5 (1.0)	47	5 (1.0)	48
	Female	7 (2.0)	45	7 (2.0)	43	7 (2.0)	43
At least 85	**Total**	**1**		**1**		**1**	
	Male	1 (<1)	11	1 (<1)	11	1 (<1)	11
	Female	0	0	0	0	0	0

Subject-time is the sum of each subject's treatment exposure in <unit>. <Subject-time> is based on the number of subjects in each category.
Note: For 'Dabrafenib + Trametinib', when deriving person time, duration of exposure for each subject is calculated as: Min (Last Dose of Dabrafenib, Last Dose of Trametinib) - Max(First Dose of Dabrafenib, First Dose of Trametinib)+1.
Source: Annex 7 Table 14.3-1.4

Treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation (Study BRF113928)

Table 4-8 Duration of exposure – Study BRF113928

Duration	Dabrafenib N=166 n (%)	Trametinib N=82 n (%)	Trametinib + dabrafenib N=82 n (%)
Less than 1 month	16 (9.6)	8 (9.8)	9 (11.0)
At least 1 month	150 (90.4)	74 (90.2)	73 (89.0)
At least 3 months	108 (65.1)	57 (69.5)	56 (68.3)
At least 6 months	74 (44.6)	38 (46.6)	39 (47.6)
At least 9 months	58 (34.9)	32 (39.0)	32 (39.0)
At least 12 months	38 (22.9)	19 (23.2)	16 (19.5)
At least 15 months	28 (16.9)	12 (14.6)	12 (14.6)
At least 18 months	21 (12.7)	6 (7.3)	4 (4.9)
At least 21 months	14 (8.4)	1 (1.2)	0
At least 24 months	8 (4.8)	0	0
Subject-time (months)	**1344**	**620**	**607**

Source: RMP v8.3 Attachment to Annex 12 Table 3.0901 and Annex 12 Table 3.0902

Table 4-9 Exposure by age group and gender – Study BRF113928

		Dabrafenib N=166		Trametinib N=82		Trametinib + dabrafenib N=82	
Age	**Sex**	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**
Total	**Total**	166 (100.0)	1344	82 (100.0)	620	82 (100.0)	607
	Male	79 (47.6)	634	39 (47.6)	311	39 (47.6)	304
	Female	87 (52.4)	710	43 (52.4)	309	43 (52.4)	303
<65	**Total**	71 (42.8)	586	35 (42.7)	302	35 (42.7)	297
65-74	**Total**	66 (39.8)	527	29 (35.4)	184	29 (35.4)	180
75-84	**Total**	22 (13.3)	178	13 (15.9)	96	13 (15.9)	92
At least 75	**Total**	29 (17.5)	231	18 (22.0)	134	18 (22.0)	130
At least 85	**Total**	7 (4.2)	54	5 (6.1)	39	5 (6.1)	38

Source: RMP v8.3 Attachment to Annex 12 Table 3.0901 and Annex 12 Table 3.0903

Exposure in paediatric combination therapy-safety pool

Table 4-10 Duration of exposure to dabrafenib in combination therapy in paediatric patients

	All Subjects N=171 n (%)
Total number of subjects receiving Combination-n (%)	171 (100.0)
Duration of exposure categories-n (%)	
< 3 Weeks	3 (1.8)
3 - < 6 Weeks	0
6 - < 12 Weeks	7 (4.1)
12 - < 24 Weeks	12 (7.0)
24 - < 48 Weeks	25 (14.6)
> 48 Weeks	124 (72.5)
Subject Time (Week)	13697.7
Subject Time (PY)*	262.51

Subject-time is the sum of each subject's treatment exposure in Weeks.
*Subjects Time in PY is calculated by time in weeks * 7/365.25
Source: [SCS Appendix 1-Table 2.1-1]

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Melanomas that have BRAF mutations that are non- V600 or do not have a BRAF mutation	The efficacy and safety of dabrafenib have not been established in patients with wild-type BRAF melanoma therefore dabrafenib should not be used as monotherapy or in combination with trametinib in patients with wild-type BRAF melanoma	No	Instructions to confirm the presence of BRAF V600 mutation in tumor specimens prior to administration of treatment with dabrafenib as monotherapy or in combination with trametinib are included in the label.
NSCLC that have BRAF mutations that are non- V600 or do not have a BRAF mutation	The efficacy and safety of trametinib in combination with dabrafenib have not been established in patients with wild-type BRAF NSCLC therefore dabrafenib should not be used as monotherapy or in combination with trametinib in patients with wild-type BRAFNSCLC or with a BRAF mutation that is not V600	No	Instructions to confirm the presence of the BRAF V600 mutation in tumor specimens prior to administration of treatment with dabrafenib in combination with trametinib are included in the label.
Age of 1 month to <1 year old	. Patients below 1 year of age were excluded from dabrafenib clinical trials due to the potential risk for renal toxicity observed in juvenile animal studies	No	There is no data to support a contraindication in this population. This is discussed under Posology and Administration section of labelling.
History or evidence of cardiovascular risk including any of the following: Left ventricular ejection fraction (LVEF) < lower limit of normal (LLN) Corrected QT (QTc) ≥ 480 msec; History of acute coronary syndromes, coronary angioplasty, or	Based on pre-clinical data, valvular toxicity was investigated as an adverse event of special interest and subjects with abnormal cardiac valve morphology (≥ grade 2) were excluded. Decreased left ventricular ejection fraction was monitored as AE of special interest in the dabrafenib clinical program because it is a potentially serious adverse reaction of many kinase inhibitors (Force 2007).	No	No clinically relevant effect of dabrafenib or its metabolites on the QTc interval was observed in QT study BRF113773. Other cardiac risks are covered under important potential risk “Non-specific cardiac toxicity”. According to the PSUR (DLP: 26-Aug-2016), the cumulative post marketing reporting rate was 0.12% (12 cases/10143 PTY) and the analysis of the clinical safety data from clinical trial and spontaneous reports did not provide evidence of increase in incidence of overall cardiac dysfunction.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
stenting Class II, III, or IV heart failure Abnormal cardiac valve morphology History or evidence of current clinically significant uncontrolled arrhythmias (except for sinus arrhythmia). Exception: Subjects with controlled atrial fibrillation for >1 month prior to randomization are eligible.			
ECOG Performance Status of 2-4	Study participation in the ISS was limited to subjects with ECOG performance status <2 to minimize subject heterogeneity for efficacy analyses. Subjects with ECOG Performance Status of 0, 1 or 2 were eligible for lung cancer study but only a few PS=2 subjects were enrolled. Because the intended population often has significant morbidity related to the underlying disease, use in less functional subjects may be anticipated. Physicians should exercise caution in treating subjects with poor performance status and individualize discussion of the potential risk: benefit prior to initiating therapy with dabrafenib monotherapy or in combination with trametinib.	No	There is no data to support a contraindication in this population. The baseline characteristics of subjects enrolled in clinical trials are included in the clinical efficacy and safety section of the labelling.
Subjects with known glucose 6 phosphate dehydrogenase (G6PD) deficiency.	Subjects with a history of known glucose-6-phosphate dehydrogenase (G6PD) deficiency were excluded from dabrafenib clinical trials as it was believed they may develop non-immune hemolytic anemia in response to dabrafenib which contains a sulphonamide, a potential risk factor for subjects with this deficiency. No cases of	No	Subjects with G6PD deficiency may develop non-immune hemolytic anemia of a different etiology including exposure to certain medications, such as sulfamethoxazole, primaquine, and dapsone (Cappellini 2008). These medications contain an aryl amine group (R-NH2) which can be readily oxidized to form a hydroxylamine (R-NOH) and potentially cause hemolytic anemia (Shear 1986,

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	hemolytic anemia have been reported to date in dabrafenib clinical trials.		Reilly 1999, Coleman 1992, Bolchoz 2002). Dabrafenib does not contain an aryl amine that can undergo oxidation to hydroxylamine. In addition, the amino-pyrimidine nitrogen of dabrafenib does not readily undergo oxidation and there has been no evidence of metabolic oxidation or other metabolism at this position in vitro or *in vivo*. Since the metabolic profile of dabrafenib is not consistent with the mechanism of hemolytic anemia, no special precautions are required in subjects with G6PD deficiency and these subjects will not be further excluded from receiving dabrafenib.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, specific to other than Caucasian population or those caused by prolonged or cumulative exposure.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: Patients with advanced moderate/severe hepatic impairment have not been studied	Not included in the clinical development program.
Patients with mild and moderate renal impairment did not have a significant effect on dabrafenib metabolite plasma concentrations. There are no clinical data in patients with severe renal impairment and the potential need for dose adjustment cannot be determined.	Not included in the clinical development program.
Patients with cardiovascular impairment were not included in the clinical development program	Not included in the clinical development program.
Immunocompromised patients	Not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Data on patients of different ethnic origins is limited
Subpopulations carrying relevant genetic polymorphisms	Not applicable

Type of special population	Exposure
Other **Paediatric patients (<18 years old)**	Paediatric patients 1 year to <18 years of age have been included in the clinical development program.
Elderly (≥ 65 years old)	Included in the clinical development program. Refer to exposure Section 4.1.

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

Dabrafenib as monotherapy and in combination therapy

An estimate of patient exposure is calculated based on worldwide sales volume in kilogram (kg) of active substance sold and the Defined Daily Dose (DDD) i.e., 300 mg dabrafenib.

6.1.2 Part II Module SV.1.2 Exposure

The estimated interval exposure during reporting interval for the PSUR (27-Aug-2022 to 29-May-2024) was approximately 39,185 patient treatment years (PTY). The cumulative exposure estimate until 31-May-2024 is 1,25,020 PTY. CCI

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

Based on the mechanism of action of dabrafenib, the potential for misuse for illegal purposes, abuse or dependence has not been identified and is considered unlikely from the knowledge of the compound to date.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

8.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable; the RMP was already approved.

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

There are no additional risks considered important for inclusion in the list of safety concerns, since the RMP is already approved.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

The following safety concerns have been removed from the RMP:

Important identified risks for dabrafenib:

- Severe photosensitivity

Important potential risks for dabrafenib:

- Non-specific cardiac toxicity
- Pregnancy and risks in breast-feeding

Important potential risks related to dabrafenib+ trametinib combination therapy only:

- Pulmonary embolism, deep vein thrombosis

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

8.3.1.1 Important identified risk: Pre-renal and Intrinsic Renal Failure

8.3.1.1.1 Dabrafenib monotherapy

For the BRF113928 NSCLC study, no patients had renal failure. Three patients had an increase in blood creatinine. One patient was observed to have a grade 3 blood creatinine increase (Source: Table 3.1310, Table 3.1710).

8.3.1.1.2 Dabrafenib + trametinib combination therapy

Table 8-1 Clinical trial data of Pre-renal and Intrinsic Renal Failure (BRF115532)

	Dabrafenib + Trametinib (N=435)	Placebo (N=432)
Number of Subjects with Events	7 (2%)	0
Number of Events	7	0
SAEs	2 (29%)	0
Maximum Grade		
Grade 3	1 (14%)	0
Grade 4	1 (14%)	0
Grade 5	0	0
Outcome[1]		
N	7	0
Recovered/Resolved	7 (100%)	0
Recovering/Resolving	0	0
Not Recovered/Not Resolved	0	0
Recovered/Resolved w/sequelae	0	0
Fatal	0	0

Numbers (n) represent counts of subjects.
Subjects may be included in more than one category
[1] Outcome worst case hierarchy: Fatal > Not Recovered/Not Resolved > Recovered/Resolved with sequelae > Recovering/Resolving > Recovered/Resolved.
Source: Annex 7 Table 14.3.1-3.15

For combination therapy, one patient (1%) had renal failure event and four patients had an increase in blood creatinine (1 patient had a grade 3 increase) (Source: Table 3.1810).

Table 8-2 Important identified risk - Pre-renal and Intrinsic Renal Failure: Other details

Pre-renal and Intrinsic Renal Failure	
Potential mechanisms	No mechanism has been identified for this event.
Evidence source(s) and strength of evidence	In juvenile toxicity studies in rats, renal toxicity (tubular deposits, increased incidence of cortical cysts and tubular basophilia and reversible increases in urea and/or creatinine concentrations) was observed (≥0.2 times adult human clinical exposure based on AUC). Renal failure has been identified in <1% of patients treated with dabrafenib alone and in ≤1% of patients treated with dabrafenib in combination with trametinib.
Characterization of the risk:	Observed cases were generally associated with pyrexia and dehydration and responded well to dose interruption and general supportive measures. Granulomatous nephritis has been reported with dabrafenib treatment. Patients should be routinely monitored for serum creatinine while on therapy. If creatinine increases, dabrafenib may need to be interrupted as clinically appropriate. Dabrafenib has not been studied in patients with renal insufficiency (defined as creatinine >1.5 x ULN) therefore caution should be used in this setting. Relevant events renal failure, acute renal failure and nephritis are ADRs labeled with 'uncommon' frequency in the SmPC. **Adjuvant treatment of patients with stage III melanoma with a BRAF V600 mutation, following complete resection** See Table 8-1 for further details on risk characterization.

Pre-renal and Intrinsic Renal Failure	
	Treatment of adult patients with advanced NSCLC with a BRAF V600 mutation No patients had renal failure in BRF113928 NSCLC study.
Risk factors and risk groups	No specific risk groups were identified during clinical trials. Risk factors may include pyrexia, dehydration with pre-renal azotemia and/or hypotension.
Preventability	Though uncommon, renal failure may be irreversible and has multiple potential etiologies (e.g., dehydration in association with pyrexia, pre-renal azotemia, drug hypersensitivity). Guidelines have been implemented in clinical trial protocols for subjects presenting with pyrexia, to minimize the incidence of related renal failure.
Impact on the benefit-risk balance of the product	For subjects experiencing renal failure events ranged from Grade 1 through Grade 4, with half of the events SAEs. All subjects recovered, half of subjects discontinued drug. Therefore, for the individual patient experiencing an event, renal failure is anticipated to be significant but manageable. The impact on the overall benefit-risk for the compound can be considered low.
Public health impact	Potential public health impact is considered to be low.

8.3.1.2 Important identified risk: Uveitis

8.3.1.2.1 Dabrafenib monotherapy

For the BRF113928 NSCLC study, one dabrafenib monotherapy patient (1%) had a grade 3 Uveitis and this was recorded as an SAE (Source: Table 3.1310, Table 3.1710).

8.3.1.2.2 Dabrafenib + trametinib combination therapy

Table 8-3 Clinical trial data of Uveitis (BRF115532)

	Dabrafenib + Trametinib (N=435)	**Placebo (N=432)**
Number of Subjects with Events	12 (3%)	0
Number of Events	13	0
SAEs	4 (33%)	0
Maximum Grade		
Grade 3	1 (8%)	0
Grade 4	1 (8%)	0
Grade 5	0	0
Outcome[1]		
Recovered/Resolved	12 (100%)	0
Recovering/Resolving	0	0
Not Recovered/Not Resolved	0	0
Recovered/Resolved w/sequelae	0	0
Fatal	0	0

Numbers (n) represent counts of subjects.
Subjects may be included in more than one category
[1] Outcome worst case hierarchy: Fatal > Not Recovered/Not Resolved > Recovered/Resolved with sequelae > Recovering/Resolving > Recovered/Resolved.
Source: Annex 7 - Table 14.3.1-3.16

Table 8-4 Important identified risk - Uveitis: Other details

Uveitis	
Potential mechanisms	Potential mechanism for dabrafenib induced uveitis has not been elucidated. Multiple hypotheses suggest either a direct inflammatory response on subclinical metastatic cells within the uveal tract or an indirect response with antigens shared by melanocytes in the melanoma and choroid (Sandhu 2012). In addition, a direct, inadvertent and paradoxical inhibition or activation of the downstream MAP-kinase pathway in the eye following BRAF-inhibition has also been suggested (Sandhu 2012).
Evidence source(s) and strength of evidence	In clinical trials ophthalmologic reactions, including uveitis, iridocyclitis and iritis, have been reported in patients treated with dabrafenib as monotherapy and in combination with trametinib.
Characterization of the risk:	Uveitis is a complex term describing any inflammation independent of etiology (i.e. infectious or non-infectious) involving the uveal tract of the eye. Uveitis is manifest by the presence of inflammatory cells and inflammation-related findings in any anatomical location of the eye where iris, ciliary body and choroid are found. The cornea, sclera, retina, vitreous and optic nerve (Larson 2011) can become involved secondarily. Uveitis has been reported as a therapy-related AE in studies conducted with BRAF small molecule inhibitors and is listed together in the label of dabrafenib. Patients should be routinely monitored for visual signs and symptoms (such as change in vision, photophobia and eye pain) while on therapy. **Adjuvant treatment of patients with stage III melanoma with a BRAF V600 mutation, following complete resection** See Table 8-3 for further details on risk characterization **Treatment of adult patients with advanced NSCLC with a BRAF V600 mutation** For the BRF113928 NSCLC study, one dabrafenib monotherapy patient (1%) had a grade 3 Uveitis and this was recorded as an SAE**.**
Risk factors and risk groups	No risk groups or risk factors have been identified.
Preventability	Monitor patients for visual signs and symptoms (such as, change in vision, photophobia and eye pain) during therapy.
Impact on the benefit-risk balance of the product	In subjects experiencing low grade uveitis or iritis, all but one case resolved at the time of data cut-off with no discontinuations due to uveitis. Therefore, the impact on the individual patient is expected to be minimal. And the impact on the benefit-risk balance of the product is relatively low if any at all.
Public health impact	Potential public health impact is considered to be low.

8.3.1.3 Important potential risk: Testicular toxicity

No testicular toxicity events have been observed in the studies BRF113928, BRF115532, MEK116513 and MEK115306.

Table 8-5 Important potential risk - Testicular toxicity: Other details

Testicular toxicity	
Potential mechanisms	No potential mechanisms have been described.
Evidence source(s) and strength of evidence	In repeat dose studies, testicular degeneration/depletion was seen in rats and dogs (≥0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period. Non clinical data See Part II Module SII: Developmental toxicity
Characterization of the risk:	No studies found reporting the incidence of testicular comorbidity among patients with lung cancer. There is no information available at this time on the prevalence of testicular comorbidity.
Risk factors and risk groups	None
Preventability	No data on predictability is available. Preventability will be addressed with labelling.

Testicular toxicity	
Impact on the benefit-risk balance of the product	Male patients should be informed of the potential risk for testicular adverse effects and impaired spermatogenesis, which may be irreversible. Based on available data no impact on the benefit-risk balance of the product is anticipated.
Public health impact	The potential risk for humans is unknown. The potential for public health safety is expected to be low.

8.3.1.4 Important potential risk: Developmental toxicity

Table 8-6 Clinical trial data of Developmental toxicity (BRF113928, BRF115532, MEK116513, MEK115306)

	Dabrafenib + Trametinib (N=435)	Placebo (N=432)
Number of Subjects with Events	3 (<1%)	2 (<1%)
Number of Events	3	2
SAEs	0	0
Maximum Grade		
Grade 3	0	0
Grade 4	0	0
Grade 5	0	0
Outcome[1]		
Recovered/Resolved	1 (33%)	1 (50%)
Recovering/Resolving	0	0
Not Recovered/Not Resolved	2 (67%)	1 (50%)
Recovered/Resolved w/sequelae	0	0
Fatal	0	0

Numbers (n) represent counts of subjects.
Subjects may be included in more than one category
[1] Outcome worst case hierarchy: Fatal > Not Recovered/Not Resolved > Recovered/Resolved with sequelae > Recovering/Resolving > Recovered/Resolved.
Source: Annex 7 – Table 8.01155

No data is available for the NSCLC indication.

Table 8-7 Important potential risk - Developmental toxicity: Other details

Developmental toxicity	
Potential mechanisms	Potential mechanism is unknown.
Evidence source(s) and strength of evidence	In rats given dabrafenib, developmental toxicities included teratogenicity and maternal toxicity. The lowest level effect for developmental toxicity (20 mg/kg/day) was associated with systemic exposure levels generally below clinical exposures (0.5X clinical exposure).
Characterization of the risk:	Pregnant women are excluded from participation in clinical studies with dabrafenib.
Risk factors and risk groups	Women of child-bearing potential.
Preventability	Dabrafenib should not be administered to pregnant women.
Impact on the benefit-risk balance of the product	No current impact to the benefit-risk has been identified.
Public health impact	Potential public health impact is considered to be low.

8.3.1.5 Important potential risk: Long-term safety in patients <18 years of age (including potential adverse effects on skeletal maturation and sexual maturation)

The safety of dabrafenib plus trametinib combination therapy has been evaluated in a pooled safety set of 171 paediatric patients across two studies in patients with BRAF V600 mutation-positive advanced solid tumours. The overall safety profile of combination therapy is presented in Table 8-16. No adverse effects on skeletal maturation and sexual maturation were reported (SCS Appendix 1-Table 3.1-1).

Table 8-8 Clinical trial data of Safety in patients <18 years of age (including potential adverse effects on skeletal maturation and sexual maturation)

	All Patients N=171	
Category	**All grades n (%)**	**Grade ≥3 n (%)**
Adverse events	169 (98.8)	98(57.3)
Treatment-related	154 (90.1)	50 (29.2)
SAEs	79 (46.2)	58 (33.9)
Treatment-related	29 (17.0)	16 (9.4)
Fatal SAEs	3 (1.8)	3 (1.8)
Treatment-related	0	0
AEs leading to discontinuation	13 (7.6)	6 (3.5)
Treatment-related	11 (6.4)	5 (2.9)
AEs leading to dose adjustment/interruption	125 (73.1)	64 (37.4)
AEs requiring additional therapy	135 (78.9)	56 (32.7)

Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 24.0, CTCAE version 4.03
Source: [SCS Appendix 1-Table 3.1-1]

Table 8-9 Important potential risk: Long-term safety in patients <18 years of age (including potential adverse effects on skeletal maturation and sexual maturation): Other details

Long-term safety in patients <18 years of age (including potential adverse effects on skeletal maturation and sexual maturation)	**Details**
Potential mechanisms	A potential mechanism is not known at this time.
Evidence source(s) and strength of evidence	Studies in juvenile animals have shown reproductive, developmental toxicity and testicular toxicity in rats. The testicular toxicity findings observed in non-clinical studies with dabrafenib + trametinib in combination indicate a risk for impaired spermatogenesis in males. The effects on bone growth are likely relevant for paediatric population, and growth will be monitored in clinical trials with paediatric patients during treatment.
Characterization of the risk:	The safety of dabrafenib plus trametinib combination therapy has been evaluated in a pooled safety set of 171 paediatric patients across two studies in

Long-term safety in patients <18 years of age (including potential adverse effects on skeletal maturation and sexual maturation)	Details
	patients with BRAF V600 mutation-positive advanced solid tumors, of which 4 (2.3%) patients were 1 to < 2 years of age, 39 (22.8%) patients were 2 to < 6 years of age, 54 (31.6%) patients were 6 to < 12 years of age, and 74 (43.3%) patients were (12 to < 18 years old). No adverse effects on skeletal maturation and sexual maturation were reported.
Risk factors and risk groups	Patients under 18 years of age.
Preventability	No data on preventability is available. Preventability is addressed by communication in labeling.
Impact on the benefit-risk balance of the product	Overall, benefit-risk balance remains favorable for paediatric population.
Public health impact	Public health impact is considered to be low.

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

There are no missing information topics for dabrafenib.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: 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

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up questionnaires:

Specific adverse event follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the risks specified below:

Important identified risk: Pre-renal or intrinsic renal failure

Other forms of routine pharmacovigilance activities:

There are no other forms of routine pharmacovigilance activities.

10.2 Part III.2. 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).

Study short name and title:

A roll-over study to assess long-term effect in pediatric patients treated with dabrafenib and/or trametinib.

Rationale and study objectives:

This study will facilitate data collection of the long-term outcomes of pediatric subjects who have been treated in clinical trials with dabrafenib, trametinib or the combination, to assess the long-term effect on growth, development and general health of these subjects. Further, for those subjects currently on treatment in the parent protocol and would benefit from continued treatment (per investigator determination), this study will offer a mechanism to continue treatment outside the parent protocols. The primary objective is to assess the long-term safety of treatment with dabrafenib, trametinib or the combination. The secondary objectives are to assess the long-term effect of treatment with dabrafenib, trametinib or the combination on general health, growth and development; and to assess efficacy as determined by institutional standard of care procedures.

Study design:

This 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 pediatric subjects who have been treated on Novartis sponsored trials. No formal hypothesis will be tested. Additionally, this study will

provide continued access to study medication(s) for subjects who have previously participated in dabrafenib and/or trametinib treatment studies (parent studies).

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 tumors.
- 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 Low Grade Glioma (LGG) or relapsed or refractory High Grade Glioma (HGG).

Study population:

Pediatric patients (or young adults at the time of consent to this study) who have participated in an eligible parent protocol will be eligible to enroll into the observational period of this study. In addition, those patients who are currently eligible to receive treatment with dabrafenib and/or trametinib in the parent protocol, and who in the opinion of the investigator, would benefit from continued treatment will be eligible to take part in the treatment period of this study.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

Milestones:

Final CSR: May-2027 (Planned)

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

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

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

11 Part IV: Plans for post-authorization efficacy studies

There are no plans for post-authorization efficacy studies.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Pre-Renal and Intrinsic Renal Failure	**Routine risk communication** Undesirable effects in Section 4.8 of the SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk:** Dabrafenib should be used with caution in patients with severe renal impairment when administered as monotherapy or in combination with trametinib. Dose modifications are included in SmPC Section 4.2. **Other routine risk minimization measures beyond the Product Information:** None
Uveitis	**Routine risk communication** SmPC Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, dabrafenib should be withheld until resolution and should be restarted reduced by one dose level. Dose modifications are included in SmPC Section 4.2. **Other routine risk minimization measures beyond the Product Information:** None
Important potential risks	
Testicular toxicity	**Routine risk communication** SmPC Section 5.3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Developmental Toxicity	**Routine risk communication** SmPC Section 5.3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Long-term safety in patients <18 years of age (including potential adverse effects on skeletal	**Routine risk communication** SmPC Section 4.2 **Routine risk minimization activities recommending specific clinical measures to address the risk:**

Safety concern	Routine risk minimization activities
maturation and sexual maturation)	None **Other routine risk minimization measures beyond the Product Information:** None.
Missing information	
None	

12.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3. Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified dabrafenib risks (also applicable to combination therapy)		
Pre-Renal and Intrinsic Renal Failure	**Routine risk minimization measures** Dose modifications in Section 4.2 of the SmPC Undesirable effects in Section 4.8 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Targeted follow-up checklist **Additional pharmacovigilance activities:** None
Uveitis	**Routine risk minimization measures** Dose modifications in Section 4.2 of the SmPC Undesirable effects in Section 4.8 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Important potential dabrafenib risks (also applicable to combination therapy)		
Testicular toxicity	**Routine risk minimization measures** Preclinical safety data in Section 5.3 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Developmental toxicity	**Routine risk minimization measures** Preclinical safety data in Section 5.3 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Long-term safety in patients <18 year old (including potential adverse effects on	**Routine risk minimization measures** SmPC section 4.2. **Additional risk minimization**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.

Safety concern	Risk minimization measures	Pharmacovigilance activities
skeletal maturation and sexual maturation)	**measures** None.	**Additional pharmacovigilance activities:** CDRB436G2401 (EudraCT number 2018-004459-19)
Missing dabrafenib monotherapy information		
None		

13 Part VI: Summary of the risk management plan for Tafinlar and Finlee (dabrafenib)

This is a summary of the risk management plan (RMP) for Tafinlar and Finlee (dabrafenib). The RMP details important risks of Tafinlar and Finlee, how these risks can be minimized, and how more information will be obtained about Tafinlar and Finlee's risks and uncertainties (missing information).

Tafinlar and Finlee's summary of product characteristics (SmPC) and package leaflet give essential information to healthcare professionals and patients on how Tafinlar and Finlee should be used.

This summary of the RMP for Tafinlar and Finlee should be read in the context of all this information including the assessment reports of the evaluation and their plain-language summaries, all which are part of the European Public Assessment Reports (EPAR).

Important new concerns or changes to the current ones will be included in updates of Tafinlar and Finlee's RMP.

13.1 Part VI: I. The medicine and what it is used for

Tafinlar capsules contain dabrafenib as the active substance and are used in the following indications:

- Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
- Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with advanced or metastatic non-small cell lung cancer (NSCLC) with BRAF V600 mutation.
- Adjuvant treatment of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection.

The recommended dose of Tafinlar capsules is 150 mg twice daily.

Finlee dispersible tablets contain dabrafenib as active substance, and are used in the following indications:

- Dabrafenib in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy.
- Dabrafenib in combination with trametinib is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment.

The recommended dose of Finlee dispersible tablets is body weight based and should be administered twice daily.

Further information about the evaluation of Tafinlar and Finlee's benefits can be found in Tafinlar and Finlee's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpages:

https://www.ema.europa.eu/en/medicines/human/EPAR/tafinlar

https://www.ema.europa.eu/en/medicines/human/EPAR/finlee

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Tafinlar and Finlee, together with measures to minimize such risks and the proposed studies for learning more about Tafinlar and Finlee's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

13.2.1 Part VI: II.A: List of important risks and missing information

Important risks of Tafinlar and Finlee are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tafinlar and Finlee. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

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

13.2.2 Part VI: II.B: Summary of important risks

Table 13-2 Important identified risk: Pre-renal and Intrinsic Renal Failure

Evidence for linking the risk to the medicine	In juvenile toxicity studies in rats, renal toxicity (tubular deposits, increased incidence of cortical cysts and tubular basophilia and reversible increases in urea and/or creatinine concentrations) was observed (≥0.2 times adult human clinical exposure based on AUC). Renal failure has been identified in <1% of patients treated with dabrafenib alone and in ≤1% of patients treated with dabrafenib in combination with trametinib.
Risk factors and risk groups	No specific risk groups were identified during clinical trials. Risk factors may include pyrexia, dehydration with pre-renal azotemia and/or hypotension.
Risk minimization measures	**Routine risk minimization measures** SmPC Sections 4.2 and 4.8. **Additional risk minimization measures** There are no additional risk minimization measures.

Table 13-3 Important identified risk: Uveitis

Evidence for linking the risk to the medicine	In clinical trials ophthalmologic reactions, including uveitis, iridocyclitis and iritis, have been reported in patients treated with dabrafenib as monotherapy and in combination with trametinib.
Risk factors and risk groups	No risk groups or risk factors have been identified.
Risk minimization measures	**Routine risk minimization measures** SmPC Sections 4.2 and 4.8 **Additional risk minimization measures** There are no additional risk minimization measures.

Table 13-4 Important potential risk: Testicular toxicity

Evidence for linking the risk to the medicine	In repeat dose studies, testicular degeneration/depletion was seen in rats and dogs (≥0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period. Non clinical data See Part II Module SII: Developmental toxicity.
Risk factors and risk groups	None
Risk minimization measures	**Routine risk minimization measures** SmPC Section 5.3. **Additional risk minimization measures** There are no additional risk minimization measures.

Table 13-5 Important potential risk: Developmental toxicity

Evidence for linking the risk to the medicine	In rats and rabbits given trametinib monotherapy, maternal and developmental toxicity (decreased fetal body weights and increased ossification variations) were observed at exposures below the exposures achieved at the recommended clinical dose of 2 mg per day. Additionally, decreased corpora lutea were observed in rats given trametinib, which may impact female fertility. It is not known whether these effects will also be seen in humans.
Risk factors and risk groups	Women of child-bearing potential.
Risk minimization measures	**Routine risk minimization measures** SmPC Sections 4.6 and 5.3. **Additional risk minimization measures** There are no additional risk minimization measures.

Table 13-6 Important potential risk: Long-term safety in patients <18 years of age (including potential adverse effects on skeletal maturation and sexual maturation)

Evidence for linking the risk to the medicine	Studies in juvenile animals have shown reproductive, developmental toxicity and testicular toxicity in rats. The testicular toxicity findings observed in non-clinical studies with dabrafenib + trametinib in combination indicate a risk for impaired spermatogenesis in males. The effects on bone growth are likely relevant for paediatric population, and growth will be monitored in clinical trials with paediatric patients during treatment.
Risk factors and risk groups	Patients under 18 years of age.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 5.3. **Additional risk minimization measures** There are no additional risk minimization measures. **Additional pharmacovigilance activities** CDRB436G2401 (EudraCT number 2018-004459-19)

13.2.3 Part VI: II.C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of dabrafenib.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

CDRB436G2401 study is a post-authorization development plan for dabrafenib.

Table 13-7 Other studies in the post-authorization development plan

Study Short name	Rationale and study objectives
CDRB436G2401	This study will facilitate data collection of the long-term outcomes of pediatric subjects who have been treated in clinical trials with dabrafenib, trametinib or the combination, to assess the long-term effect on growth, development and general health of these subjects. Further, for those subjects currently on treatment in the parent protocol and would benefit from continued treatment (per investigator determination), this study will offer a mechanism to continue treatment outside the parent protocols. The primary objective is to assess the long-term safety of treatment with dabrafenib, trametinib or the combination. The secondary objectives are to assess the long-term effect of treatment with dabrafenib, trametinib or the combination on general health, growth and development; and to assess efficacy as determined by institutional standard of care procedures.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Targeted Follow-up Checklist (Version 4/Jun-2022)

Targeted Follow-up Checklist
Renal Impairment or Failure

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Event Description:

Did the patient present with any of the following signs or symptoms? **Check all that apply**

☐ Fever
☐ Increased urinary output
☐ Pain upon urinating
☐ Dehydration
☐ Hematuria/red or cola colored urine
☐ Arthralgia
☐ Nausea/vomiting
☐ Loss of Appetite
☐ Muscle Cramps
☐ Pain around costovertebral angle
☐ Edema
☐ Skin rash
☐ Urinary urgency
☐ Lethargy
☐ Flank pain
☐ Infections ☐ Confusion
☐ Dry/itchy skin
☐ Change in size of urine stream
☐ Burning sensation upon urinating
☐ Shortness of breath
☐ Trouble sleeping
☐ Difficulty starting or maintaining urine stream ☐ Decreased urinary output ☐ Bradycardia
☐ Hypotension
☐ Hypertension
☐ Tachycardia
☐ None of the above

Is the patient participating in a clinical trial for any drug/device or other investigational product?

☐ Yes, please specify_____ ☐ No

Were any of the following diagnostic tests performed? **Check all that apply and please specify which test(s) and include dates, results and reference range for pre- and post- treatment values:**

☐ Urine protein/Urine creatinine
☐ Kidney biopsy
☐ CT scan
☐ BUN
☐ Albumin
☐ Renal ultrasound
☐ Serum creatinine
☐ Serum total protein
☐ Cystoscopy
☐ Hemoglobin
☐ Myoglobin
☐ Echocardiogram
☐ CPK
☐ Electrolytes
☐ Urinalysis (including microscopic)
☐ Glomerular filtration rate (estimated/measured)
☐ Complement studies
☐ Chest x-ray
☐ Pulmonary angiography
☐ Metabolic Acidosis
☐ Blood pressure
☐ Abdominal x-ray
☐ Antinuclear antibodies
☐ C-reactive protein
☐ Magnetic resonance imaging
☐ Liver function tests
☐ Lipid levels
☐ Electrocardiogram
☐ Erythrocyte Sedimentation rate
☐ Coagulation studies
☐ None of the above

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset)

Does the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply:**

☐ Congestive heart failure ☐Multiple myeloma ☐ Exposure to chemical dyes
☐ Diabetes mellitus (Type I or Type II) ☐ Urinary tract infection☐ Myocardial infarction
☐ Reflux nephropathy ☐ Thromboembolic disease☐ Coronary artery disease
☐ Renal disease (including nephrolithiasis) ☐ Obstructive uropathy☐ Hypercalcemia
☐ Autoimmune disease (specify: _____) ☐ Sickle cell disease☐ History of renal transplant
☐ Hypertension ☐ Hyperuricemia ☐ Hepatorenal syndrome
☐ Trauma/ burns ☐ Renal artery obstruction☐ Hemolytic uremic syndrome
☐ Kidney or bladder problems/Stones ☐ Drug allergies *(please specify)*☐ Dehydration
☐ Disease of the prostate ☐ Hemorrhage ☐ Rhabdomyolysis
☐ Intravenous contrast ☐ History of dialysis☐ Cystic kidney disease
☐ Other relevant history (specify: _____)☐ None of the above

Relevant family history

☐ Chronic kidney disease ☐Hearing loss/deafness☐ Kidney cancer
☐ kidney genetic abnormalities

Was the patient taking any of the following drugs? Check all that apply:

☐ACE Inhibitors ☐Lithium☐Quinolones ☐Immunosuppressants☐Actaminophen
☐Amphotericin B ☐Foscarnet☐Aminoglycosides☐Diphenhydramine☐Doxylamine
☐Rifampin ☐Sulfonamides☐Vancomycin☐Adefovir,Cidofovir, Tenofovir, Indinavir, Acyclovir, Ganciclovir
☐Benzodiazepines ☐Clopidogrel☐Carmustine☐Cisplatin☐Interferon-alfa
☐Methotrexate ☐Mitomycin-C☐Contrast dye☐Diuretics☐Pamidronate
☐Herbals (specify: _____) ☐PPIs☐Allopurinol☐Gold Therapy☐Quinine
☐Phenytoin ☐Ranitidine☐Zoledronate☐Haloperidol☐COX-2 Inhibitors
☐Amitriptyline ☐Doxepin☐Fluoxetine☐Pentamidine☐Vitamin D-3
☐NSAIDS ☐Calcium☐ Angiotension II Receptor Blockers
☐Penicillins ☐Drugs of Abuse (specify: _____)

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

None