Mekinist® 0.5 mg
Mekinist® 2 mg

1. NAME OF THE MEDICINAL PRODUCT

Mekinist® 0.5 mg film-coated tablets
Mekinist® 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mekinist 0.5 mg film-coated tablets
Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 0.5 mg of trametinib.

Mekinist 2 mg film-coated tablets
Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 2 mg of trametinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Mekinist 0.5 mg film-coated tablets
Yellow, modified oval, biconvex, film-coated tablets, approximately 5.0 x 9.0 mm, with the company logo debossed on one face and "TT" on the opposing face.

Mekinist 2 mg film-coated tablets
Pink, round, biconvex, film-coated tablets, approximately 7.6 mm, with the company logo debossed on one face and "LL" on the opposing face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

Trametinib as monotherapy or in combination with dabrafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1). Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (see section 5.1).

Adjuvant treatment of melanoma

Trametinib in combination with dabrafenib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

Non-small cell lung cancer (NSCLC)

Trametinib in combination with dabrafenib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.

Anaplastic Thyroid Cancer (ATC)

Trametinib is indicated, in combination with dabrafenib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options (see section 4.2).

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors

Trametinib is indicated, in combination with dabrafenib, for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options (see section 4.2).

Limitations of Use: Trametinib is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition (see section 5.1).

BRAF V600E Mutation-Positive Low-Grade Glioma

Trametinib is indicated, in combination with dabrafenib, for the treatment of pediatric patients 6 years of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy *(see section 4.2)*.

4.2 Posology and method of administration

Treatment with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.
Before taking trametinib, patients must have confirmation of BRAF V600 mutation using a validated test. In ATC, solid tumors and Low-Grade Glioma, confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with trametinib and dabrafenib (see section 5.1)

Posology

The recommended dose of trametinib in adult patients, either used as monotherapy or in combination with dabrafenib, is 2 mg once daily. The recommended dose of dabrafenib, when used in combination with trametinib, is 150 mg twice daily.

The recommended dose for trametinib in pediatric patients who weigh at least 26 kg is based on body weight (Table 1). A recommended dose has not been established in patients who weigh less than 26 kg.

Table 1. Dosing in Pediatric Patients from 6 to 17 Years Old (Weight-Based Dose)*

Body Weight	Recommended Dose
26 to 37 kg	1 mg (two 0.5 mg tablets) orally once daily
38 to 50 kg	1.5 mg (three 0.5 mg tablets) orally once daily
51 kg or greater	2 mg orally once daily

* Refer to the dabrafenib prescribing information for recommended dabrafenib dosing information.

Duration of treatment

It is recommended that patients continue treatment with trametinib until patients no longer derive benefit or the development of unacceptable toxicity (see Table 4). In the adjuvant melanoma setting, patients should be treated for a period of 12 months unless there is disease recurrence or unacceptable toxicity. In ATC and solid tumors, treatment should continue until disease progression or unacceptable toxicity.
The optimal duration of combination therapy in the paediatric LGG population is not defined.

Missed doses

If a dose of trametinib is missed, it should only be taken if it is more than 12 hours until the next scheduled dose.

If a dose of dabrafenib is missed, when trametinib is given in combination with dabrafenib, the dose of dabrafenib should only be taken if it is more than 6 hours until the next scheduled dose.

Dose modification

The management of adverse reactions may require dose reduction, treatment interruption or treatment discontinuation (see Tables 2, 3 and 4).

Dose modifications are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (see dabrafenib Prescribing Information for further details).

Table 2. Recommended dose level reductions in Adult Patients

Dose level	**Trametinib dose** Used as monotherapy or in combination with dabrafenib	**Dabrafenib dose*** Only when used in combination with trametinib
Starting dose	2 mg once daily	150 mg twice daily
1st dose reduction	1.5 mg once daily	100 mg twice daily
2nd dose reduction	1 mg once daily	75 mg twice daily
3rd dose reduction (combination only)	1 mg once daily	50 mg twice daily
Dose adjustment for trametinib below 1 mg once daily is not recommended, whether used as monotherapy or in combination with dabrafenib. Dose adjustment for dabrafenib below 50 mg twice daily is not recommended when used in combination with trametinib.		
*Please refer to the dabrafenib Prescribing Information, Posology and method of administration, for dosing instructions for treatment with dabrafenib monotherapy.		

Table 3. Recommended Dose Reductions for trametinib for Adverse Reactions in Pediatric Patients (6 to 17 Years Old)

Action	**Recommended Dosage *(See Table 1)***		
	1 mg *(two 0.5 mg tablets)* *orally once daily*	*1.5 mg* *(three 0.5 mg tablets)* *orally once daily*	*2 mg* *orally once daily*
First Dose Reduction	0.5 mg orally once daily	1 mg (two 0.5 mg tablets) orally once daily	1.5 mg (three 0.5 mg tablets) orally once daily
Second Dose Reduction	-	0.5 mg orally once daily	1 mg (two 0.5 mg tablets) orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate a maximum of two trametinib dose reductions		

Table 4. Dose modification schedule based on the grade of any adverse reactions (excluding pyrexia)

Grade (CTCAE)*	**Recommended trametinib dose modifications** Used as monotherapy or in combination with dabrafenib
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is Grade 0 to 1 and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy.
* The intensity of clinical adverse reactions graded by the Common Terminology Criteria for Adverse Events (CTCAE)	

When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The trametinib dose should not exceed the recommended dose.

Pyrexia
If a patient's temperature is ≥38ºC, therapy should be interrupted (trametinib when used as monotherapy, and both trametinib and dabrafenib when used in combination). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection and, if necessary, treated in line with local practice (see section 4.4). Trametinib, or both trametinib and dabrafenib when used in combination, should be restarted if the patient is symptom-free for at least 24 hours either (1) at the same dose level, or (2) reduced by one dose level if pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure.

If treatment-related toxicities occur when trametinib is used in combination with dabrafenib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for only one of the two treatments are detailed below for uveitis, RAS mutation-positive non-cutaneous malignancies (primarily related to dabrafenib), left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and interstitial lung disease (ILD)/pneumonitis (primarily related to trametinib).

Dose modification exceptions (where only one of the two therapies is dose reduced) for selected adverse reactions

Uveitis
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 of ocular inflammation, and then dabrafenib should be restarted reduced by one dose level. No dose modification of trametinib is required when taken in combination with dabrafenib (see section 4.4).

RAS mutation-positive non-cutaneous malignancies
The benefits and risks must be considered before continuing treatment with dabrafenib in patients with a non-cutaneous malignancy that has a RAS mutation. No dose modification of trametinib is required when taken in combination with dabrafenib.

Left ventricular ejection fraction (LVEF) reduction/Left ventricular dysfunction
Trametinib should be interrupted in patients who have an asymptomatic, absolute decrease of >10% in

LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN) (see section 4.4). No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib. If the LVEF recovers, treatment with trametinib may be restarted, but the dose should be reduced by one dose level with careful monitoring (see section 4.4).

Trametinib should be permanently discontinued in patients with Grade 3 or 4 left ventricular cardiac dysfunction or clinically significant LVEF reduction which does not recover within 4 weeks (see section 4.4).

Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED)
If patients report new visual disturbances such as diminished central vision, blurred vision or loss of vision at any time while on trametinib therapy, a prompt ophthalmological assessment is recommended. In patients who are diagnosed with RVO, treatment with trametinib, whether given as monotherapy or in combination with dabrafenib, should be permanently discontinued. No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib. If RPED is diagnosed, follow the dose modification schedule in Table 5 below for trametinib (see section 4.4).

Table 5. Recommended dose modifications for trametinib for RPED

Grade 1 RPED	Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below and withhold trametinib for up to 3 weeks.
Grade 2-3 RPED	Withhold trametinib for up to 3 weeks.
Grade 2-3 RPED that improves to Grade 0-1 within 3 weeks	Resume trametinib at a lower dose level (see Tables 2 and 3) or discontinue trametinib in patients on the lowest dose level.
Grade 2-3 RPED that does not improve to at least Grade 1 within 3 weeks	Permanently discontinue trametinib.

Interstitial lung disease (ILD)/Pneumonitis
Trametinib must be withheld in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Trametinib must be permanently discontinued in patients diagnosed with treatment-related ILD or pneumonitis. No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib for cases of ILD or pneumonitis.

Special populations
Renal impairment
No dosage adjustment is required in patients with mild or moderate renal impairment (see section 5.2). There are no data with trametinib in patients with severe renal impairment; therefore, the potential need for starting dose adjustment cannot be determined. Trametinib should be used with caution in patients with severe renal impairment when administered as monotherapy or in combination with dabrafenib.

Hepatic impairment
No dosage adjustment is required in patients with mild hepatic impairment. Available data from a clinical pharmacology study indicate a limited impact of moderate to severe hepatic impairment on trametinib exposure (see section 5.2). Trametinib should be used with caution in patients with moderate or severe hepatic impairment when administered as monotherapy or in combination with dabrafenib.

Non-Caucasian patients
The safety and efficacy of trametinib in non-Caucasian patients have not been established. No data are

available.

Elderly
No initial dose adjustment is required in patients >65 years of age. More frequent dose adjustments (see Tables 2 and 4 above) may be required in patients >65 years of age (see section 4.8).

Paediatric population
BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors and LGG
The safety and effectiveness of trametinib tablets in combination with dabrafenib have been established in pediatric patients 6 years of age and older that weigh at least 26 kg with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options; or with LGG with BRAF V600E mutation who require systemic therapy. Use of trametinib in combination with dabrafenib for these indications is supported by evidence from studies X2101 and G2201 that enrolled 171 patients (1 to < 18 years) with BRAF V600 mutation-positive advanced solid tumors, of which 4 (2.3%) patients were 1 to < 2 years of age, 39 (23%) patients were 2 to < 6 years of age, 54 (32%) patients were 6 to < 12 years of age, and 74 (43%) patients were 12 to < 18 years of age. *(see sections 4.8, 5.1 and 5.2).*
The safety and effectiveness of trametinib tablets in combination with dabrafenib have not been established for these indications in pediatric patients less than 6 years old.
The safety and effectiveness of trametinib as a single agent in pediatric patients have not been established.

There are no adequate data on the safety and efficacy of combination therapy for long-term paediatric use in LGG.

Studies in juvenile animals have shown adverse effects of trametinib which were not observed in adult animals (see section 5.3).

Method of administration

Trametinib should be taken orally with a full glass of water. The tablets should not be chewed or crushed and they should be taken without food, at least 1 hour before or 2 hours after a meal.

It is recommended that the dose of trametinib is taken at a similar time every day. When trametinib and dabrafenib are taken in combination, the once-daily dose of trametinib should be taken at the same time each day with either the morning dose or the evening dose of dabrafenib.

If a patient vomits after taking trametinib, the patient should not retake the dose and should take the next scheduled dose.

Please refer to dabrafenib Prescribing Information for information on method of administration when given in combination with trametinib.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

When trametinib is given in combination with dabrafenib, the Prescribing Information of dabrafenib must be consulted prior to initiation of treatment. For additional information on warnings and precautions associated with dabrafenib treatment, please refer to the dabrafenib Prescribing Information.

BRAF V600 testing

The efficacy and safety of trametinib have not been evaluated in patients whose solid tumor tested negative for the BRAF V600 mutation.

Trametinib monotherapy compared to BRAF inhibitors

Trametinib monotherapy has not been compared with a BRAF inhibitor in a clinical study in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. Based on cross-study comparisons, overall survival and progression-free survival data appear to show similar effectiveness between trametinib and BRAF inhibitors; however, overall response rates were lower in patients treated with trametinib than those reported in patients treated with BRAF inhibitors.

Trametinib in combination with dabrafenib in patients with melanoma who have progressed on a BRAF inhibitor

There are limited data in patients taking the combination of trametinib with dabrafenib who have progressed on a prior BRAF inhibitor. These data show that the efficacy of the combination will be lower in these patients (see section 5.1). Therefore other treatment options should be considered before treatment with the combination in this prior BRAF inhibitor treated population. The sequencing of treatments following progression on a BRAF inhibitor therapy has not been established.

New malignancies

New malignancies, cutaneous and non-cutaneous, can occur when trametinib is used in combination with dabrafenib.

Cutaneous malignancies

Cutaneous squamous cell carcinoma (cuSCC)

Cases of cuSCC (including keratoacanthoma) have been reported in patients treated with trametinib in combination with dabrafenib. Cases of cuSCC can be managed with excision and do not require treatment modification. Please refer to the dabrafenib Prescribing Information (section 4.4).

New primary melanoma

New primary melanoma was reported in patients receiving trametinib in combination with dabrafenib. Cases of new primary melanoma can be managed with excision and do not require treatment modification. Please refer to the dabrafenib Prescribing Information (section 4.4).

Non-cutaneous malignancies

Based on its mechanism of action, dabrafenib may increase the risk of non-cutaneous malignancies when RAS mutations are present. When trametinib is used in combination with dabrafenib please refer to the dabrafenib Prescribing Information (section 4.4). No dose modification of trametinib is required for RAS mutation-positive malignancies when taken in combination with dabrafenib.

Haemorrhage

Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages, have occurred in patients taking trametinib as monotherapy and in combination with dabrafenib (see section 4.8).
The potential for these events in patients with low platelet counts (<75,000) has not been established as such patients were excluded from clinical trials. The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy. If haemorrhage occurs, patients should be treated as clinically indicated.

LVEF reduction/Left ventricular dysfunction

Trametinib has been reported to decrease LVEF, when used as monotherapy or in combination with dabrafenib (see section 4.8). In clinical trials, the median time to onset of the first occurrence of left ventricular dysfunction, cardiac failure and LVEF decrease was between 2 and 5 months.

Trametinib should be used with caution in patients with impaired left ventricular function. Patients with left ventricular dysfunction, New York Heart Association Class II, III, or IV heart failure, acute coronary syndrome within the past 6 months, clinically significant uncontrolled arrhythmias, and uncontrolled hypertension were excluded from clinical trials; safety of use in this population is therefore unknown. LVEF should be evaluated in all patients prior to initiation of treatment with trametinib, one month after initiation of therapy, and then at approximately 3-monthly intervals while on treatment (see section 4.2 regarding dose modification).

In patients receiving trametinib in combination with dabrafenib, there have been occasional reports of acute, severe left ventricular dysfunction due to myocarditis. Full recovery was observed when stopping treatment. Physicians should be alert to the possibility of myocarditis in patients who develop new or worsening cardiac signs or symptoms.

Pyrexia

Fever has been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib (see section 4.8). The incidence and severity of pyrexia are increased with the combination therapy (see dabrafenib Prescribing Information section 4.4). In patients receiving trametinib in combination with dabrafenib, pyrexia may be accompanied by severe rigors, dehydration, and hypotension which in some cases can lead to acute renal insufficiency.

Therapy (trametinib when used as monotherapy, and both trametinib and dabrafenib when used in combination) should be interrupted if the patient's temperature is ≥38ºC (see section 5.1). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection. Therapy can be restarted once the fever resolves. If fever is associated with other severe signs or symptoms, therapy should be restarted at a reduced dose once fever resolves and as clinically appropriate (see section 4.2).

Hypertension

Elevations in blood pressure have been reported in association with trametinib as monotherapy and in combination with dabrafenib, in patients with or without pre-existing hypertension (see section 4.8). Blood pressure should be measured at baseline and monitored during treatment with trametinib, with control of hypertension by standard therapy as appropriate.

Interstitial lung disease (ILD)/Pneumonitis

In a Phase III trial, 2.4% (5/211) of patients treated with trametinib monotherapy developed ILD or pneumonitis; all five patients required hospitalisation. The median time to first presentation of ILD or pneumonitis was 160 days (range: 60 to 172 days). In studies MEK115306 and MEK116513 <1% (2/209) and 1 % (4/350), respectively, of patients treated with trametinib in combination with dabrafenib developed pneumonitis or ILD (see section 4.8).

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

section 4.2). If trametinib is being used in combination with dabrafenib then therapy with dabrafenib may be continued at the same dose.

Visual impairment

Disorders associated with visual disturbance, including RPED and RVO, may occur with trametinib as monotherapy and in combination with dabrafenib. Symptoms such as blurred vision, decreased acuity, and other visual phenomena have been reported in the clinical trials with trametinib (see section 4.8). In clinical trials uveitis and iridocyclitis have also been reported in patients treated with trametinib in combination with dabrafenib.

Trametinib is not recommended in patients with a history of RVO. The safety of trametinib in subjects with predisposing factors for RVO, including uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes, has not been established.

If patients report new visual disturbances, such as diminished central vision, blurred vision or loss of vision at any time while on trametinib therapy, a prompt ophthalmological assessment is recommended. If RPED is diagnosed, the dose modification schedule in Table 5 should be followed (see section 4.2); if uveitis is diagnosed, please refer to dabrafenib Prescribing Information section 4.4. In patients who are diagnosed with RVO, treatment with trametinib should be permanently discontinued. No dose modification of dabrafenib is required when taken in combination with trametinib following diagnosis of RVO or RPED. No dose modification of trametinib is required when taken in combination with dabrafenib following diagnosis of uveitis.

Rash

Rash has been observed in about 60% of patients in trametinib monotherapy studies and in about 24% of adult patients and 54% of pediatric patients when trametinib is used in combination with dabrafenib (see section 4.8). The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions.

Rhabdomyolysis

Rhabdomyolysis has been reported in patients taking trametinib as monotherapy or in combination with dabrafenib (see section 4.8). In some cases, patients were able to continue trametinib. In more severe cases hospitalisation, interruption or permanent discontinuation of trametinib or trametinib and dabrafenib combination was required. Signs or symptoms of rhabdomyolysis should warrant an appropriate clinical evaluation and treatment as indicated.

Renal failure

Renal failure has been identified in patients treated with trametinib in combination with dabrafenib in clinical trials. Please refer to the dabrafenib Prescribing Information (section 4.4).

Pancreatitis

Pancreatitis has been reported in patients treated with trametinib in combination with dabrafenib in clinical trials. Please refer to the dabrafenib Prescribing Information (section 4.4).

Hepatic events

Hepatic adverse reactions have been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib (see section 4.8). It is recommended that patients receiving treatment with trametinib monotherapy or in combination with dabrafenib have liver function monitored every four weeks for 6 months after treatment initiation with trametinib. Liver monitoring may be continued

thereafter as clinically indicated.

Hepatic impairment

As metabolism and biliary excretion are the primary routes of elimination of trametinib, administration of trametinib should be undertaken with caution in patients with moderate to severe hepatic impairment (see sections 4.2 and 5.2).

Deep vein thrombosis (DVT)/Pulmonary embolism (PE)

Pulmonary embolism or deep vein thrombosis can occur when trametinib is used as monotherapy or in combination with dabrafenib. If patients develop symptoms of pulmonary embolism or deep vein thrombosis such as shortness of breath, chest pain, or arm or leg swelling, they should immediately seek medical care. Permanently discontinue trametinib and dabrafenib for life-threatening pulmonary embolism.

Severe cutaneous adverse reactions

Cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with dabrafenib/trametinib combination therapy. Before initiating treatment, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of SCARs appear, dabrafenib and trametinib should be withdrawn.

Gastrointestinal disorders

Colitis and gastrointestinal perforation, including fatal outcome, have been reported in patients taking trametinib as monotherapy and in combination with dabrafenib (see section 4.8). Treatment with trametinib monotherapy or in combination with dabrafenib should be used with caution in patients with risk factors for gastrointestinal perforation, including history of diverticulitis, metastases to the gastrointestinal tract and concomitant use of medicinal products with a recognised risk of gastrointestinal perforation.

Sarcoidosis

Cases of sarcoidosis have been reported in patients treated with trametinib in combination with dabrafenib, mostly involving the skin, lung, eye and lymph nodes. In the majority of the cases, treatment with trametinib and dabrafenib was maintained. In case of a diagnosis of sarcoidosis, relevant treatment should be considered. It is important not to misinterpret sarcoidosis as disease progression.

Haemophagocytic lymphohistiocytosis

In post-marketing experience, haemophagocytic lymphohistiocytosis (HLH) has been observed in patients treated with trametinib in combination with dabrafenib. Caution should be taken when trametinib is administered in combination with dabrafenib. If HLH is confirmed, administration of trametinib and dabrafenib should be discontinued and treatment for HLH initiated.

Tumour lysis syndrome (TLS)

The occurrence of TLS, which may be fatal, has been associated with the use of trametinib in combination with dabrafenib (see section 4.8). Risk factors for TLS include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension and acidic urine. Patients with risk factors for TLS should be closely monitored and prophylactic hydration should be considered. TLS should be treated promptly, as clinically indicated.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on trametinib

As trametinib is metabolised predominantly via deacetylation mediated by hydrolytic enzymes (e.g. carboxyl-esterases), its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions (see section 5.2). Drug-drug interactions via these hydrolytic enzymes cannot be ruled out and could influence the exposure to trametinib.

Trametinib is an *in vitro* substrate of the efflux transporter P-gp. As it cannot be excluded that strong inhibition of hepatic P-gp may result in increased levels of trametinib, caution is advised when co-administering trametinib with medicinal products that are strong inhibitors of P-gp (e.g. verapamil, cyclosporine, ritonavir, quinidine, itraconazole).

Effect of trametinib on other medicinal products

Based on *in vitro* and *in vivo* data, trametinib is unlikely to significantly affect the pharmacokinetics of other medicinal products via interaction with CYP enzymes or transporters (see section 5.2). Trametinib may result in transient inhibition of BCRP substrates (e.g. pitavastatin) in the gut, which may be minimised with staggered dosing (2 hours apart) of these agents and trametinib.

Based on clinical data, no loss of efficacy of hormonal contraceptives is expected when co-administered with trametinib monotherapy (see section 5.2).

Combination with dabrafenib

When trametinib is used in combination with dabrafenib see sections 4.4 and 4.5 of the dabrafenib Prescribing Information for interactions.

Effect of food on trametinib

Patients should take trametinib as monotherapy or in combination with dabrafenib at least one hour prior to or two hours after a meal due to the effect of food on trametinib absorption (see section 4.2 and 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Female patients of reproductive potential must be advised to use effective methods of contraception during treatment with trametinib and for at least 16 weeks after stopping treatment.

Use with dabrafenib may render hormonal contraceptives less effective and therefore an alternative method of contraception, such as a barrier method, should be used when trametinib is used in combination with dabrafenib. Refer to the dabrafenib Prescribing Information for further information.

Pregnancy

There are no adequate and well-controlled studies of trametinib in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). Trametinib should not be administered to pregnant

women. If trametinib is used during pregnancy, or if the patient becomes pregnant while taking trametinib, the patient should be informed of the potential hazard to the foetus.

Breast-feeding

It is not known whether trametinib is excreted in human milk. Because many medicinal products are excreted in human milk, a risk to the breast-feeding infant cannot be excluded. Trametinib should not be administered to breast-feeding mothers. A decision should be made whether to discontinue breast-feeding or discontinue trametinib, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data in humans for trametinib as monotherapy or in combination with dabrafenib. In animals, no fertility studies have been performed, but adverse effects were seen on female reproductive organs (see section 5.3). Trametinib may impair fertility in humans.

Men taking trametinib in combination with dabrafenib

Effects on spermatogenesis have been observed in animals given dabrafenib. Male patients taking trametinib in combination with dabrafenib should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. Refer to the dabrafenib Prescribing Information for further information.

4.7 Effects on ability to drive and use machines

Trametinib has minor influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor and cognitive skills. Patients should be made aware of potential for fatigue, dizziness or eye problems that might affect these activities.

4.8 Undesirable effects

Summary of the safety profile

The safety of trametinib monotherapy has been evaluated in the integrated safety population of 329 patients with BRAF V600 mutant unresectable or metastatic melanoma treated with trametinib 2 mg once daily in studies MEK114267, MEK113583, and MEK111054. Of these patients, 211 were treated with trametinib for BRAF V600 mutant melanoma in the randomised open label Phase III study MEK114267 (METRIC) (see section 5.1). The most common adverse reactions (incidence ≥20%) for trametinib were rash, diarrhoea, fatigue, oedema peripheral, nausea, and dermatitis acneiform.

The safety of trametinib in combination with dabrafenib has been evaluated in the integrated safety population of 1,076 patients with BRAF V600 mutant unresectable or metastatic melanoma Stage III BRAF V600 mutant melanoma following complete resection (adjuvant treatment) and advanced NSCLC treated with trametinib 2 mg once daily and dabrafenib 150 mg twice daily. Of these patients, 559 were treated with the combination for BRAF V600 mutant melanoma in two randomised Phase III studies, MEK115306 (COMBI-d) and MEK116513 (COMBI-v), 435 were treated with the combination in the adjuvant treatment of Stage III BRAF V600 mutant melanoma after complete resection in a randomised Phase III study BRF115532 (COMBI-AD) and 82 were treated with the combination for BRAF V600 mutant NSCLC in a multi-cohort, non-randomised Phase II study BRF113928 (see section 5.1).

The most common adverse reactions (incidence ≥ 20 %) for trametinib in combination with dabrafenib were: pyrexia, fatigue, nausea, chills, headache, diarrhoea, vomiting, arthralgia and rash.

The safety of trametinib when administered with dabrafenib was also evaluated in a multi-cohort, multi-center, non-randomized, open-label study in adult patients with cancers with the BRAF V600E mutation (Study BRF117019). A total of 206 patients were enrolled in the trial, 36 of whom were enrolled in the ATC cohort, 105 were enrolled in specific solid tumor cohorts, and 65 in other malignancies *(see section 5.1)* Patients received trametinib 2 mg orally once daily and dabrafenib 150 mg orally twice daily until disease progression or unacceptable toxicity.

Among these 206 patients, 101 (49%) were exposed to trametinib for ≥ 1 year and 103 (50%) were exposed to dabrafenib for ≥ 1 year. The median age was 60 years (range: 18 to 89); 56% were male; 79% were White; and 34% had baseline ECOG performance status of 0 and 60% had ECOG performance status of 1.

The adverse reaction profile among all patients in study BRF117019 was similar to that observed in other approved indications.

Tabulated list of adverse reactions

Adverse reactions associated with trametinib obtained from clinical studies and post marketing surveillance are tabulated below for trametinib monotherapy (Table 6) and trametinib in combination with dabrafenib (Table 7).

Adverse reactions are listed below by MedDRA system organ class.
The following convention has been utilised for the classification of frequency:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
Very rare <1/10,000
Not known (cannot be estimated from the available data)
Categories have been assigned based on absolute frequencies in the clinical trial data. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 6. Adverse reactions with trametinib monotherapy

System Organ Class	Frequency (all grades)	Adverse Reactions
Infections and infestations	Common	Folliculitis
		Paronychia
		Cellulitis
		Rash pustular
Blood and lymphatic system disorders	Common	Anaemia
Immune system disorders	Common	Hypersensitivity[a]
Metabolism and nutrition disorders	Common	Dehydration
Nervous system disorders	Common	Peripheral neuropathy (including sensory and motor neuropathy)
Eye disorders	Common	Vision blurred
		Periorbital oedema
		Visual impairment
	Uncommon	Chorioretinopathy
		Papilloedema
		Retinal detachment
		Retinal vein occlusion

Cardiac disorders	Common	Left ventricular dysfunction
		Ejection fraction decreased
		Bradycardia
	Uncommon	Cardiac failure
	Not known	Atrioventricular block[b]
Vascular disorders	Very common	Hypertension
		Haemorrhage[c]
	Common	Lymphoedema
Respiratory, thoracic and mediastinal disorders	Very common	Cough
		Dyspnoea
	Common	Pneumonitis
	Uncommon	Interstitial lung disease
Gastrointestinal disorders	Very common	Diarrhoea
		Nausea
		Vomiting
		Constipation
		Abdominal pain
		Dry mouth
	Common	Stomatitis
	Uncommon	Gastrointestinal perforation
		Colitis
Skin and subcutaneous tissue disorders	Very common	Rash
		Dermatitis acneiform
		Dry skin
		Pruritus
		Alopecia
	Common	Erythema
		Palmar-plantar erythrodysaesthesia syndrome
		Skin fissures
		Skin chapped
Musculoskeletal and connective tissue disorders	Uncommon	Rhabdomyolysis
General disorders and administration site conditions	Very common	Fatigue
		Oedema peripheral
		Pyrexia
	Common	Face oedema
		Mucosal inflammation
		Asthenia
Investigations	Very common	Aspartate aminotransferase increased
	Common	Alanine aminotransferase increased
		Blood alkaline phosphatase increased
		Blood creatine phosphokinase increased

[a] May present with symptoms such as fever, rash, increased liver transaminases, and visual disturbances.
[b] Including atrioventricular block complete.
[c] Events include but are not limited to: epistaxis, haematochezia, gingival bleeding, haematuria, and rectal, haemorrhoidal, gastric, vaginal, conjunctival, intracranial and post procedural haemorrhage.

Table 7. Adverse reactions with trametinib in combination with dabrafenib

System Organ Class	Frequency (all grades)	Adverse Reactions
Infections and infestations	Very common	Nasopharyngitis
	Common	Urinary tract infection
		Cellulitis
		Folliculitis
		Paronychia
		Rash pustular
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Cutaneous squamous cell carcinoma[a]
		Papilloma[b]
		Seborrhoeic keratosis
	Uncommon	New primary melanoma[c]
		Acrochordon (skin tags)
Blood and lymphatic system disorders	Common	Neutropenia
		Anaemia
		Thrombocytopenia
		Leukopenia
Immune system disorders	Uncommon	Hypersensitivity[d]
		Sarcoidosis
	Rare	Haemophagocytic lymphohistiocytosis
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Dehydration
		Hyponatraemia
		Hypophosphataemia
		Hyperglycaemia
	Not known	Tumour lysis syndrome
Nervous system disorders	Very common	Headache
		Dizziness
	Common	Peripheral neuropathy (including sensory and motor neuropathy)
Eye disorders	Common	Vision blurred
		Visual impairment
		Uveitis
	Uncommon	Chorioretinopathy
		Retinal detachment
		Periorbital oedema
Cardiac disorders	Common	Ejection fraction decreased
	Uncommon	Atrioventricular block[e]
		Bradycardia
	Not known	Myocarditis
Vascular disorders	Very common	Hypertension
		Haemorrhage[f]
	Common	Hypotension
		Lymphoedema

Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea
	Uncommon	Pneumonitis
Gastrointestinal disorders	Very common	Abdominal pain[g]
		Constipation
		Diarrhoea
		Nausea
		Vomiting
	Common	Dry mouth
		Stomatitis
	Uncommon	Pancreatitis
		Colitis
	Rare	Gastrointestinal perforation
Skin and subcutaneous tissue disorders	Very common	Dry skin
		Pruritus
		Rash
		Erythema[h]
	Common	Dermatitis acneiform
		Actinic keratosis
		Night sweats
		Hyperkeratosis
		Alopecia
		Palmar-plantar erythrodysaesthesia syndrome
		Skin lesion
		Hyperhidrosis
		Panniculitis
		Skin fissures
		Photosensitivity
	Not Known	Stevens-Johnson syndrome
		Drug reaction with eosinophilia and systemic symptoms
		Dermatitis exfoliative generalised

Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
		Muscle spasms[i]
Renal and urinary disorders	Uncommon	Renal failure
		Nephritis
General disorders and administration site conditions	Very common	Fatigue
		Chills
		Asthenia
		Oedema peripheral
		Pyrexia
		Influenza-like illness
	Common	Mucosal inflammation
		Face oedema
Investigations	Very common	Alanine aminotransferase increased
		Aspartate aminotransferase increased
	Common	Blood alkaline phosphatase increased
		Gamma-glutamyltransferase increased
		Blood creatine phosphokinase increased

The safety profile from MEK116513 is generally similar to that of MEK115306 with the following exceptions: 1) The following adverse reactions have a higher frequency category as compared to MEK115306: muscle spasm (very common); renal failure and lymphoedema (common); acute renal failure (uncommon); 2) The following adverse reactions have occurred in MEK116513 but not in MEK115306: cardiac failure, left ventricular dysfunction, interstitial lung disease (uncommon); 3) The following adverse reaction has occurred in MEK116513 and BRF115532 but not in MEK115306 and BRF113928: rhabdomyolysis (uncommon).

[a] Cutaneous squamous cell carcinoma (cuSCC): SCC, SCC of the skin, SCC *in situ* (Bowen's disease) and keratoacanthoma

[b] Papilloma, skin papilloma

[c] Malignant melanoma, metastatic malignant melanoma, and superficial spreading melanoma Stage III

[d] Includes drug hypersensitivity

[e] Including atrioventricular block complete

[f] Bleeding from various sites, including intracranial bleeding and fatal bleeding

[g] Abdominal pain upper and abdominal pain lower

[h] Erythema, generalised erythema

[i] Muscle spasms, musculoskeletal stiffness

Description of selected adverse reactions

New malignancies

New malignancies, cutaneous and non-cutaneous, can occur when trametinib is used in combination with dabrafenib. Please refer to the dabrafenib Prescribing Information.

Haemorrhage

Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages, occurred in patients taking trametinib as monotherapy and in combination with dabrafenib. The majority of bleeding events were mild. Fatal intracranial haemorrhages occurred in the integrated safety population of trametinib in combination with dabrafenib in <1% (8/1076) of patients. The median time to onset of the first occurrence of haemorrhagic events for the combination of trametinib and dabrafenib was 94 days in the melanoma Phase III studies and 75 days in the NSCLC study for the patients who had received prior anti-cancer therapy.

The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy. If haemorrhage occurs, treat as clinically indicated (see section 4.4).

LVEF reduction/Left ventricular dysfunction

Trametinib has been reported to decrease LVEF when used as monotherapy or in combination with dabrafenib. In clinical trials, the median time to first occurrence of left ventricular dysfunction, cardiac failure and LVEF decrease was between 2 to 5 months. In the integrated safety population of trametinib in combination with dabrafenib, decreased LVEF has been reported in 6% (65/1076) of patients, with most cases being asymptomatic and reversible. Patients with LVEF lower than the institutional lower limit of normal were not included in clinical trials with trametinib. Trametinib should be used with caution in patients with conditions that could impair left ventricular function (see sections 4.2 and 4.4).

Pyrexia

Pyrexia has been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib; however, the incidence and severity of pyrexia are increased with the combination therapy. Please refer to sections 4.4 and 4.8 of the dabrafenib Prescribing Information.

Hepatic events

Hepatic adverse reactions have been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib. Of the hepatic adverse reactions, increased ALT and AST were the most common events and the majority were either Grade 1 or 2. For trametinib monotherapy, more than 90% of these liver events occurred within the first 6 months of treatment. Liver events were detected in clinical trials with monitoring every four weeks. It is recommended that patients receiving treatment with trametinib monotherapy or in combination with dabrafenib have liver function monitored every four weeks for 6 months. Liver monitoring may be continued thereafter as clinically indicated (see section 4.4).

Hypertension

Elevations in blood pressure have been reported in association with trametinib as monotherapy and in combination with dabrafenib, in patients with or without pre-existing hypertension. Blood pressure should be measured at baseline and monitored during treatment, with control of hypertension by standard therapy as appropriate (see section 4.4).

Interstitial lung disease (ILD)/Pneumonitis

Patients treated with trametinib or combination with dabrafenib may develop ILD or pneumonitis. Trametinib should be withheld in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. For patients diagnosed with treatment-related ILD or pneumonitis trametinib should be permanently discontinued (see sections 4.2 and 4.4).

Visual impairment

Disorders associated with visual disturbances, including RPED and RVO, have been observed with trametinib. Symptoms such as blurred vision, decreased acuity, and other visual disturbances have been reported in the clinical trials with trametinib (see sections 4.2 and 4.4).

Rash

Rash has been observed in about 60% of patients when given as monotherapy and in about 24% of patients in trametinib and dabrafenib combination studies in the integrated safety population. The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions

(see sections 4.2 and 4.4).

Rhabdomyolysis

Rhabdomyolysis has been reported in patients taking trametinib alone or in combination with dabrafenib. Signs or symptoms of rhabdomyolysis should warrant an appropriate clinical evaluation and treatment as indicated (see section 4.4).

Pancreatitis

Pancreatitis has been reported with dabrafenib in combination with trametinib. Please see the dabrafenib Prescribing Information.

Renal failure

Renal failure has been reported with dabrafenib in combination with trametinib. Please see the dabrafenib Prescribing Information.

Special populations

Paediatric

Pediatric Safety Pool

The pediatric pooled safety population reflects exposure to weight-based trametinib orally, once daily administered in combination with dabrafenib in 166 pediatric patients across two trials: a multi-center, open-label, multi-cohort study in pediatric patients with BRAF V600E mutation-positive glioma requiring systemic therapy (Study G2201; n = 123) and a multi-center, open-label, multi-cohort study in pediatric patients with refractory or recurrent solid tumors with MAPK pathway activation (Study X2101; n = 43) (see section 5.1). Among 166 patients who received trametinib administered with dabrafenib, 85% were exposed for 6 months and 69% were exposed for greater than one year. The most common (> 20%) adverse reactions were pyrexia (66%), rash (54%), headache (40%), vomiting (38%), musculoskeletal pain (36%), fatigue (31%), dry skin (31%), diarrhea (30%), nausea (26%), epistaxis and other bleeding events (25%), abdominal pain (24%), and dermatitis acneiform (23%). The most common (> 2%) Grade 3 or 4 laboratory abnormalities were decreased neutrophil count (20%), increased alanine aminotransferase (3.1%), and increased aspartate aminotransferase (3.1%).

BRAF V600E Mutation-Positive Solid Tumors in Pediatric Patients

Study CTMT212X2101 (X2101)

The safety of trametinib when administered with dabrafenib was evaluated in Study X2101, a multi-center, open-label, multi-cohort study in pediatric patients (n=48) with refractory or recurrent solid tumors activation *(see section 5.1)* The median duration of exposure to trametinib in Parts C (dose escalation) and D (cohort expansion) was 20.8 and 24.4 months, respectively. The median duration of exposure to dabrafenib in Parts C and D was 20.8 and 24.9 months, respectively. The median age of pediatric patients who received trametinib with dabrafenib was 9 years (range: 1 to 17).

Serious adverse reactions occurred in 46% of patients who received trametinib in combination with dabrafenib. Serious adverse reactions in > 5% of patients included pyrexia (25%) and decreased ejection fraction (6%). Permanent treatment discontinuation due to an adverse reaction occurred in 21% of patients. Adverse reactions which resulted in permanent treatment discontinuation in > 3% of patients included increased ALT (6%), increased AST (4.2%) and decreased ejection fraction (4.2%). Dose interruptions due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dose interruption in > 5% of patients included pyrexia (56%), vomiting (19%), neutropenia (13%), rash (13%), decreased ejection fraction (6%) and uveitis (6%).

Dose reductions due to an adverse reaction occurred in 25% of patients. Adverse reactions which required dose reductions in > 5% of patients included pyrexia (13%).

The most common (≥20%) adverse reactions, including laboratory abnormalities, are listed in Table 8 and Table 9.

Table 8 summarizes the adverse reactions in Study X2101.

Table 8. Adverse Reactions (≥20%) in Pediatric Patients Treated with Trametinib Plus Dabrafenib in Study X2101

Adverse Reactions	Trametinib plus Dabrafenib[a] (N=48)	
	All Grades (%)	Grade 3 or 4 (%)
General		
Pyrexia	75	17
Fatigue[b]	48	0
Skin and subcutaneous tissue		
Rash[c]	73	2.1
Dry skin	48	0
Dermatitis acneiform[d]	40	0
Gastrointestinal		
Vomiting	52	4.2
Diarrhea	42	2.1
Abdominal pain[e]	33	4.2
Nausea	33	2.1
Constipation	23	0
Respiratory system		
Cough	44	0
Nervous system		
Headache	35	0
Vascular		
Hemorrhage[f]	33	0
Infections and infestations		
Paronychia	23	0

[a] NCI CTCAE version 4.0.
[b] Includes fatigue, asthenia and malaise.
[c] Includes rash, rash maculo-papular, rash erythematous, rash papular, rash pustular, and rash macular.
[d] Includes dermatitis acneiform and acne.
[e] Includes abdominal pain and abdominal pain upper.
[f] Includes epistaxis, hematuria, contusion, hematoma, petechiae, rectal hemorrhage, and red blood cell count decreased.

Clinically relevant adverse reactions for trametinib in Study X2101 observed in less than 20% of patients (N=48) who received trametinib in combination with dabrafenib were: atrioventricular block (2.1%).

Table 9 summarizes the laboratory abnormalities in Study X2101.

Table 9. Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in Pediatric Patients Treated with Trametinib Plus Dabrafenib in Study X2101

Laboratory Abnormality	Trametinib plus Dabrafenib[a]	
	All Grades (%)	Grade 3 or 4 (%)
Chemistry		
Hyperglycemia	65	2.2
Hypoalbuminemia	48	2.1
Hypocalcemia	40	2.1
Decreased phosphate	38	0
Decreased magnesium	33	2.1

Hypernatremia	27	0
Hypokalemia	21	2.1
Hepatic		
Increased AST	55	4.2
Increased ALT	40	6
Increased alkaline phosphatase	28	6
Increased total bilirubin	21	2.1
Hematology		
Decreased hemoglobin	60	6
Decreased neutrophils	49	28

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a] The denominator used to calculate the rate varied from 39 to 48 based on the number of patients with a baseline value and at least one post-treatment value.

BRAF V600E Mutation-Positive Low-Grade Glioma in Pediatric Patients

Study CDRB436G2201 (G2201)

The safety of trametinib in combination with dabrafenib was evaluated in pediatric patients 1 to < 18 years of age in Study G2201. Patients with low-grade glioma (LGG) who required first systemic therapy were randomized (2:1) to trametinib plus dabrafenib (n = 73) or carboplatin plus vincristine (n = 33). Nine patients crossed over from the carboplatin plus vincristine arm to the trametinib and dabrafenib arm. Pediatric patients received weight-based trametinib orally once daily administered in combination with dabrafenib until disease progression or intolerable toxicity. Patients in the control arm received carboplatin and vincristine at doses of 175 mg/m^2 and 1.5 mg/m^2, respectively in 10-week induction course followed by eight 6-week cycles of maintenance therapy or until disease progression or intolerable toxicity. Among patients with low-grade glioma who were randomized to trametinib plus dabrafenib (n = 73), 95% were exposed for 6 months or longer and 71% were exposed for greater than one year.

The median age of these patients was 10 years (range: 1 to 17); 60% female; 75% White, 7% Asian, 2.7% Black or African American, 4% other race and 11% where race was unknown or not reported.

Serious adverse reactions occurred in 40% of these patients. Serious adverse reactions in > 3% of patients included pyrexia (14%) and vomiting (4%).

Permanent discontinuation of trametinib due to an adverse reaction occurred in 4% of patients. Adverse reactions which resulted in permanent discontinuation of trametinib included chills, fatigue, pyrexia, weight increased, and headache.

Dosage interruptions of trametinib due to an adverse reaction occurred in 70% of patients. Adverse reactions which required a dosage interruption in > 5% of patients included pyrexia (52%).

Dose reductions of trametinib due to an adverse reaction occurred in 12% of patients. Adverse reactions which required dose reductions in > 2% of patients included weight increased (2.7%).

The most common (≥ 15%) adverse reactions were pyrexia (68%), rash (51%), headache (47%), vomiting (34%), musculoskeletal pain (34%), fatigue (33%), diarrhea (29%), dry skin (26%), nausea (25%), hemorrhage (25%), abdominal pain (25%), dermatitis acneiform (22%), dizziness (15%), upper respiratory tract infection (15%), and weight increased (15%).

The most common (≥ 20%) laboratory abnormalities that worsened from baseline were leukopenia (59%), increased alkaline phosphatase (55%), anemia (46%), decreased neutrophils (44%), increased AST (37%), decreased magnesium (34%), increased magnesium (32%), decreased platelets (30%), increased ALT (29%), and increased lymphocytes (24%).

Table 10 summarizes the adverse reactions in Study G2201.

Table 10. Adverse Reactions (≥ 15%) in Pediatric LGG Patients Who Received Trametinib in Combination with Dabrafenib in Study G2201[a]

Adverse Reactions	Trametinib plus Dabrafenib N = 73		Carboplatin plus Vincristine N = 33	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Gastrointestinal				
Vomiting	34	1	48	3
Diarrhea[b]	29	0	18	6
Nausea	25	0	45	0
Abdominal pain[c]	25	0	24	0
Constipation	12	0	36	0
Stomatitis[d]	10	0	18	0
General				
Pyrexia[e]	68	8	18	3
Fatigue[f]	33	0	39	0
Nervous system				
Headache[g]	47	1	33	3
Dizziness[h]	15	0	9	3
Peripheral neuropathy[i]	7	0	45	6
Vascular				
Hemorrhage[j]	25	0	12	0
Skin and subcutaneous tissue				
Rash[k]	51	2.7	18	3
Dry skin	26	0	3	0
Dermatitis acneiform[l]	22	0	0	0
Alopecia	3	0	24	0
Musculoskeletal and connective tissue				
Musculoskeletal pain[m]	34	0	30	0
Pain in jaw	1.4	0	18	0
Metabolism and nutrition				
Decreased appetite	5	0	24	0
Respiratory, thoracic and mediastinal				
Oropharyngeal pain	11	0	18	0
Psychiatric				
Anxiety	1.4	0	15	3
Immune system				
Hypersensitivity	0	0	15	3
Infections and infestations				
Upper respiratory tract infection	15	0	6	0
Injury, poisoning and procedural complications				
Infusion related reaction	0	0	15	3
Investigations				
Weight increased	15	7	0	0

[a]NCI CTCAE version 4.03.
[b]Includes diarrhea, colitis, enterocolitis, and enteritis.
[c]Includes abdominal pain and upper abdominal pain.
[d]Includes stomatitis, cheilitis, mouth ulceration, aphthous ulcer, and glossitis.
[e]Includes pyrexia and body temperature increased.
[f]Includes fatigue and asthenia.
[g]Includes headache and migraine with aura.
[h]Includes dizziness and vertigo.
[i]Includes peripheral neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paresthesia, neuralgia, hypoaesthesia, and peripheral sensory neuropathy.
[j]Includes epistaxis, post-procedural hemorrhage, hematuria, upper gastrointestinal hemorrhage, and hemorrhage intracranial.
[k]Includes rash, rash macular, rash maculo-papular, rash pustular, rash papular, rash erythematous, eczema, erythema multiforme, dermatitis, dermatitis exfoliative, skin exfoliation, palmar-plantar erythrodysaesthesia syndrome, and dermatitis bullous.
[l]Includes dermatitis acneiform, acne, and acne pustular.
[m]Includes back pain, myalgia, pain in extremity, arthralgia, bone pain, non-cardiac chest pain, neck pain, and musculoskeletal stiffness.

Table 11 summarizes the laboratory abnormalities in Study G2201.

Table 11. Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Pediatric LGG Patients Who Received Trametinib in Combination with Dabrafenib in Study G2201[a]

Laboratory Abnormality	Trametinib plus Dabrafenib N = 73		Carboplatin plus Vincristine N = 33	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hepatic				
Increased alkaline phosphatase	55	0	13	0
Increased AST	37	1.4	55	0
Increased ALT	29	3	61	9
Chemistry				
Decreased magnesium	34	4.1	76	6
Increased magnesium	32	0	24	3
Increased potassium	15	4.2	21	6
Decreased calcium	14	4.1	22	9
Decreased potassium	8	1.4	70	0
Decreased phosphate	7	2.7	33	3
Decreased sodium	5	1.4	27	6
Increased serum fasting glucose	0	0	44	0
Hematology				
Decreased leukocytes	59	0	91	18
Decreased hemoglobin	46	0	94	36
Decreased neutrophils	44	17	84	75
Decreased platelets	30	0	73	18
Increased lymphocytes	24	0	13	3.1
Decreased lymphocytes	16	1.4	56	6

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]The denominator used to calculate the rate varied from 70 to 73 in D+T arm and 9 to 33 in C + V arm based on the number of patients with a baseline value and at least one post-treatment value.

Elderly

In the Phase III study with trametinib in patients with unresectable or metastatic melanoma (n = 211), 49 patients (23%) were ≥65 years of age, and 9 patients (4%) were ≥75 years of age. The proportion of subjects experiencing adverse reactions (AR) and serious adverse reactions (SAR) was similar in the subjects aged <65 years and those aged ≥65 years. Patients ≥65 years were more likely to experience ARs leading to permanent discontinuation of medicinal product, dose reduction and dose interruption than those <65 years.

In the integrated safety population of trametinib in combination with dabrafenib (n=1,076) 265 patients (25%) were ≥65 years of age; 62 patients (6%) were ≥75 years of age. The proportion of patients experiencing ARs was similar in those aged <65 years and those aged ≥65 years in all studies. Patients ≥65 years were more likely to experience SARs and ARs leading to permanent discontinuation of medicinal product, dose reduction and dose interruption than those <65 years.

Of the 26 patients with ATC who received trametinib in Study BRF117019, 77% were aged 65 years and older and 31% were aged 75 years and older (see section 5.1). This study did not include sufficient numbers of younger adults to determine whether they respond differently compared to geriatric patients.

Renal impairment

No dosage adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Trametinib should be used with caution in patients with severe renal impairment (see sections 4.2 and 4.4).

Hepatic impairment

No dosage adjustment is required in patients with mild hepatic impairment (see section 5.2). Trametinib should be used with caution in patients with moderate or severe hepatic impairment (see sections 4.2 and 4.4)

Trametinib in combination with dabrafenib in patients with brain metastases

The safety and efficacy of the combination of trametinib and dabrafenib have been evaluated in a multi-cohort, open-label, Phase II study in patients with BRAF V600 mutant melanoma with brain metastases. The safety profile observed in these patients appears to be consistent with the integrated safety profile of the combination.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il
And to Novartis using the following email address: safetydesk.israel@novartis.com

4.9 Overdose

In clinical trials with trametinib monotherapy one case of accidental overdose was reported; a single dose of 4 mg. No AEs were reported following this event of trametinib overdose. In clinical trials with the combination of trametinib and dabrafenib 11 patients reported trametinib overdose (4 mg); no SAEs were reported. There is no specific treatment for overdose. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitor, Mitogen-activated protein

kinase (MEK) inhibitors, ATC code: L01EE01

Mechanism of action

Trametinib is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. MEK proteins are components of the extracellular signal-related kinase (ERK) pathway. In melanoma and other cancers, this pathway is often activated by mutated forms of BRAF which activates MEK. Trametinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity. Trametinib inhibits growth of BRAF V600 mutant melanoma cell lines and demonstrates anti-tumour effects in BRAF V600 mutant melanoma animal models.

In the setting of BRAF-mutant colorectal cancer, induction of EGFR-mediated MAPK pathway re-activation has been identified as a mechanism of intrinsic resistance to BRAF inhibitors *(see section 4.1)*.

Combination with dabrafenib

Dabrafenib is an inhibitor of RAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway. Thus, trametinib and dabrafenib inhibit two kinases in this pathway, MEK and RAF, and therefore the combination provides concomitant inhibition of the pathway. The combination of trametinib with dabrafenib has shown anti-tumour activity in BRAF V600 mutation-positive melanoma cell lines *in vitro* and delays the emergence of resistance *in vivo* in BRAF V600 mutation-positive melanoma xenografts.

Determination of BRAF mutation status

Before taking trametinib or the combination with dabrafenib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test.

In clinical trials, central testing for BRAF V600 mutation using a BRAF mutation assay was conducted on the most recent tumour sample available. Primary tumour or tumour from a metastatic site was tested with a validated polymerase chain reaction (PCR) assay developed by Response Genetics Inc. The assay was specifically designed to differentiate between the V600E and V600K mutations. Only patients with BRAF V600E or V600K mutation-positive tumours were eligible for study participation.

Subsequently, all patient samples were re-tested using the CE-marked bioMerieux (bMx) THxID BRAF validated assay. The bMx THxID BRAF assay is an allele-specific PCR performed on DNA extracted from FFPE tumour tissue. The assay was designed to detect the BRAF V600E and V600K mutations with high sensitivity (down to 5% V600E and V600K sequence in a background of wild-type sequence using DNA extracted from FFPE tissue). Non-clinical and clinical trials with retrospective bi-directional Sanger sequencing analyses have shown that the test also detects the less common BRAF V600D mutation and V600E/K601E mutation with lower sensitivity. Of the specimens from the non-clinical and clinical trials (n = 876) that were mutation-positive by the THxID BRAF assay and subsequently were sequenced using the reference method, the specificity of the assay was 94%.

Pharmacodynamic effects

Trametinib suppressed levels of phosphorylated ERK in BRAF mutant melanoma tumour cell lines and melanoma xenograft models.

In patients with BRAF and NRAS mutation-positive melanoma, administration of trametinib resulted in dose-dependent changes in tumour biomarkers including inhibition of phosphorylated ERK, inhibition of Ki67 (a marker of cell proliferation) and increases in p27 (a marker of apoptosis). The

mean trametinib concentrations observed following repeat dose administration of 2 mg once daily exceeds the preclinical target concentration over the 24-hr dosing interval, thereby providing sustained inhibition of the MEK pathway.

Clinical efficacy and safety

Unresectable or metastatic melanoma
In the clinical trials only patients with cutaneous melanoma were studied. Efficacy in patients with ocular or mucosal melanoma has not been assessed.

- *Trametinib in combination with dabrafenib*

Treatment naïve patients
The efficacy and safety of the recommended dose of trametinib (2 mg once daily) in combination with dabrafenib (150 mg-twice daily) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation was studied in two Phase III studies and one supportive Phase I/II study.

MEK115306 (COMBI-d):
MEK115306 was a Phase III, randomised, double-blinded study comparing the combination of dabrafenib and trametinib to dabrafenib and placebo in first-line therapy for subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The primary endpoint of the study was progression-free survival (PFS), with a key secondary endpoint of overall survival (OS). Subjects were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ULN) and BRAF mutation (V600E versus V600K).

A total of 423 subjects were randomised 1:1 to either combination (N = 211) or dabrafenib (N = 212). Most subjects were Caucasian (>99%) and male (53%), with a median age of 56 years (28% were ≥65 years). The majority of subjects had Stage IVM1c disease (67%). Most subjects had LDH ≤ULN (65%), Eastern Cooperative Oncology Group (ECOG) performance status of 0 (72%), and visceral disease (73%) at baseline. The majority of subjects had a BRAF V600E mutation (85%). Subjects with brain metastases were not included in the trial.

Median OS and estimated 1-year, 2-year, 3-year, 4-year and 5-year survival rates are presented in Table 12. From an OS analysis at 5 years, the median OS for the combination arm was approximately 7 months longer than for dabrafenib monotherapy (25.8 months versus 18.7 months) with 5-year survival rates of 32% for the combination versus 27% for dabrafenib monotherapy (Table 12, Figure 1). The Kaplan-Meier OS curve appears to stabilise from 3 to 5 years (see Figure 1). The 5-year overall survival rate was 40% (95% CI: 31.2, 48.4) in the combination arm versus 33% (95% CI: 25.0, 41.0) in the dabrafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 8.4, 26.0) in the combination arm versus 14% (95% CI: 6.8, 23.1) in the dabrafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline.

Table 12. Overall Survival results for Study MEK115306 (COMBI-d)

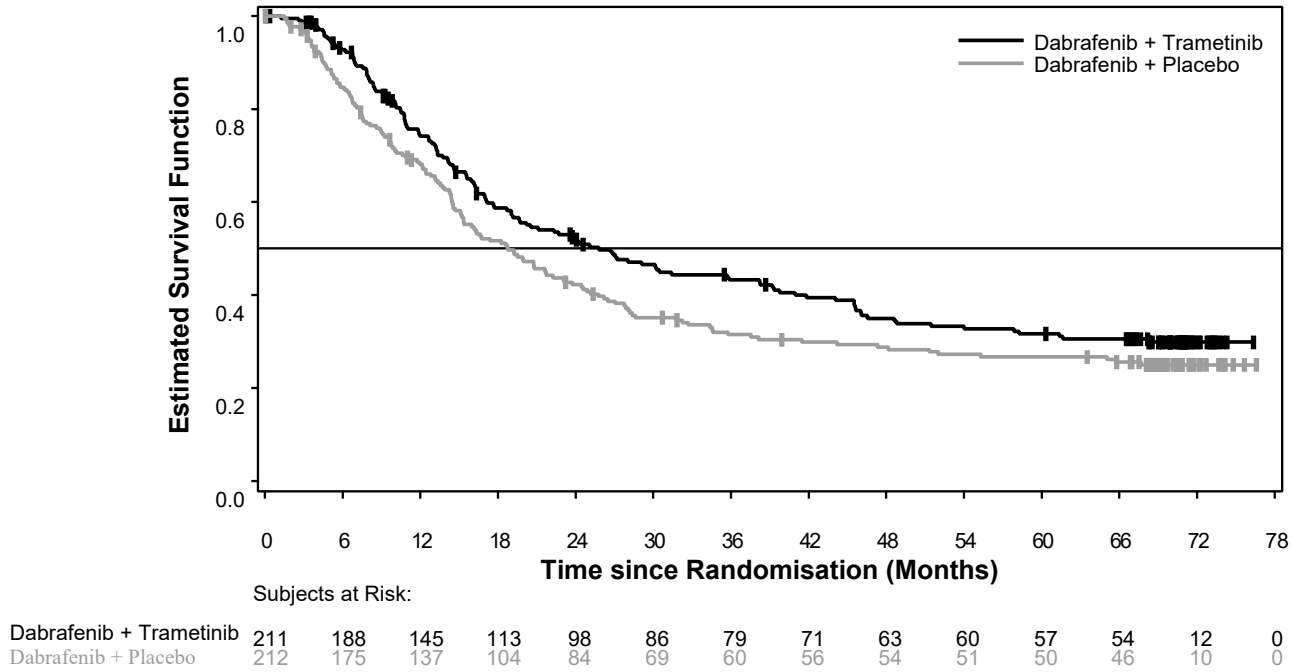
	OS analysis (data cut-off: 12-Jan-2015)		**5-year OS analysis (data cut-off: 10-Dec-2018)**	
	Dabrafenib + Trametinib (n=211)	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib+ Placebo (n=212)**
Number of patients				
Died (event), n (%)	99 (47)	123 (58)	135 (64)	151 (71)
Estimates of OS (months)				

Median (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.7)	25.8 (19.2, 38.2)	18.7 (15.2, 23.1)
Hazard ratio (95% CI)	0.71 (0.55, 0.92)		0.80 (0.63, 1.01)	
p-value	0.011		NA	

Overall survival estimate, % (95% CI)	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**
At 1 year	74 (66.8, 79.0)	68 (60.8, 73.5)
At 2 years	52 (44.7, 58.6)	42 (35.4, 48.9)
At 3 years	43 (36.2, 50.1)	31 (25.1, 37.9)
At 4 years	35 (28.2, 41.8)	29 (22.7, 35.2)
At 5 years	32 (25.1, 38.3)	27 (20.7, 33.0)

NR = Not reached, NA = Not applicable

Figure 1 Kaplan-Meier overall survival curves for Study MEK115306 (ITT population)



Improvements for the primary endpoint of PFS were sustained over a 5 year timeframe in the combination arm compared to dabrafenib monotherapy. Improvements were also observed for overall response rate (ORR) and a longer duration of response (DoR) was observed in the combination arm compared to dabrafenib monotherapy (Table 13).

Table 13. Efficacy results for Study MEK115306 (COMBI-d)

	Primary analysis (data cut-off: 26-Aug-2013)		**Updated analysis (data cut-off: 12-Jan-2015)**		**5-year analysis (data cut-off: 10-Dec-2018)**	
Endpoint	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**
PFS[a]						

Progressive disease or death, n (%)	102 (48)	109 (51)	139 (66)	162 (76)	160 (76)	166 (78)
Median PFS (months) (95% CI)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)	10.2 (8.1, 12.8)	8.8 (5.9, 9.3)
Hazard Ratio (95% CI)	0.75 (0.57, 0.99)		0.67 (0.53, 0.84)		0.73 (0.59, 0.91)	
P value	0.035		<0.001[f]		NA	
ORR[b] % (95% CI)	67 (59.9, 73.0)	51 (44.5, 58.4)	69 (61.8, 74.8)	53 (46.3, 60.2)	69 (62.5, 75.4)	54 (46.8, 60.6)
ORR difference (95% CI)	15[e] (5.9, 24.5)		15[e] (6.0, 24.5)		NA	
P value	0.0015		0.0014[f]		NA	
DoR[c] **(months)** Median (95% CI)	9.2[d] (7.4, NR)	10.2[d] (7.5, NR)	12.9 (9.4,19.5)	10.6 (9.1, 13.8)	12.9 (9.3, 18.4)	10.2 (8.3, 13.8)

a – Progression-free survival (investigator assessed)
b – Overall Response Rate = Complete Response + Partial Response
c – Duration of response
d – At the time of the reporting the majority (≥59%) of investigator-assessed responses were still ongoing.
e – ORR difference calculated based on the ORR result not rounded
f – Updated analysis was not pre-planned and the p-value was not adjusted for multiple testing
NR = Not reached
NA = Not applicable

MEK116513 (COMBI-v):
Study MEK116513 was a 2-arm, randomised, open-label, Phase III study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive unresectable or metastatic melanoma. The primary endpoint of the study was OS with a key secondary endpoint of PFS. Subjects were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ULN) and BRAF mutation (V600E versus V600K).

A total of 704 subjects were randomised 1:1 to either combination or vemurafenib. Most subjects were Caucasian (>96%) and male (55%), with a median age of 55 years (24% were ≥65 years). The majority of subjects had Stage IV M1c disease (61% overall). Most subjects had LDH ≤ULN (67%), ECOG performance status of 0 (70%), and visceral disease (78%) at baseline. Overall, 54% of subjects had <3 disease sites at baseline. The majority of subjects had BRAF V600E mutation-positive melanoma (89%). Subjects with brain metastases were not included in the trial.

Median OS and estimated 1-year, 2-year, 3-year, 4-year and 5-year survival rates are presented in Table 14. From an OS analysis at 5 years, the median OS for the combination arm was approximately 8 months longer than the median OS for vemurafenib monotherapy (26.0 months versus 17.8 months) with 5-year survival rates of 36% for the combination versus 23% for vemurafenib monotherapy (Table 14, Figure 2). The Kaplan-Meier OS curve appears to stabilise from 3 to 5 years (see Figure 2). The 5-year overall survival rate was 46% (95% CI: 38.8, 52.0) in the combination arm versus 28% (95% CI: 22.5, 34.6) in the vemurafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 9.3, 23.3) in the combination arm versus 10% (95% CI: 5.1, 17.4) in the vemurafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline.

Table 14. Overall Survival results for Study MEK116513 (COMBI-v)

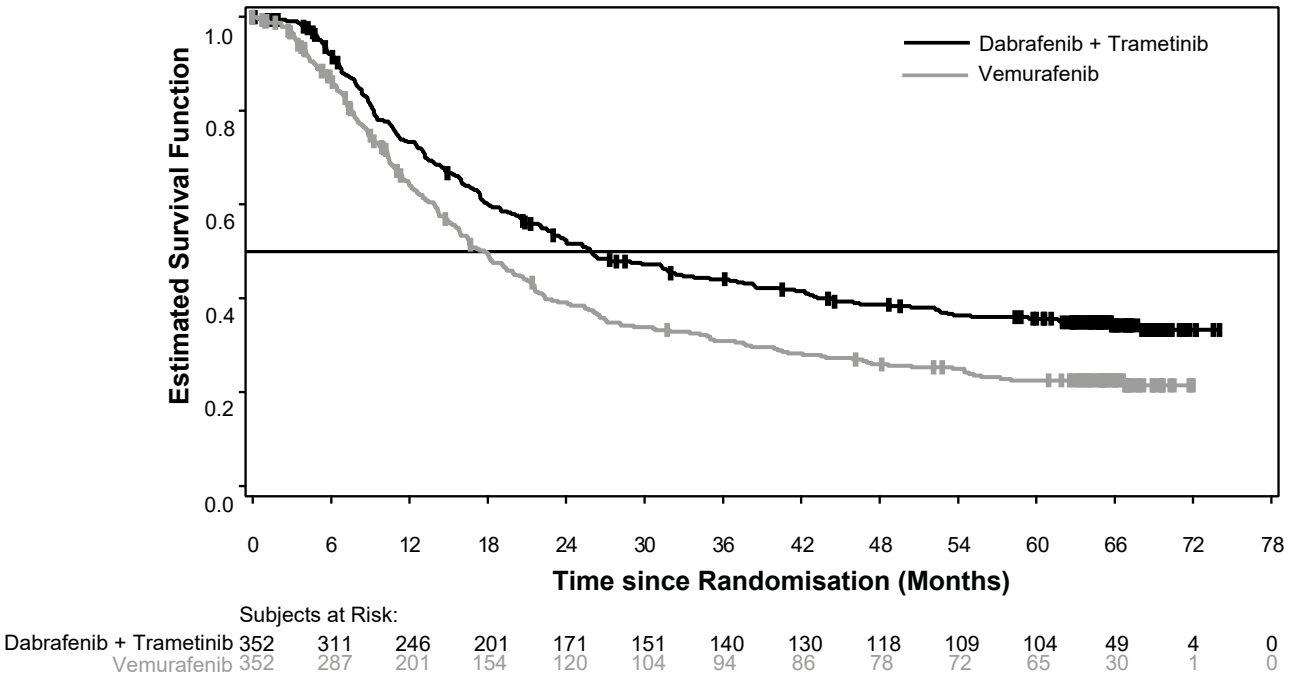
	OS analysis data cut-off: 13-Mar-2015)	**5-year OS analysis (data cut-off: 08-Oct-2018)**

	Dabrafenib + Trametinib (n=352)	Vemurafenib (n=352)	Dabrafenib + Trametinib (n=352)	Vemurafenib (n=352)
Number of patients				
Died (event), n (%)	155 (44)	194 (55)	216 (61)	246 (70)
Estimates of OS (months)				
Median (95% CI)	25.6 (22.6, NR)	18.0 (15.6, 20.7)	26.0 (22.1, 33.8)	17.8 (15.6, 20.7)
Adjusted hazard ratio (95% CI)	0.66 (0.53, 0.81)		0.70 (0.58, 0.84)	
p-value	<0.001		NA	

Overall survival estimate, % (95% CI)	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
At 1 year	72 (67, 77)	65 (59, 70)
At 2 years	53 (47.1, 57.8)	39 (33.8, 44.5)
At 3 years	44 (38.8, 49.4)	31 (25.9, 36.2)
At 4 years	39 (33.4, 44.0)	26 (21.3, 31.0)
At 5 years	36 (30.5, 40.9)	23 (18.1, 27.4)

NR = Not reached, NA = Not applicable

Figure 2 Kaplan-Meier curves Updated OS analysis for Study MEK116513



Improvements for the secondary endpoint of PFS were sustained over a 5 year timeframe in the combination arm compared to vemurafenib monotherapy. Improvements were also observed for ORR and a longer DoR was observed in the combination arm compared to vemurafenib monotherapy (Table 15).

Table 15. Efficacy results for Study MEK116513 (COMBI-v)

	Primary analysis (Data cut-off: 17-Apr-2014)		5-year analysis (Data cut-off: 08-Oct-2018)	
Endpoint	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
PFS[a]				
Progressive disease or death, n (%)	166 (47)	217 (62)	257 (73)	259 (74)
Median PFS (months) (95% CI)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)	12.1 (9.7, 14.7)	7.3 (6.0, 8.1)
Hazard Ratio (95% CI)	0.56 (0.46, 0.69)		0.62 (0.52, 0.74)	
P value	<0.001		NA	
ORR[b] % (95% CI)	64 (59.1, 69.4)	51 (46.1, 56.8)	67 (62.2, 72.2)	53 (47.2, 57.9)
ORR difference (95% CI)	13 (5.7, 20.2)		NA	
P value	0.0005		NA	
DoR[c] (months) Median (95% CI)	13.8[d] (11.0, NR)	7.5[d] (7.3, 9.3)	13.8 (11.3, 18.6)	8.5 (7.4, 9.3)

a – Progression-free survival (investigator assessed)
b – Overall Response Rate = Complete Response + Partial Response
c – Duration of response
d – At the time of the reporting the majority (59% of dabrafenib+trametinib and 42% of vemurafenib) of investigator-assessed responses were still ongoing
NR = Not reached
NA = Not applicable

Prior BRAF inhibitor therapy
There are limited data in patients taking the combination of trametinib with dabrafenib who have progressed on a prior BRAF inhibitor.

Part B of study BRF113220 included a cohort of 26 patients that had progressed on a BRAF inhibitor. The trametinib 2 mg once daily and dabrafenib 150 mg twice daily combination demonstrated limited clinical activity in patients who had progressed on a BRAF inhibitor (see section 4.4). The investigator-assessed confirmed response rate was 15% (95% CI: 4.4, 34.9) and the median PFS was 3.6 months (95% CI: 1.9, 5.2). Similar results were seen in the 45 patients who crossed over from dabrafenib monotherapy to the trametinib 2 mg once daily and dabrafenib 150 mg twice daily combination in Part C of this study. In these patients a 13% (95% CI: 5.0, 27.0) confirmed response rate was observed with a median PFS of 3.6 months (95% CI: 2, 4).

Patients with brain metastases
The efficacy and safety of trametinib in combination with dabrafenib in patients with BRAF mutation-positive melanoma that has metastasised to the brain was studied in a non-randomised, open-label, multicentre, Phase II study (COMBI-MB study). A total of 125 patients were enrolled into four cohorts:

- Cohort A: patients with BRAF V600E mutant melanoma with asymptomatic brain metastases without prior local brain-directed therapy and ECOG performance status of 0 or 1.

- Cohort B: patients with BRAF V600E mutant melanoma with asymptomatic brain metastases with prior local brain-directed therapy and ECOG performance status of 0 or1.
- Cohort C: patients with BRAF V600D/K/R mutant melanoma with asymptomatic brain metastases, with or without prior local brain-directed therapy and ECOG performance status of 0 or 1.
- Cohort D: patients with BRAF V600D/E/K/R mutant melanoma with symptomatic brain metastases, with or without prior local brain-directed therapy and ECOG performance status of 0 or 1 or 2.

The primary endpoint of the study was intracranial response in Cohort A, defined as the percentage of patients with a confirmed intracranial response assessed by the investigator using modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Intracranial response assessed by the investigator in Cohorts B, C and D were secondary endpoints of the study. Due to small sample size reflected by wide 95% CIs, the results in Cohorts B, C, and D should be interpreted with caution. Efficacy results are summarised in Table 16.

Table 16. Efficacy data by investigator assessment from COMBI-MB study

	All treated patients population			
Endpoints/ assessment	**Cohort A N=76**	**Cohort B N=16**	**Cohort C N=16**	**Cohort D N=17**
Intracranial response rate, % (95 % CI)				
	59% (47.3, 70.4)	56% (29.9, 80.2)	44% (19.8, 70.1)	59% (32.9, 81.6)
Duration of intracranial response, median, months (95% CI)				
	6.5 (4.9, 8.6)	7.3 (3.6, 12.6)	8.3 (1.3, 15.0)	4.5 (2.8, 5.9)
Overall response rate, % (95% CI)				
	59% (47.3, 70.4)	56% (29.9, 80.2)	44% (19.8, 70.1)	65% (38.3, 85.8)
Progression-free survival, median, months (95% CI)				
	5.7 (5.3, 7.3)	7.2 (4.7, 14.6)	3.7 (1.7, 6.5)	5.5 (3.7, 11.6)
Overall survival, median, months (95% CI)				
	10.8 (8.7, 17.9)	24.3 (7.9, NR)	10.1 (4.6, 17.6)	11.5 (6.8, 22.4)
CI = Confidence Interval NR = Not reached				

- *Trametinib monotherapy*

Treatment naïve patients
The efficacy and safety of trametinib in patients with BRAF unresectable or metastatic mutant melanoma (V600E and V600K) were evaluated in a randomised open-label Phase III study (MEK114267 [METRIC]). Measurement of patients' BRAF V600 mutation status was required.

Patients (N = 322) who were treatment naïve or may have received one prior chemotherapy treatment in the metastatic setting [Intent to Treat (ITT) population] were randomised 2:1 to receive trametinib 2 mg once daily or chemotherapy (dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks). Treatment for all patients continued until disease progression, death or withdrawal.

The primary endpoint of the study was to evaluate the efficacy of trametinib compared to chemotherapy with respect to PFS in patients with advanced/metastatic BRAF V600E/K mutation-positive melanoma without a prior history of brain metastases (N = 273) which is considered the primary efficacy population. The secondary endpoints were PFS in the ITT population and OS, ORR,

and DoR in the primary efficacy population and ITT population. Patients in the chemotherapy arm were allowed to cross-over to the trametinib arm after independent confirmation of progression. Of the patients with confirmed disease progression in the chemotherapy arm, a total of 51 (47%) crossed over to receive trametinib.

Baseline characteristics were balanced between treatment groups in the primary efficacy population and the ITT population. In the ITT population, 54% of patients were male and all were Caucasian. The median age was 54 years (22% were ≥65 years); all patients had an ECOG performance score of 0 or 1; and 3 % had history of brain metastases. Most patients (87%) in the ITT population had BRAF V600E mutation and 12% of patients had BRAF V600K. Most patients (66%) received no prior chemotherapy for advanced or metastatic disease.

The efficacy results in the primary efficacy population were consistent with those in the ITT population; therefore, only the efficacy data for the ITT population are presented in Table 17. Kaplan-Meier curves of investigator assessed OS (post-hoc analysis 20 May 2013) is presented in Figure 3.

Table 17. Investigator assessed efficacy results (ITT population)

Endpoint	**Trametinib**	**Chemotherapy[a]**
Progression-Free Survival	**(N = 214)**	**(N = 108)**
Median PFS (months) (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
Hazard Ratio (95% CI) P value	0.45 (0.33, 0.63) <0.0001	
Overall Response Rate (%)	22	8

ITT = Intent to Treat; PFS = Progression-free survival; CI = confidence interval.

[a] Chemotherapy included patients on dacarbazine (DTIC) 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks.

The PFS result was consistent in the subgroup of patients with V600K mutation-positive melanoma (HR = 0.50; [95% CI: 0.18, 1.35], p=0.0788).

An additional OS analysis was undertaken based upon the 20 May 2013 data cut, see Table 18.

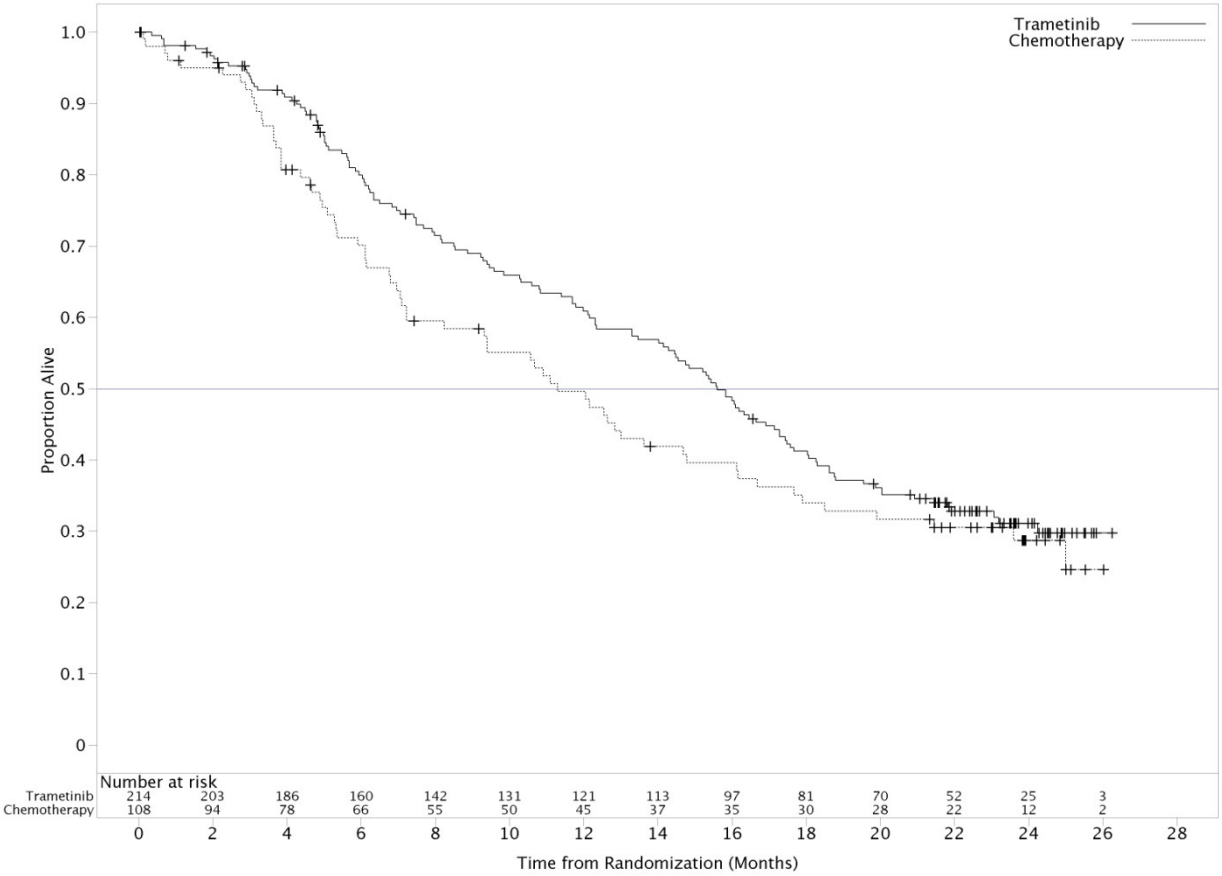
For October 2011, 47% of subjects had crossed over, while for May 2013, 65% of subjects had crossed over.

Table 18. Survival data from the primary and post-hoc analyses

Cut-off dates	**Treatment**	**Number of deaths (%)**	**Median months OS (95% CI)**	**Hazard ratio (95% CI)**	**Percent survival at 12 months (95% CI)**
October 26, 2011	Chemotherapy (n=108)	29 (27)	NR	0.54 (0.32, 0.92)	NR
	Trametinib (n=214)	35 (16)	NR		NR
May 20, 2013	Chemotherapy (n=108)	67 (62)	11.3 (7.2, 14.8)	0.78 (0.57, 1.06)	50 (39,59)
	Trametinib (n=214)	137 (64)	15.6 (14.0, 17.4)		61(54, 67)

NR=not reached

Figure 3 Kaplan-Meier curves of overall survival (OS –ad hoc analysis 20 May 2013)



Prior BRAF inhibitor therapy
In a single-arm Phase II study, designed to evaluate the objective response rate, safety, and pharmacokinetics following dosing of trametinib at 2 mg once daily in patients with BRAF V600E, V600K, or V600D mutation-positive metastatic melanoma (MEK113583), two separate cohorts were enrolled: Cohort A: patients with prior treatment with a BRAF inhibitor either with or without other prior therapy, Cohort B: patients with at least 1 prior chemotherapy or immunotherapy, without prior treatment with a BRAF inhibitor.

In Cohort A of this study, trametinib did not demonstrate clinical activity in patients who had progressed on a prior BRAF inhibitor therapy.

Adjuvant treatment of Stage III melanoma

BRF115532 (COMBI-AD)
The efficacy and safety of trametinib in combination with dabrafenib were studied in a Phase III, multicentre, randomised, double-blind, placebo-controlled study in patients with Stage III (Stage IIIA [lymph node metastasis >1 mm], IIIB, or IIIC) cutaneous melanoma with a BRAF V600 E/K mutation, following complete resection.

Patients were randomised 1:1 to receive either combination therapy (dabrafenib 150 mg twice daily and trametinib 2 mg once daily) or two placebos for a period of 12 months. Enrollment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomisation. Any prior systemic anti-cancer treatment, including radiotherapy, was not allowed. Patients with a history of prior malignancy, if disease-free for at least 5 years, were eligible. Patients presenting with malignancies with confirmed activating RAS mutations were not eligible. Patients

were stratified by BRAF mutation status (V600E versus V600K) and stage of disease prior to surgery using the American Joint Committee on Cancer (AJCC) 7th edition Melanoma Staging System (by Stage III sub-stage, indicating different levels of lymph node involvement and primary tumour size and ulceration). The primary endpoint was investigator-assessed relapse-free survival (RFS), defined as the time from randomisation to disease recurrence or death from any cause. Radiological tumour assessment was conducted every 3 months for the first two years and every 6 months thereafter, until first relapse was observed. Secondary endpoints include overall survival (OS; key secondary endpoint), freedom from relapse (FFR) and distant metastasis-free survival (DMFS).

A total of 870 patients were randomised to the combination therapy (n=438) and placebo (n=432) arms. Most patients were Caucasian (99%) and male (55%), with a median age of 51 years (18% were ≥65 years). The study included patients with all sub-stages of Stage III disease prior to resection; 18% of these patients had lymph node involvement only identifiable by microscope and no primary tumour ulceration. The majority of patients had a BRAF V600E mutation (91%). At the time of the primary analysis, the median duration of follow-up (time from randomisation to last contact or death) was 2.83 years in the dabrafenib and trametinib combination arm and 2.75 years in the placebo arm.

Results for the primary analysis of RFS are presented in Table 19. The study showed a statistically significant difference for the primary outcome of RFS between treatment arms, with a median RFS of 16.6 months for the placebo arm and not yet reached for the combination arm (HR: 0.47; 95% confidence interval: (0.39, 0.58); $p=1.53\times10^{-14}$). The observed RFS benefit was consistently demonstrated across subgroups of patients including age, sex and race. Results were also consistent across stratification factors for disease stage and BRAF V600 mutation type.

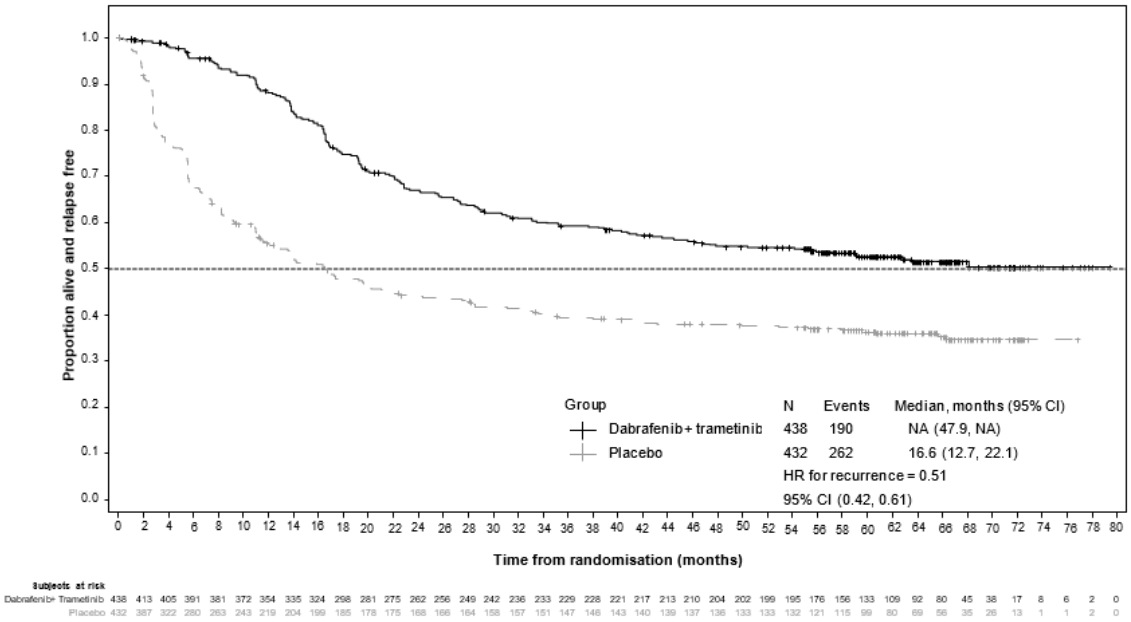
Table 19. Investigator-assessed RFS results for Study BRF115532 (COMBI-AD primary analysis)

RFS parameter	Dabrafenib + Trametinib N=438	Placebo N=432
Number of events, n (%)	166 (38%)	248 (57%)
Recurrence	163 (37%)	247 (57%)
Relapsed with distant metastasis	103 (24%)	133 (31%)
Death	3 (<1%)	1 (<1%)
Median (months)	NE	16.6
(95% CI)	(44.5, NE)	(12.7, 22.1)
Hazard ratio[1]	0.47	
(95% CI)	(0.39, 0.58)	
p-value[2]	1.53×10^{-14}	
1-year rate (95% CI)	0.88 (0.85, 0.91)	0.56 (0.51, 0.61)
2-year rate (95% CI)	0.67 (0.63, 0.72)	0.44 (0.40, 0.49)
3-year rate (95% CI)	0.58 (0.54, 0.64)	0.39 (0.35, 0.44)

[1] Hazard ratio is obtained from the stratified Pike model.
[2] P-value is obtained from the two-sided stratified logrank test (stratification factors were disease stage – IIIA vs. IIIB vs. IIIC – and BRAF V600 mutation type – V600E vs. V600K)
NE = not estimable

Based on updated data with an additional 29 months of follow-up compared to the primary analysis (minimum follow-up of 59 months), the RFS benefit was maintained with an estimated HR of 0.51 (95% CI: (0.42, 0.61) (Figure 4). The 5-year RFS rate was 52% (95% CI: 48, 58) in the combination arm compared to 36% (95% CI: 32, 41) in the placebo arm.

Figure 4 Kaplan-Meier RFS curves for Study BRF115532 (ITT population, updated results)



Based on 153 events (60 [14%] in the combination arm and 93 [22%] in the placebo arm) corresponding to a 26% information fraction of the total target of 597 OS events, the estimated hazard ratio for OS was 0.57 (95% CI: 0.42, 0.79; p=0.0006). These results did not meet the pre-specified boundary to claim statistical significance at this first OS interim analysis (HR=0.50; p=0.000019). Survival estimates at 1 and 2 years from randomisation were 97% and 91% in the combination arm and 94% and 83% in the placebo arm, respectively.

Non-small cell lung cancer

Study BRF113928
The efficacy and safety of trametinib in combination with dabrafenib was studied in a Phase II, three-cohort, multicentre, non-randomised and open-label study in which patients with Stage IV BRAF V600E mutant NSCLC were enrolled. The primary endpoint was ORR using the RECIST 1.1 assessed by the investigator. Secondary endpoints included DoR, PFS, OS, safety and population pharmacokinetics. ORR, DoR and PFS were also assessed by an Independent Review Committee (IRC) as a sensitivity analysis.

Cohorts were enrolled sequentially:
- Cohort A: Monotherapy (dabrafenib 150 mg twice daily), 84 patients enrolled. 78 patients had previous systemic treatment for their metastatic disease.
- Cohort B: Combination therapy (dabrafenib 150 mg twice daily and trametinib 2 mg once daily), 59 patients enrolled. 57 patients had 1-3 lines of previous systemic treatment for their metastatic disease. 2 patients had no previous systemic treatment and were included in the analysis for patients enrolled in Cohort C.
- Cohort C: Combination therapy (dabrafenib 150 mg twice daily and trametinib 2 mg once daily), 34 patients. All patients received study medicinal product as first-line treatment for metastatic disease.

Among the total of 93 patients who were enrolled in the combination therapy cohorts B and C, most patients were Caucasian (>90%), and similar female versus male (54% versus 46%), with a median age of 64 years in second line or higher patients and 68 years in the first line patients. Most patients (94%) enrolled in the combination- therapy- treated cohorts had an ECOG performance status of 0 or 1. 26 (28%) had never smoked. The majority of patients had a non-squamous histology. In the

previously- treated population, 38 patients (67%) had one line of systemic anti-cancer therapy for metastatic disease.

At the time of the primary analysis, the primary endpoint of investigator-assessed ORR, in the first line population was 61.1% (95% CI, 43.5%, 76.9%) and in the previously-treated population was 66.7% (95% CI, 52.9%, 78.6%). These met the statistical significance to reject the null hypothesis that the ORR of dabrafenib in combination with trametinib for this NSCLC population was less than or equal to 30%. The ORR results assessed by IRC were consistent with the investigator assessment. The final analysis of efficacy performed 5 years after last subject first dose is presented in Table 20.

Table 20. Summary of efficacy in the combination treatment cohorts based on investigator and independent radiology review

Endpoint	Analysis	Combination 1st Line N=36[1]	Combination 2nd Line Plus N=57[1]
Overall confirmed response n (%) (95% CI)	By Investigator	23 (63.9%) (46.2, 79.2)	39 (68.4%) (54.8, 80.1)
	By IRC	23 (63.9%) (46.2, 79.2))	36 (63.2%) (49.3, 75.6)
Median DoR Months (95% CI)	By Investigator	10.2 (8.3, 15.2)15.2 (7.8, 23.5)	9.8 (6.9, 18.3)
	By IRC		12.6 (5.8, 26.2)
Median PFS Months (95% CI)	By Investigator	10.8 (7.0, 14.5)	10.2 (6.9, 16.7)
	By IRC	14.6 (7.0, 22.1)	8.6 (5.2, 16.8)
Median OS Months (95% CI)	-	17.3 (12.3, 40.2)	18.2 (14.3, 28.6)

[1] Data cut-off: 7 January 2021

Other studies - pyrexia management analysis

Study CPDR001F2301 (COMBI-i) and Study CDRB436F2410 (COMBI-Aplus)

Pyrexia is observed in patients treated with dabrafenib and trametinib combination therapy. The initial registration studies for the combination therapy in the unresectable or metastatic melanoma setting (COMBI-d and COMBI-v; total N=559) and in the adjuvant melanoma setting (COMBI-AD, N=435) recommended to interrupt only dabrafenib in case of pyrexia (fever ≥38.5°C). In two subsequent studies in unresectable or metastatic melanoma (COMBI-i control arm, N=264) and in the adjuvant melanoma setting (COMBI-Aplus, N=552), interruption of both medicinal products when patient's temperature is ≥38ºC (COMBI-Aplus), or at the first symptom of pyrexia (COMBI-i; COMBI-Aplus for recurrent pyrexia) was advised. In COMBI-i and COMBI-Aplus there was a lower incidence of grade 3/4 pyrexia, complicated pyrexia, hospitalisation due to serious pyrexia adverse events of special interest (AESIs), the time spent in pyrexia AESIs, and permanent discontinuations from both medicinal products due to pyrexia AESIs (the latter in the adjuvant setting only) compared to COMBI-d, COMBI-v and COMBI-AD. The COMBI-Aplus study met its primary endpoint with a composite rate of 8.0% (95% CI: 5.9, 10.6) for grade 3/4 pyrexia, hospitalisation due to pyrexia, or permanent treatment discontinuation due to pyrexia compared to 20.0% (95% CI: 16.3, 24.1) for the historical control (COMBI-AD).

Anaplastic Thyroid Cancer (ATC)

The safety and efficacy of trametinib administered with dabrafenib was evaluated in an activity-estimating, nine-cohort, multi-center, non-randomized, open-label trial (Study BRF117019; NCT02034110) in patients with rare cancers with the BRAF V600E mutation, including locally advanced, unresectable, or metastatic anaplastic thyroid cancer (ATC) with no standard locoregional treatment options. Trial BRF117019 excluded patients who could not swallow or retain the medication; who received prior treatment with BRAF or MEK inhibitors; with symptomatic or

untreated CNS metastases; or who had airway obstruction. Patients received trametinib 2 mg once daily and dabrafenib 150 mg twice daily. The major efficacy outcome measure was overall response rate (ORR) per RECIST v1.1 as assessed by independent review committee (IRC) and duration of response (DoR).

Thirty-six patients were enrolled and were evaluable for response in the ATC cohort. The median age was 71 years (range 47-85); 44% were male, 50% White, 44% Asian; and 94% had ECOG performance status of 0 or 1. Prior anti-cancer treatments included surgery and external beam radiotherapy (83% each), and systemic therapy (67%).

Efficacy results are summarized in Table 21.

Table 21. Efficacy Results in the ATC Cohort Based on Independent Review of Study BRF117019

ATC Cohort Population	**N = 36**
Overall Response Rate	
ORR (95%CI)	53% (35.5%, 69.6%)
Complete response	6%
Partial response	47%
Duration of Response	n = 19
Median DoR, months (95% CI)	13.6 (3.8, NE)
% with DoR ≥6 months	68%
% with DoR ≥ 12 months	53%

Abbreviations: ATC, anaplastic thyroid cancer; CI, confidence interval; DoR, duration of response; ORR, overall response rate; NE, not estimable.

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors

The safety and efficacy of trametinib in combination with dabrafenib for the treatment of BRAF V600E mutation-positive unresectable or metastatic solid tumors were evaluated in Trials BRF117019, NCI-MATCH, and CTMT212X2101, and supported by results in COMBI-d, COMBI-v, and BRF113928. In adult studies, patients received trametinib 2 mg once daily and dabrafenib 150 mg twice daily. The major efficacy outcome measures were ORR per RECIST v1.1, RANO [HGG] or modified RANO [LGG] criteria and duration of response (DoR).

BRF117019 Study and NCI-MATCH Study

Study BRF117019 (NCT02034110) is a multi-cohort, multi-center, non-randomized, open-label trial in adult patients with selected tumors with the BRAF V600E mutation, including high grade glioma (HGG) (n = 45), biliary tract cancer (BTC) (n = 43), low grade glioma (LGG) (n = 13), adenocarcinoma of small intestine (ASI) (n = 3), gastrointestinal stromal tumor (GIST) (n = 1), and anaplastic thyroid cancer. Patients were enrolled based on local assessments of BRAF V600E mutation status; a central laboratory confirmed the BRAF V600E mutation in 93 of 105 patients.

Arm H (EAY131-H) of the NCI-MATCH study (NCT02465060) is a single-arm, open-label study that enrolled patients with a BRAF V600E mutation. Patients with melanoma, thyroid cancer, or CRC were excluded. BRAF mutation status for enrollment was determined either by central or local laboratory test. The study included adult patients with solid tumors including gastrointestinal tumors (n = 14), lung tumors (n = 7), gynecologic or peritoneal tumors (n = 6), CNS tumors (n = 4), and ameloblastoma of mandible (n = 1).

Among the 131 patients enrolled in BRF117019 and NCI-MATCH with the tumor types shown in Table 22, the baseline characteristics were: median age of 51 years with 20% age 65 or older; 56%

female; 85% White, 9% Asian, 3% Black, 3% Other; and 37% ECOG 0, 56% ECOG 1, and 6% ECOG 2. Of the 131 patients, 90% received prior systemic therapy.

Efficacy results in patients with solid tumors are summarized in Table 22.

Table 22. Efficacy Results Based on Independent Review in Study BRF117019 and NCI MATCH Arm H

Tumor Type[a]	N	Objective Response Rate		Duration of Response
		%	95% CI	Range (months)
Biliary tract cancer[b]	48	46	(31, 61)	1.8[d], 40[d]
High grade glioma[c]	48	33	(20, 48)	3.9, 44
Glioblastoma	32	25	(12, 43)	3.9, 27
Anaplastic pleomorphic xanthoastrocytoma	6	67	(22, 96)	6, 43
Anaplastic astrocytoma	5	20	(0.5, 72)	15
Astroblastoma	2	100	(16, 100)	15, 23[d]
Undifferentiated	1	PR	(2.5, 100)	6
Anaplastic ganglioglioma	1	0	NA	NA
Anaplastic oligodendroglioma	1	0	NA	NA
Low grade glioma	14	50	(23, 77)	6, 29[d]
Astrocytoma	4	50	(7, 93)	7, 23
Ganglioglioma	4	50	(7, 93)	6, 13
Pleomorphic xanthoastrocytoma	2	50	(1.3, 99)	6
Pilocytic astrocytoma	2	0	NA	NA
Choroid plexus papilloma	1	PR	(2.5, 100)	29[d]
Gangliocytoma/ganglioglioma	1	PR	(2.5, 100)	18[d]
Low grade serous ovarian carcinoma	5	80	(28, 100)	12, 42[d]
Adenocarcinoma small intestine	4	50	(7, 93)	7, 8
Adenocarcinoma pancreas	3	0	NA	NA
Mixed ductal / adenoneuroendocrine carcinoma	2	0	NA	NA
Neuroendocrine carcinoma of colon	2	0	NA	NA
Ameloblastoma of mandible	1	PR	(2.5, 100)	30
Combined small cell-squamous carcinoma of lung	1	PR	(2.5, 100)	5
Mucinous-papillary serous adenocarcinoma of peritoneum	1	PR	(2.5, 100)	8
Adenocarcinoma of anus	1	0	NA	NA
Gastrointestinal stromal tumor	1	0	NA	NA

Abbreviations: PR, partial response.

[a] Excludes NSCLC (n=6) and ATC (n=36) (previously approved tumor types for trametinib in combination with dabrafenib).

[b] Median DoR 9.8 months (95% CI: 5.3, 20.4).

[c] Median DoR 13.6 months (95% CI: 5.5, 26.7).

[d] Denotes a right-censored DoR.

CTMT212X2101 (X2101) Study

Study X2101 (NCT02124772) was a multi-center, open-label, multi-cohort study in pediatric patients with refractory or recurrent solid tumors. Part C was a dose escalation of trametinib in combination with dabrafenib in patients with a BRAF V600E mutation. Part D was a cohort expansion phase of trametinib in combination with dabrafenib in patients with LGG with a BRAF V600E mutation. The major efficacy outcome measure was ORR as assessed by independent review committee per RANO criteria.

The efficacy of trametinib in combination with dabrafenib was evaluated in 48 pediatric patients, including 34 patients with LGG and 2 patients with HGG.

For patients with BRAF V600E mutant LGG in Parts C and D, the median age was 10 years (range: 1 to 17); 50% were male, 75% White, 8% Asian, 3% Black; and 58% had Karnofsky/Lansky performance status of 100. Prior anti-cancer treatments included surgery (83%), external beam radiotherapy (2.8%), and systemic therapy (92%). The ORR was 25% (95% CI: 12%, 42%). For the 9 patients who responded, DoR was ≥6 months for 78% of patients, and ≥24 months for 44% of patients.

CDRB436G2201 (G2201) Study – High-Grade Glioma Cohort

Study G2201 (NCT02684058) was a multi-center, randomized, open-label, Phase II study of dabrafenib and trametinib in chemotherapy naïve pediatric patients with BRAF V600E mutant low-grade glioma (LGG) and patients with relapsed or progressive BRAF V600E mutant HGG. Patients with HGG were enrolled in a single-arm cohort. The major efficacy outcome measure for the HGG cohort was ORR as assessed by independent review committee per RANO 2010 criteria.

The efficacy of trametinib in combination with dabrafenib was evaluated in 41 pediatric patients with relapsed or progressive HGG.

For patients with BRAF V600E mutant HGG enrolled in the HGG cohort, the median age was 13 years (range: 2 to 17); 56% were female, 61% White, 27% Asian, 2.4% Black and 37% had Karnofsky/Lansky performance status of 100. Prior anti-cancer treatments included surgery (98%), radiotherapy (90%), and chemotherapy (81%). The ORR was 56% (95% CI: 40, 72). The median DoR was not reached (95% CI: 9.2, NE). For the 23 patients who responded in the HGG cohort, DoR was ≥ 6 months for 78% of patients, ≥ 12 months for 48% of patients, and ≥ 24 months for 22% of patients.

BRAF V600E Mutation-Positive Low-Grade Glioma

CDRB436G2201 (G2201) Study – Low-Grade Glioma Cohort

The safety and efficacy of trametinib in combination with dabrafenib for the treatment of BRAF V600E mutation-positive low-grade glioma (LGG) in pediatric patients aged 1 to < 18 years of age were evaluated in the multi-center, open-label trial (Study CDRB436G2201; NCT02684058). Patients with LGG (WHO grades 1 and 2) who required first systemic therapy were randomized in a 2:1 ratio to dabrafenib plus trametinib (D + T) or carboplatin plus vincristine (C + V).

BRAF mutation status was identified prospectively via a local assessment or a central laboratory test. In addition, retrospective testing of available tumor samples by the central laboratory was performed to evaluate BRAF V600E mutation status.

Patients received age- and weight-based dosing of trametinib and dabrafenib until loss of clinical benefit or until unacceptable toxicity. Carboplatin and vincristine were dosed based on body surface area at doses 175 mg/m2 and 1.5 mg/m2 (0.05 mg/kg for patients < 12 kg), respectively, as one 10-week induction course followed by eight 6-week cycles of maintenance therapy.

The major efficacy outcome measure was overall response rate (ORR) by independent review based on RANO LGG (2017) criteria. Additional efficacy outcome measures were progression-free survival

and overall survival. The primary analysis was performed when all patients had completed at least 32 weeks of therapy.

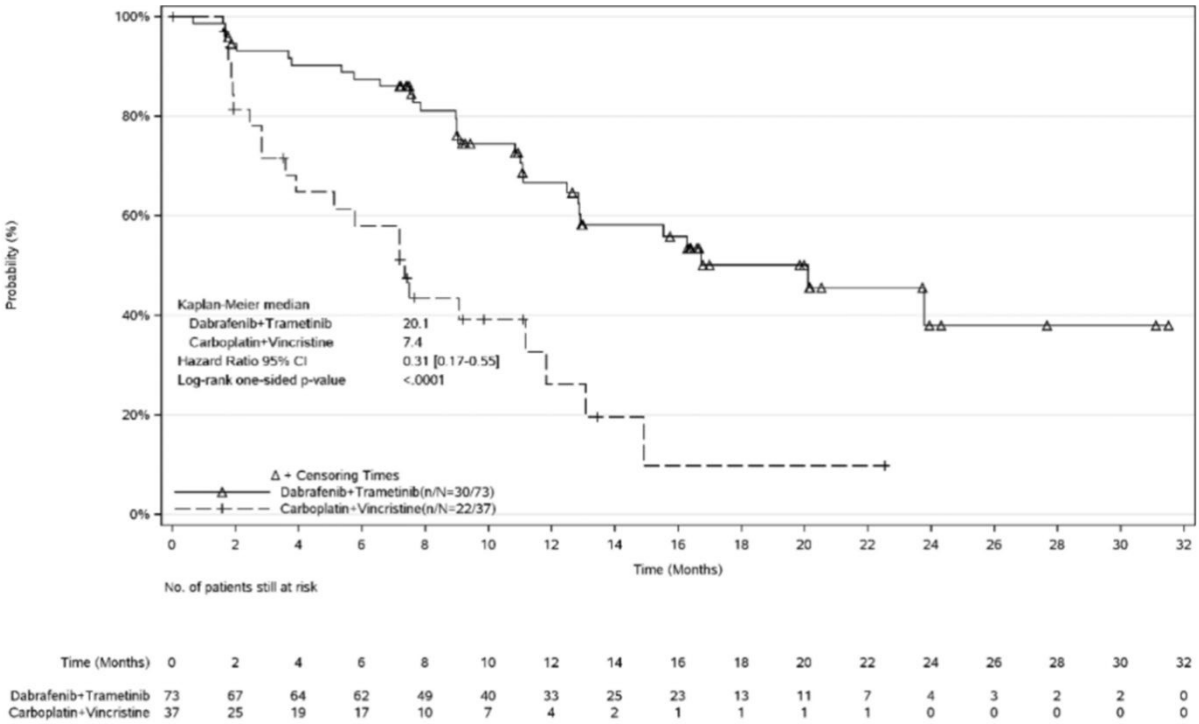
In the LGG cohort, 110 patients were randomized to D + T (n = 73) or C + V (n = 37). Median age was 9.5 years (range: 1 to 17); 60% were female. Study G2201 showed a statistically significant improvement in ORR and PFS in patients with LGG randomized to D + T compared to those randomized to C + V. Efficacy results are shown in Table 23.

Table 23. Efficacy Results Based on Independent Review in Study G2201 (LGG cohort)

	Trametinib plus Dabrafenib N = 73	**Carboplatin plus Vincristine N = 37**
Overall Response Rate		
ORR% (95% CI)[a]	46.6 (34.8, 58.6)	10.8 (3.0, 25.4)
P value	< 0.001	
Complete response, n (%)	2 (2.7)	1 (2.7)
Partial response, n (%)	32 (44)	3 (8)
Duration of Response		
Median (95% CI)[b], months	23.7 (14.5, NE)	NE (6.6, NE)
% with observed DoR ≥ 12 months	56	50
% with observed DoR ≥ 24 months	15	25
Progression-Free Survival		
Median (95% CI)[b], months	20.1 (12.8, NE)	7.4 (3.6, 11.8)
Hazard ratio (95% CI)[c]	0.31 (0.17, 0.55)	
P value	< 0.001	

Abbreviations: CI, confidence interval; NE, not estimable.
[a]Based on Clopper-Pearson exact confidence interval
[b]Based on Kaplan-Meier method
[c]Based on proportional hazards model

Figure 5. Kaplan-Meier Curves for Progression-Free Survival in Study G2201 (LGG cohort)



Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
Dabrafenib+Trametinib	73	67	64	62	49	40	33	25	23	13	11	7	4	3	2	2	0
Carboplatin+Vincristine	37	25	19	17	10	7	4	2	1	1	1	1	0	0	0	0	0

At the time of the interim analysis of overall survival (OS), conducted when all patients had completed at least 32 weeks of treatment or had discontinued earlier, there was one death on the C + V arm. The OS results at interim analysis did not reach statistical significance.

5.2 Pharmacokinetic properties

Absorption

Trametinib is absorbed orally with median time to achieve peak concentrations of 1.5 hours post-dose. The mean absolute bioavailability of a single 2 mg tablet dose is 72% relative to an intravenous (IV) microdose. The increase in exposure (C_{max} and AUC) was dose-proportional following repeat dosing. Following administration of 2 mg once daily, steady-state geometric mean C_{max}, $AUC_{(0-\tau)}$ and predose concentration were 22.2 ng/ml, 370 ng*hr/ml and 12.1 ng/ml, respectively with a low peak:trough ratio (1.8). Inter-subject variability at steady state was low (<28%).

Trametinib accumulates with repeat daily dosing with a mean accumulation ratio of 6.0 at 2 mg once daily dose. Steady state was achieved by Day 15.

Administration of a single dose of trametinib with a high-fat, high-calorie meal resulted in a 70% and 10% decrease in C_{max} and AUC, respectively compared to fasted conditions (see sections 4.2 and 4.5).

Distribution

Binding of trametinib to human plasma proteins is 97.4%. Trametinib has a volume of distribution of approximately 1200 L determined following administration of a 5 μg intravenous microdose.

Biotransformation

In vitro and *in vivo* studies demonstrated that trametinib is metabolised predominantly via deacetylation alone or in combination with mono-oxygenation. The deacetylated metabolite was further metabolised by glucuronidation. CYP3A4 oxidation is considered a minor pathway of metabolism. The deacetylation is mediated by the carboxyl-esterases 1b, 1c and 2, with possible

contributions by other hydrolytic enzymes.

Following single and repeated doses of trametinib, trametinib as parent is the main circulating component in plasma.

Elimination

Mean terminal half-life is 127 hours (5.3 days) after single dose administration. Trametinib plasma IV clearance is 3.21 L/hr.

Total dose recovery was low after a 10-day collection period (<50%) following administration of a single oral dose of radiolabelled trametinib as a solution, due to the long elimination half-life. Drug-related material was excreted predominantly in the faeces (>80% of recovered radioactivity) and to a minor extent in urine (≤19%). Less than 0.1% of the excreted dose was recovered as parent in urine.

Special patient populations

Hepatic impairment

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

Renal impairment

Renal impairment is unlikely to have a clinically relevant effect on trametinib pharmacokinetics given the low renal excretion of trametinib. The pharmacokinetics of trametinib were characterised in 223 patients enrolled in clinical trials with trametinib who had mild renal impairment and 35 patients with moderate renal impairment using a population pharmacokinetic analysis. Mild and moderate renal impairment had no effect on trametinib exposure (<6% for either group). No data are available in patients with severe renal impairment (see section 4.2).

Elderly

Based on the population pharmacokinetic analysis (range 19 to 92 years), age had no relevant clinical effect on trametinib pharmacokinetics. Safety data in patients ≥75 years is limited (see section 4.8).

Race

There are insufficient data to evaluate the potential effect of race on trametinib pharmacokinetics as clinical experience is limited to Caucasians.

Pediatric Patients

The pharmacokinetics of trametinib were evaluated in 95 pediatric patients after single or repeat weight-adjusted dosing. The pharmacokinetic exposures of trametinib at the recommended weight-adjusted dosage in pediatric patients were within range of those observed in adults.

Body weight and gender

Based on a population pharmacokinetic analysis, gender and body weight were found to influence trametinib oral clearance. Although smaller female subjects are predicted to have higher exposure than heavier male subjects, these differences are unlikely to be clinically relevant and no dosage adjustment is warranted in adults.

Medicinal product interactions

Effects of trametinib on drug-metabolising enzymes and transporters: *In vitro* and *in vivo* data suggest that trametinib is unlikely to affect the pharmacokinetics of other medicinal products. Based on *in vitro* studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP3A4. Trametinib was found to be an *in vitro* inhibitor of CYP2C8, CYP2C9 and CYP2C19, an inducer of CYP3A4 and an inhibitor of the transporters OAT1, OAT3, OCT2, MATE1, OATP1B1, OATP1B3, P-gp and BCRP. However, based on the low dose and low clinical systemic exposure relative to the *in vitro* potency of inhibition or induction values, trametinib is not considered to be an *in vivo* inhibitor or inducer of these enzymes or transporters, although transient inhibition of BCRP substrates in the gut may occur (see section 4.5).

Effects of other medicinal products on trametinib: *In vivo* and *in vitro* data suggest that the pharmacokinetics of trametinib are unlikely to be affected by other medicinal products. Trametinib is not a substrate of CYP enzymes or of the transporters BCRP, OATP1B1, OATP1B3, OATP2B1, OCT1, MRP2, and MATE1. Trametinib is an *in vitro* substrate of BSEP and the efflux transporter P-gp. Although trametinib exposure is unlikely to be affected by inhibition of BSEP, increased levels of trametinib upon strong inhibition of hepatic P-gp cannot be excluded (see section 4.5).

Effects of trametinib on other medicinal products: the effect of repeat-dose trametinib on the steady state pharmacokinetics of combination oral contraceptives, norethindrone and ethinyl estradiol, was assessed in a clinical study that consisted of 19 female patients with solid tumours. Norethindrone exposure increased by 20% and ethinyl estradiol exposure was similar when co-administered with trametinib. Based on these results, no loss of efficacy of hormonal contraceptives is expected when co-administered with trametinib monotherapy.

5.3 Preclinical safety data

Carcinogenicity studies with trametinib have not been conducted. Trametinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells and micronuclei in the bone marrow of rats.

Trametinib may impair female fertility in humans, as in repeat-dose studies, increases in cystic follicles and decreases in corpora lutea were observed in female rats at exposures below the human clinical exposure based on AUC.

Additionally, in juvenile rats given trametinib, decreased ovarian weights, slight delays in hallmarks of female sexual maturation (vaginal opening and increased incidence of prominent terminal end buds within the mammary gland) and slight hypertrophy of the surface epithelium of the uterus were observed. All of these effects were reversible following an off-treatment period and attributable to pharmacology. However, in rat and dog toxicity studies up to 13 weeks in duration, there were no treatment effects observed in male reproductive tissues.

In embryo-foetal developmental toxicity studies in rats and rabbits, trametinib induced maternal and developmental toxicity. In rats decreased foetal weights-and increased post-implantation loss were seen at exposures below or slightly above the human clinical exposures based on AUC. In an embryo-foetal developmental toxicity study with rabbits, decreased foetal body weight, increased abortions, increased incidence of incomplete ossification and skeletal malformations were seen at sub-clinical human exposures based on AUC).

In repeat-dose studies the effects seen after trametinib exposure are found mainly in the skin, gastrointestinal tract, haematological system, bone and liver. Most of the findings are reversible after drug-free recovery. In rats, hepatocellular necrosis and transaminase elevations were seen after 8 weeks at ≥0.062 mg/kg/day (approximately 0.8 times human clinical exposure based on AUC).

In mice, lower heart rate, heart weight and left ventricular function were observed without cardiac

histopathology after 3 weeks at ≥0.25 mg/kg/day trametinib (approximately 3 times human clinical exposure based on AUC) for up to 3 weeks. In adult rats, mineralisation of multiple organs was associated with increased serum phosphorus and was closely associated with necrosis in heart, liver and kidney and haemorrhage in the lung at exposures comparable to the human clinical exposure. In rats, hypertrophy of the physis and increased bone turnover were observed, but the physeal hypertrophy is not expected to be clinically relevant for adult humans. In rats and dogs given trametinib at or below human clinical exposures, bone marrow necrosis, lymphoid atrophy in thymus and GALT and lymphoid necrosis in lymph nodes, spleen and thymus were observed, which have the potential to impair immune function. In juvenile rats, increased heart weight with no histopathology was observed at 0.35 mg/kg/day (approximately twice the adult human clinical exposure based on AUC).

Trametinib was phototoxic in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay at significantly higher concentrations than human clinical exposures (IC_{50} at 2.92 µg/ml, ≥130 times the human clinical exposure based on C_{max}), indicating that there is low risk for phototoxicity to patients taking trametinib.

Combination with dabrafenib

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mekinist 0.5 mg film-coated tablets

Tablet core
Mannitol (E421)
Microcrystalline cellulose (E460)
Hypromellose (E464)
Croscarmellose sodium (E468)
Magnesium stearate (E470b)
Sodium lauryl sulfate
Colloidal silicon dioxide (E551)

Tablet film-coating
Hypromellose (E464)
Titanium dioxide (E171)
Polyethylene glycol
Iron oxide yellow(E172)

Mekinist 2 mg film-coated tablets

Tablet core
Mannitol (E421)
Microcrystalline cellulose (E460)
Hypromellose (E464)
Croscarmellose sodium (E468)
Magnesium stearate (E470b)
Sodium lauryl sulfate
Colloidal silicon dioxide (E551)

Tablet film-coating
Hypromellose (E464)
Titanium dioxide (E171)
Polyethylene glycol
Polysorbate 80 (E433)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Opened bottle:
30 days at not more than 30ºC.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Store in the original package in order to protect from light and moisture.
Keep the bottle tightly closed.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with child resistant polypropylene closure. The bottle contains a desiccant.

Pack sizes: One bottle contains 30 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. REGISTRATION HOLDER AND IMPORTER AND ITS ADDRESS

Novartis Israel Ltd., P.O.B 7126, Tel Aviv.

8. REGISTRATION NUMBER

Mekinist 0.5 mg 1549534309
Mekinist 2 mg 1549634322

Revised in June 2024.