ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 (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 adults and adolescents aged 12 years and older with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1).

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 adults and adolescents aged 12 years and older 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 adults with advanced non-small cell lung cancer with a BRAF V600 mutation.

Differentiated thyroid cancer (DTC)

Trametinib in combination with dabrafenib is indicated for the treatment of adult patients with locally advanced or metastatic differentiated thyroid cancer with a BRAF V600E mutation, refractory to or not eligible for radioactive iodine (RAI) who have progressed during or after prior systemic therapy (for biomarker-based patient selection, 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.

Patient selection

Before taking trametinib, patients must have confirmation of tumour BRAF V600 mutation assessed by a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose. If no CE-marked IVD is available, an alternative validated test should be used.

Posology

In adults, the recommended dose of trametinib is 2 mg once daily, regardless of body weight.

In adolescents (aged 12 to <18 years) with melanoma, the recommended dose of trametinib is based on body weight (see also Table 1):

- 1 mg trametinib once daily for a body weight of 26 to 37 kg
- 1.5 mg trametinib once daily for a body weight of 38 to 50 kg
- 2 mg trametinib once daily for a body weight of 51 kg or more

The recommended dose of trametinib film-coated tablets for patients with a body weight less than 26 kg has not been established.

Please refer to the dabrafenib summary of product characteristics (SmPC) for information on the recommended dose of dabrafenib, when used in combination with trametinib.

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 2). In the adjuvant melanoma setting, patients should be treated for a period of 12 months unless there is disease recurrence or unacceptable toxicity.

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 1 and 2).

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

Table 1 Recommended dose level reductions

Dose level	Adults	Adolescents		
		Body weight 26 to 37 kg	Body weight 38 to 50 kg	Body weight ≥51 kg
Recommended starting dose	2 mg once daily	1 mg once daily	1.5 mg once daily	2 mg once daily
1st dose reduction level	1.5 mg once daily	0.5 mg once daily	1 mg once daily	1.5 mg once daily
2nd dose reduction level	1 mg once daily	NA	0.5 mg once daily	1 mg once daily
NA = Not applicable Dose adjustment for trametinib below 1 mg once daily is not recommended for adults and adolescents with a body weight ≥51 kg.				

Table 2 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 starting dose indicated in Table 1.

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 3 below for trametinib (see section 4.4).

Table 3 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 (reduced by 0.5 mg) or discontinue trametinib in patients taking trametinib 1 mg daily.
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.

Race

Limited safety and efficacy data have been collected on trametinib in non-Caucasian patients. The population pharmacokinetic analysis showed no significant differences in the pharmacokinetics of trametinib between Asian and Caucasian patients. No trametinib dose adjustment is needed in Asian patients.

Elderly

No initial dose adjustment is required in patients >65 years of age. More frequent dose adjustments (see Tables 1 and 2 above) may be required in patients >65 years of age (see section 4.8).

Paediatric population

The safety and efficacy of trametinib film-coated tablets in children and adolescents (<18 years) have not been established, except in adolescents aged 12 years and older with melanoma. No clinical data are available. 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 SmPC 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 SmPC 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 SmPC.

BRAF V600 testing

The efficacy and safety of trametinib have not been evaluated in patients whose melanoma 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 SmPC (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 SmPC (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 SmPC (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 studies. 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 studies, 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 studies; 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 studies 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 SmPC 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 study, 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 studies with trametinib (see section 4.8). In clinical studies 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 3 should be followed (see section 4.2); if uveitis is diagnosed, please refer to dabrafenib SmPC 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 27% of 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 studies. Please refer to the dabrafenib SmPC (section 4.4).

Pancreatitis

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

Hepatic events

Hepatic adverse reactions have been reported in clinical studies 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 SmPC 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 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 SmPC 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 SmPC 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 1 188 adult patients with BRAF V600 mutant unresectable or metastatic melanoma, Stage III BRAF V600 mutant melanoma following complete resection (adjuvant treatment), advanced NSCLC and advanced DTC treated with trametinib 2 mg once daily and dabrafenib 150 mg twice daily. The mean treatment duration was 16 months (see section 5.1).

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

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 4) and trametinib in combination with dabrafenib (Table 5).

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 study data. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4 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 5 Adverse reactions with trametinib in combination with dabrafenib

System organ class	Frequency (all grades)	Adverse reactions
Infections and infestations	Very common	Nasopharyngitis
		Urinary tract infection
	Common	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	Very common	Neutropenia
		Anaemia
	Common	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
		Bradycardia
	Uncommon	Cardiac failure
		Left ventricular dysfunction
		Atrioventricular block[e]
	Not known	Myocarditis
Vascular disorders	Very common	Hypertension
		Haemorrhage[f]
	Common	Hypotension
		Lymphoedema
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Pneumonitis
		Dyspnoea
	Rare	Interstitial lung disease

Gastrointestinal disorders	Very common	Abdominal pain[g]
		Constipation
		Diarrhoea
		Nausea
		Vomiting
	Common	Dry mouth
		Stomatitis
	Uncommon	Gastrointestinal perforation
		Pancreatitis
		Colitis
Skin and subcutaneous tissue disorders	Very common	Dry skin
		Pruritus
		Rash
		Erythema
		Dermatitis acneiform
	Common	Dermatitis exfoliative generalised[h]
		Actinic keratosis
		Night sweats
		Hyperkeratosis
		Alopecia
		Palmar-plantar erythrodysaesthesia syndrome
		Skin lesion
		Hyperhidrosis
		Panniculitis
		Skin fissures
		Photosensitivity
	Uncommon	Acute febrile neutrophilic dermatosis
	Not known	Stevens-Johnson syndrome
		Drug reaction with eosinophilia and systemic symptoms
		Tattoo-associated skin reactions
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
		Muscle spasms[i]
	Uncommon	Rhabdomyolysis
Renal and urinary disorders	Common	Renal failure, acute kidney injury
	Rare	Nephritis
General disorders and administration site conditions	Very common	Fatigue
		Chills
		Asthenia
		Oedema peripheral
		Pyrexia
		Weight increase (abnormal weight gain)[j]
		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

[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, and superficial spreading melanoma Stage unspecified
[d] Includes drug hypersensitivity
[e] Including atrioventricular block complete
[f] Bleeding from various sites, including intracranial bleeding and fatal bleeding
[g] Includes abdominal pain upper and abdominal pain lower
[h] Includes skin exfoliation
[i] Muscle spasms, musculoskeletal stiffness
[j] Weight increase (abnormal weight gain) has only been reported in the paediatric population.

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 SmPC.

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% 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 studies, 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 8% 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 studies 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 studies 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 SmPC.

Hepatic events

Hepatic adverse reactions have been reported in clinical studies 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 studies 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 studies 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 27% 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 SmPC.

Renal failure

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

Paediatric population

The safety of trametinib film-coated tablets has not been evaluated in prospective clinical studies of adolescent patients with melanoma. In a published retrospective Italian study of 6 paediatric participants with advanced BRAF V600 mutation-positive melanoma treated with trametinib in combination with dabrafenib (see section 5.1), the most frequently reported adverse events were fever and increased creatine phosphokinase. Two adolescent patients experienced an asymptomatic decrease of more than 10% in LVEF, which resolved after temporary trametinib interruption, and both patients resumed trametinib at a reduced dose without further cardiac toxicity.

In clinical studies in other indications, the safety profile of trametinib in combination with dabrafenib in paediatric patients was largely consistent with the safety profile previously established in adult patients. Weight increase (abnormal weight gain) has only been reported in the paediatric population. It was reported as an adverse reaction in 15% of adolescent patients including Grade 3 cases in 4% of patients.

Other special populations

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=1 188) 27% of patients were ≥65 years of age, and 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.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical studies 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 studies 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.

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 melanoma clinical studies, 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 studies 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 studies (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 studies 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 study.

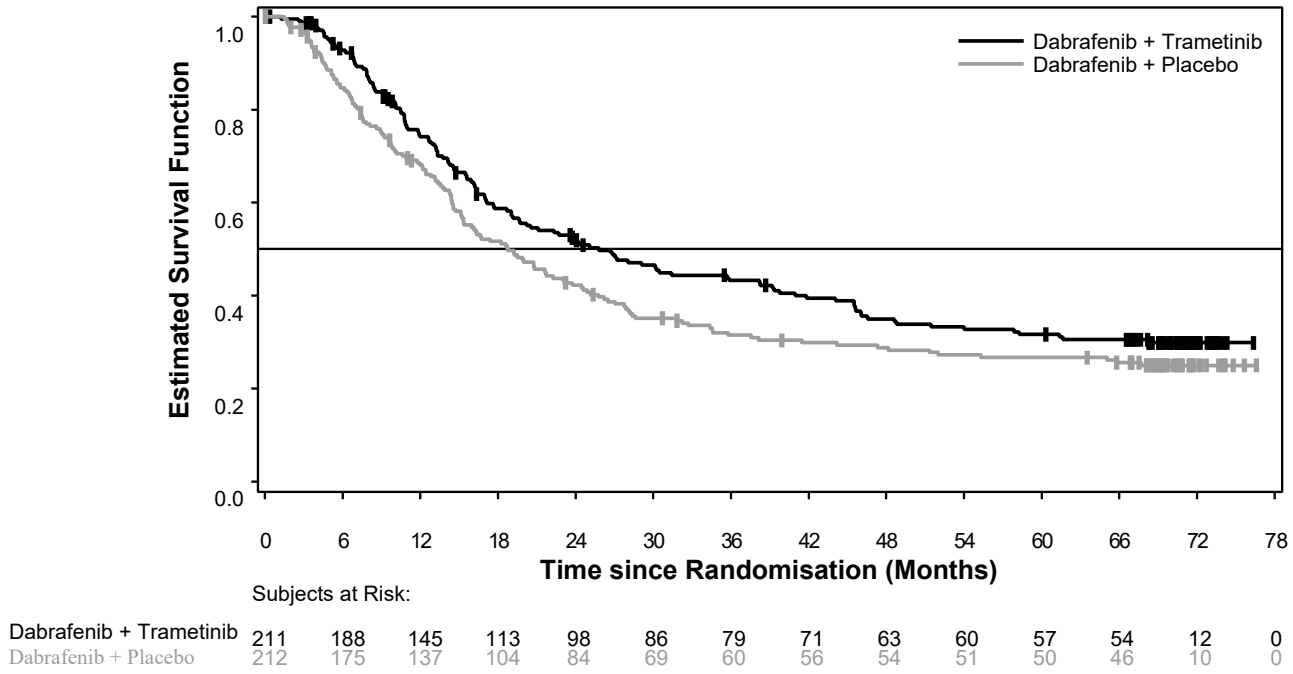
Median OS and estimated 1-year, 2-year, 3-year, 4-year and 5-year survival rates are presented in Table 6. From an OS analysis at 5 years, the median OS for the combination arm was approximately 7 months longer than for dabrafenib monotherapy (25.8 months versus 18.7 months) with 5-year survival rates of 32% for the combination versus 27% for dabrafenib monotherapy (Table 6, 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 6 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 7).

Table 7 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 study.

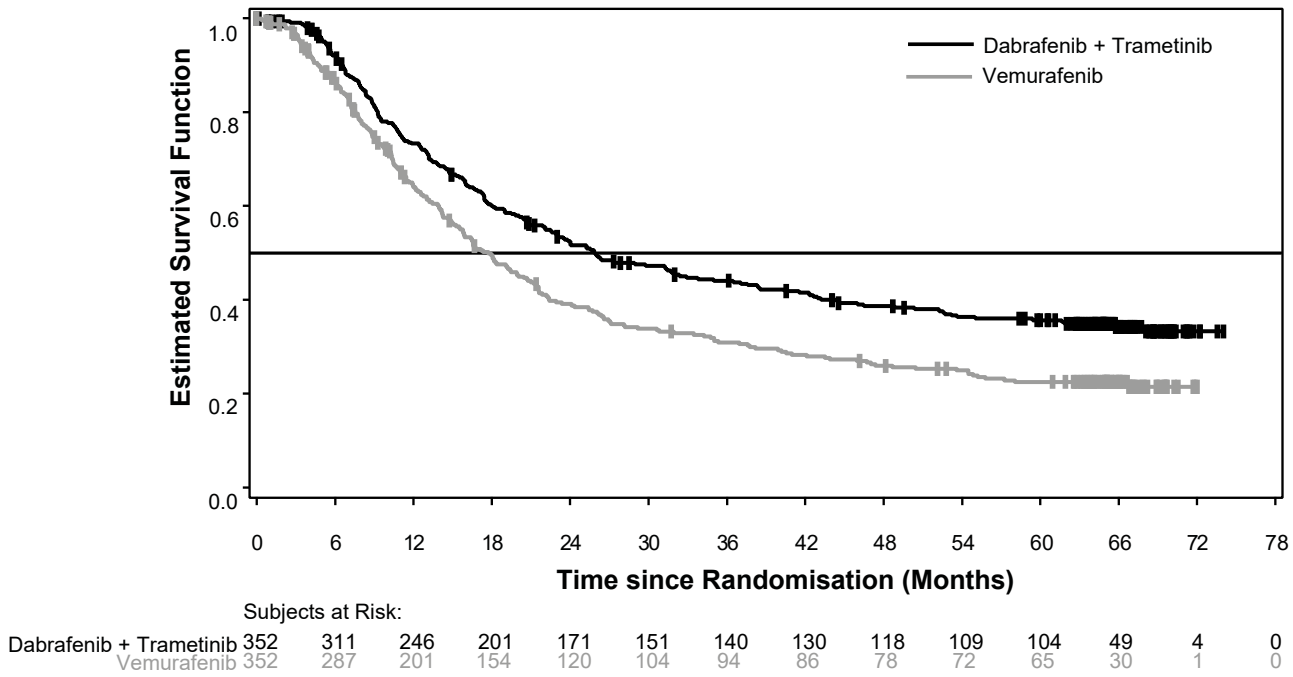
Median OS and estimated 1-year, 2-year, 3-year, 4-year and 5-year survival rates are presented in Table 8. From an OS analysis at 5 years, the median OS for the combination arm was approximately 8 months longer than the median OS for vemurafenib monotherapy (26.0 months versus 17.8 months) with 5-year survival rates of 36% for the combination versus 23% for vemurafenib monotherapy (Table 8, 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 8 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 9).

Table 9 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 10.

Table 10 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 1 000 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 11. Kaplan-Meier curves of investigator-assessed OS (post-hoc analysis 20 May 2013) is presented in Figure 3.

Table 11 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) 1 000 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).

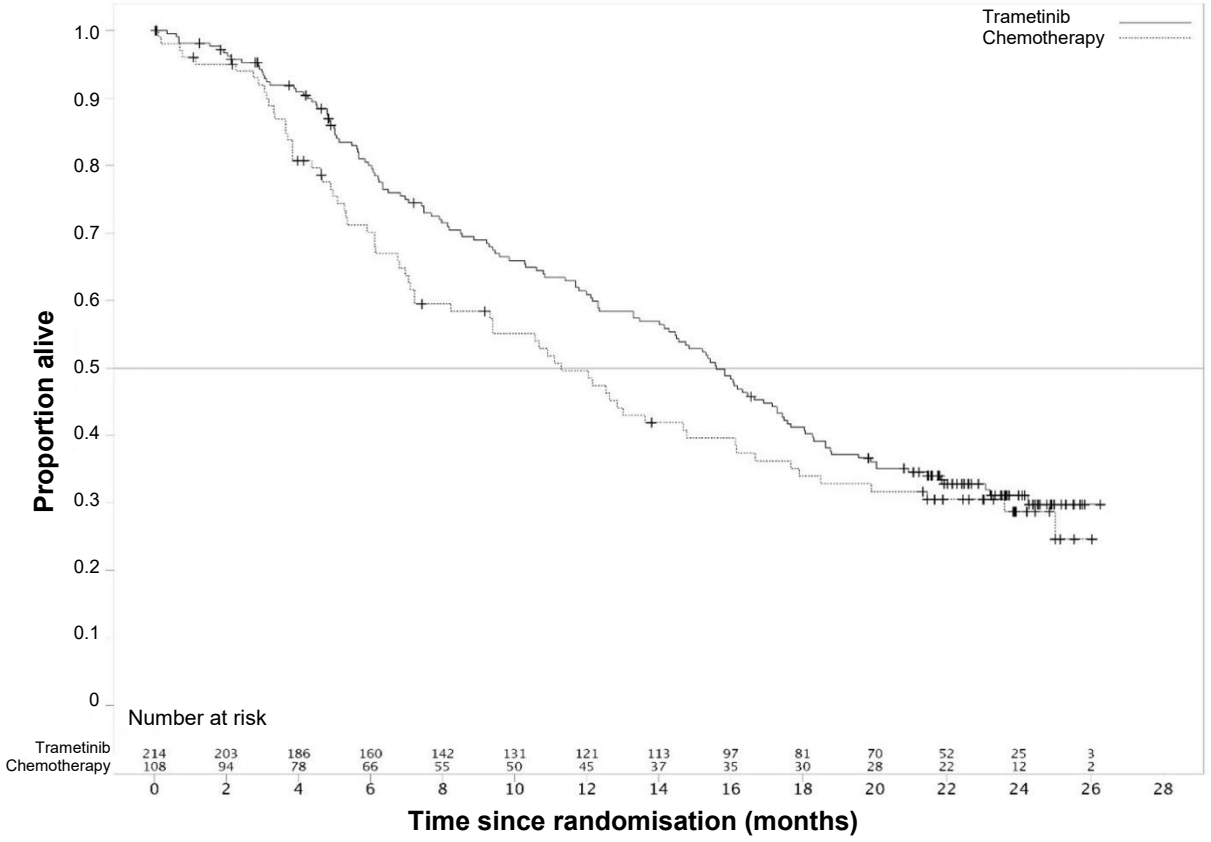
An additional OS analysis was undertaken based upon the 20 May 2013 data cut, see Table 12.

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

Table 12 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%).

The median duration of follow-up at the time of the primary analysis 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 13. The study showed a statistically significant difference for the primary outcome of investigator-assessed 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.

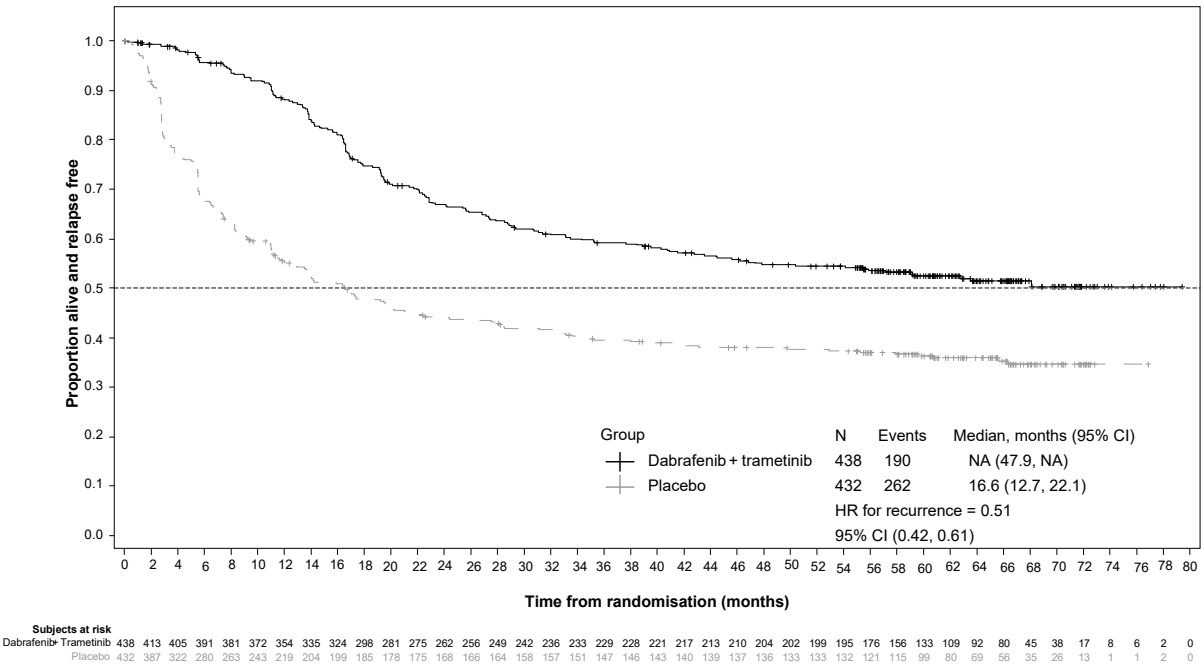
Table 13 Investigator-assessed RFS results for Study BRF115532 (COMBI-AD primary analysis)

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 log-rank 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)



At the time of the final OS analysis, the median duration of follow-up was 8.3 years in the combination arm and 6.9 years in the placebo arm. The observed difference in OS was not statistically significant (HR: 0.80; 95% CI: 0.62, 1.01) with 125 events (29%) in the combination arm and 136 events (31%) in the placebo arm. Estimated 5-year OS rates were 79% in the combination arm and 70% in the placebo arm, and estimated 10-year OS rates were 66% in the combination arm and 63% in the placebo arm.

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 14.

Table 14 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)	9.8 (6.9, 18.3)
	By IRC	15.2 (7.8, 23.5)	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			

Differentiated thyroid cancer (DTC)

Study CDRB436J12301 (J12301)
The safety and efficacy of trametinib in combination with dabrafenib (D+T) was evaluated in study J12301, a randomised (2:1), double-blind, placebo-controlled, multicentre phase III study in adult patients with BRAF V600E-mutation positive, locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer that had progressed following up to two prior VEGFR-targeting therapies (including, but not limited to, lenvatinib or sorafenib). BRAF V600E mutation status was centrally confirmed using the Cobas® 4800 assay.

153 patients were randomised to receive trametinib 2 mg orally once daily in combination with dabrafenib 150 mg orally twice daily (N=101) or placebo (N=52). Patients with a RET-fusion positive tumour were excluded. Randomisation was stratified by prior receipt of lenvatinib (yes versus no) and number of prior VEGFR targeted therapies (1 versus 2). Eligible patients randomised to placebo were allowed to cross over to D+T upon confirmation of progressive disease by blinded independent radiology review committee (BIRC). Patients continued blinded study treatment as long as they experienced clinical benefit or until there was unacceptable toxicity. The primary endpoint was progression-free survival (PFS) assessed by BIRC. The key secondary endpoints were overall response rate (ORR) as assessed by BIRC, and overall survival (OS).

The median age was 64 years (range 36 to 82 years) with 12 (8%) aged ≥75 years. The majority of patients were Asian (86%) and 52% were female. All patients had a confirmed diagnosis of papillary thyroid carcinoma. No patients with follicular thyroid carcinoma were included in the study. Prior lenvatinib use was reported for 31% of patients, and the majority (78%) had received one prior VEGFR-targeted therapy. Baseline ECOG performance status was 0 (50%), 1 (47%) or 2 (3%). The median duration of treatment was 14.5 months in the D+T arm and 5.5 months in the placebo arm.

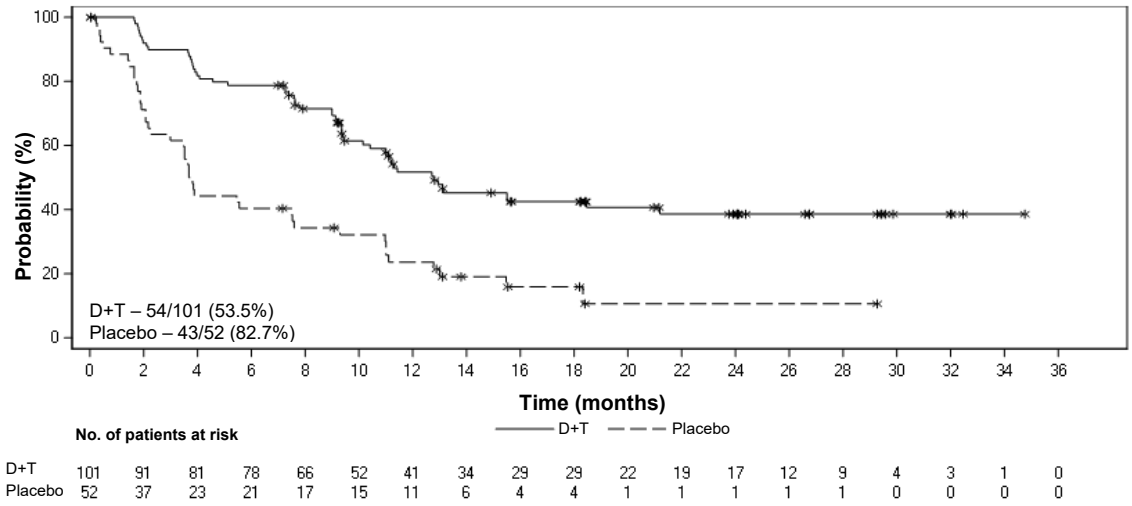
The results of the primary analysis (with a cut-off date of 22 January 2025 and a median follow-up of 17 months) are presented in Table 15 and Figure 5. The study demonstrated a statistically significant improvement in both PFS and ORR.

Table 15 Efficacy results in DTC (study J12301 primary analysis, ITT)

	Dabrafenib + trametinib n=101	**Placebo n=52**
Progression-free survival* (PFS) per BIRC		
Events (%)	54 (53.5%)	43 (82.7%)
Median PFS in months (95% CI)[a]	12.8 (10.2, 21.2)	3.7 (2.3, 7.5)
Hazard ratio (95% CI)[b]	0.38 (0.25, 0.57)	
p-value (one-sided)[c]	<0.001	
Confirmed best overall response per BIRC		
Confirmed ORR, n (%)	58 (57.4%)	2 (3.8%)
(95% CI)[d]	(47.2, 67.2)	(0.5, 13.2)
p-value (one-sided)[e]	<0.001	
Overall survival (OS)[f]		
Deaths, n (%)	27 (26.7%)	19 (36.5%)
Hazard ratio (95% CI)[b]	0.66 (0.36, 1.19)	

***** The primary analysis of PFS included censoring for new anti-cancer treatment. Results for PFS with and without censoring for new anti-cancer treatment were consistent.
CI: confidence interval, ORR=overall response rate (CR+PR); PR and CR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response is first met.
[a] Based on Kaplan-Meier estimate.
[b] Based on Cox regression model stratified by receipt of prior lenvatinib (yes vs. no) and number of prior VEGFR-targeted therapies (1 vs. 2).
[c] Based on a log rank test stratified by receipt of prior lenvatinib (yes vs. no) and number of prior VEGFR-targeted therapies (1 vs. 2).
[d] Clopper and Pearson exact binomial 95% CI.
[e] Based on a Cochran-Mantel-Haenszel test stratified by receipt of prior lenvatinib (yes vs. no) and number of prior VEGFR-targeted therapies (1 vs. 2).
[f] The improvement in OS was not statistically significant (at the time of the primary analysis, 30 patients [57.7%] had already crossed over from the placebo arm to the D+T arm).

Figure 5 Kaplan-Meier PFS curves for Study J12301 (primary analysis)



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).

Paediatric population

Data from clinical studies in adolescent patients with melanoma is very limited and extrapolation from adult data has been used to establish efficacy. A published retrospective Italian study described 6 paediatric participants with advanced BRAF V600 mutation-positive melanoma treated with trametinib in combination with dabrafenib. The median age at diagnosis was 15 years, and starting doses ranged from 125 mg to 150 mg twice daily for dabrafenib and from 1.5 mg to 2 mg once daily for trametinib. No disease recurrence was noted in 4 patients in the adjuvant setting after a median follow-up of 22 months. In the metastatic setting, one case of complete response and one case of progressive disease were reported.

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 1 200 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 studies 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

The population pharmacokinetic analysis showed no significant differences in the pharmacokinetics of trametinib between Asian and Caucasian patients. There are insufficient data to evaluate the potential effect of other races on trametinib pharmacokinetics.

Paediatric population

The pharmacokinetic exposures of trametinib at a weight-adjusted dosage in adolescent 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.

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 laurilsulfate
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 laurilsulfate
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

Unopened bottle

3 years

Opened bottle

After opening, store at not more than 30ºC and use within 30 days.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
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 either 7 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Mekinist 0.5 mg film-coated tablets

EU/1/14/931/001
EU/1/14/931/002

Mekinist 2 mg film-coated tablets

EU/1/14/931/005
EU/1/14/931/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 June 2014
Date of latest renewal: 14 February 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Lek Pharmaceuticals d.d.
Verovskova ulica 57
1526, Ljubljana
Slovenia

Novartis Pharmaceutical Manufacturing LLC
Verovskova ulica 57
1000, Ljubljana
Slovenia

Glaxo Wellcome, S.A.
Avda. Extremadura, 3
09400, Aranda de Duero
Burgos
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURS)**

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

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Mekinist 0.5 mg film-coated tablets
trametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

7 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant, do not remove or eat.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package to protect from light and moisture. Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/931/001 7 film-coated tablets
EU/1/14/931/002 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

mekinist 0.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Mekinist 0.5 mg tablets
trametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

7 tablets
30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle. Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/931/001 7 film-coated tablets
EU/1/14/931/002 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Mekinist 2 mg film-coated tablets
trametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

7 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains desiccant, do not remove or eat.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package to protect from light and moisture. Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/931/005 7 film-coated tablets
EU/1/14/931/006 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

mekinist 2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Mekinist 2 mg tablets
trametinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

7 tablets
30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle. Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/931/005 7 film-coated tablets
EU/1/14/931/006 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

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

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Mekinist is and what it is used for
2. What you need to know before you take Mekinist
3. How to take Mekinist
4. Possible side effects
5. How to store Mekinist
6. Contents of the pack and other information

1. What Mekinist is and what it is used for

Mekinist is a medicine that contains the active substance trametinib. It is used either on its own or in combination with another medicine containing dabrafenib in adults and adolescents aged 12 years and older to treat a type of skin cancer called melanoma that has spread to other parts of the body, or cannot be removed by surgery.

Mekinist in combination with dabrafenib is also used in adults and adolescents aged 12 years and older to prevent melanoma from coming back after it has been removed by surgery.

Mekinist in combination with dabrafenib is also used in adults to treat a type of lung cancer called non-small cell lung cancer (NSCLC).

Mekinist in combination with dabrafenib is also used in adults to treat a type of thyroid cancer called differentiated thyroid cancer (DTC).

These cancers have a particular change (mutation) in a gene called BRAF at the V600 position. This mutation in the gene may have caused the cancer to develop. Your medicine targets proteins made from this mutated gene and slows down or stops the development of your cancer.

2. What you need to know before you take Mekinist

Mekinist should only be used to treat cancers with the BRAF mutation. Therefore, before starting treatment your doctor will test for this mutation.

If your doctor decides that you will receive treatment with the combination of Mekinist and dabrafenib, **read the dabrafenib leaflet carefully as well as this leaflet**.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Do not take Mekinist
- if you are allergic to trametinib or any of the other ingredients of this medicine (listed in section 6).

Check with your doctor if you think this applies to you.

Warnings and precautions
Talk to your doctor before taking your medicine. Your doctor needs to know if you:
- have any **liver problems**. Your doctor may take blood samples to monitor your liver function while you are taking this medicine.
- have or have ever had **kidney problems**.
- have or have ever had **lung or breathing problems**.
- have heart problems such as heart failure (which can cause shortness of breath, difficulty in breathing when lying down, swelling of the feet or legs) or problems with the way your heart beats. Your doctor should check your heart function before and during treatment.
- have eye problems including blockage of the vein draining the eye (retinal vein occlusion) or swelling in the eye which may be caused by fluid blockage (chorioretinopathy).

Before you take Mekinist in combination with dabrafenib your doctor needs to know if you:
- **have had a different type of cancer other than melanoma, NSCLC or DTC**, as you may be at greater risk of developing non-skin cancers when taking Mekinist.

Check with your doctor if you think any of these may apply to you.

Conditions you need to look out for

Some people taking Mekinist develop other conditions which can be serious. You need to know about important symptoms to look out for.

Bleeding
Taking Mekinist or the combination of Mekinist and dabrafenib can cause serious bleeding including in your brain, the digestive system (such as stomach, rectum or intestine), lungs, and other organs, and can lead to death. Symptoms may include:
- headaches, dizziness, or feeling weak
- passing blood in the stools or passing black stools
- passing blood in the urine
- stomach pain
- coughing / vomiting up blood

Tell your doctor as soon as possible if you get any of these symptoms.

Fever
Taking Mekinist or the combination of Mekinist and dabrafenib may cause fever, although it is more likely if you are taking the combination treatment (see also section 4). In some cases, people with fever may develop low blood pressure, dizziness or other symptoms.
Tell your doctor immediately if you get a temperature above 38°C or if you feel a fever coming on while you are taking this medicine.

Heart disorder
Mekinist can cause heart problems, or make existing heart problems worse (see also "Heart conditions" in section 4) in people taking Mekinist in combination with dabrafenib.
Tell your doctor if you have a heart disorder. Your doctor will run tests to check that your heart is working properly before and during your treatment with this medicine. Tell your doctor immediately if it feels like your heart is pounding, racing, or beating irregularly, or if you experience dizziness, tiredness, light-headedness, shortness of breath or swelling in the legs. If necessary, your doctor may decide to interrupt your treatment or to stop it altogether.

Changes in your skin which may indicate new skin cancer
Your doctor will check your skin before you start taking this medicine and regularly while you are taking it. **Tell your doctor immediately** if you notice any changes to your skin while taking this medicine or after treatment (see also section 4).

Eye problems
You should have your eyes examined by your doctor while you are taking this medicine.
Tell your doctor immediately if you get eye redness and irritation, blurred vision, eye pain or other vision changes during your treatment (see also section 4).
Mekinist can cause eye problems including blindness. Mekinist is not recommended if you have ever had blockage of the vein draining the eye (retinal vein occlusion). Tell your doctor immediately if you get the following symptoms of eye problems: blurred vision, loss of vision or other vision changes, coloured dots in your vision or halos (seeing blurred outline around objects) during your treatment. If necessary, your doctor may decide to interrupt your treatment or to stop it altogether.

Liver problems
Mekinist, or the combination with dabrafenib, can cause problems with your liver which may develop into serious conditions such as hepatitis and liver failure, which may be fatal. Your doctor will monitor you periodically. Signs that your liver may not be working properly may include:
- loss of appetite
- feeling sick (nausea)
- being sick (vomiting)
- pain in your stomach (abdomen)
- yellowing of your skin or the whites of your eyes (jaundice)
- dark-coloured urine
- itching of your skin

Tell your doctor as soon as possible if you get any of these symptoms.

Lung or breathing problems
Tell your doctor if you have any lung or breathing problems, including difficulty in breathing often accompanied by a dry cough, shortness of breath and fatigue. Your doctor may arrange to check your lung function before you start taking your medicine.

Muscle pain
Mekinist can result in the breakdown of muscle (rhabdomyolysis), **Tell your doctor** as soon as possible if you get any of these symptoms:
- muscle pain
- dark urine due to kidney damage

If necessary, your doctor may decide to interrupt your treatment or to stop it altogether.

→ **Read the information "Possible serious side effects" in section 4 of this leaflet.**

Hole in the stomach or intestine (perforation)
Taking Mekinist or the combination of Mekinist and dabrafenib may increase the risk of developing holes in the gut wall. Tell your doctor as soon as possible if you have severe abdominal pain.

Serious skin reactions
Serious skin reactions have been reported in people taking Mekinist in combination with dabrafenib. Tell your doctor immediately if you notice any changes to your skin (see section 4 for symptoms to be aware of).

Inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes
An inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes (sarcoidosis). Common symptoms of sarcoidosis may include coughing, shortness of breath, swollen lymph nodes, visual disturbances, fever, fatigue, pain and swelling in the joints and tender bumps on your skin. Tell your doctor if you get any of these symptoms.

Immune system disorders
Mekinist in combination with dabrafenib may in rare instances cause a condition (haemophagocytic lymphohistiocytosis or HLH) in which the immune system makes too many infection-fighting cells, called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems. Tell your doctor immediately if you experience multiple symptoms such as fever, swollen lymph glands, bruising or skin rash, at the same time.

Tumour lysis syndrome
If you experience the following symptoms, tell your doctor immediately as this can be a life-threatening condition: nausea, shortness of breath, irregular heartbeat, muscular cramps, seizures, clouding of urine, decrease in urine output and tiredness. These may be caused by a group of metabolic complications that can occur during treatment of cancer that are caused by the breakdown products of dying cancer cells (tumour lysis syndrome or TLS) and can lead to changes in kidney function (see also section 4).

Children and adolescents
Mekinist is not recommended for children and adolescents under 18 years of age, except for adolescents aged 12 years and older with melanoma.

Other medicines and Mekinist
Before starting treatment, tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription. Keep a list of the medicines you take, so you can show it to your doctor, pharmacist or nurse when you get a new medicine.

Mekinist with food and drink
It is important to take Mekinist on an empty stomach because food affects the way the medicine is absorbed into your body (see section 3).

Pregnancy, breast-feeding and fertility
Mekinist is not recommended for use during pregnancy.
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Mekinist can harm the unborn baby.
- If you are a woman who could become pregnant, you must use reliable birth control (contraception) while you are taking Mekinist and for at least 16 weeks after you stop taking it.
- Birth control using hormones (such as pills, injections or patches) may not work as well if you are taking Mekinist in combination with dabrafenib. You need to use another effective method of birth control so you do not become pregnant while you are taking this combination of medicines. Ask your doctor, pharmacist or nurse for advice.
- If you do become pregnant while you are taking Mekinist, tell your doctor immediately.

Mekinist is not recommended while breast-feeding
It is not known whether the ingredients of Mekinist can pass into breast milk.
If you are breast-feeding, or planning to breast-feed, you must tell your doctor. It is recommended that you do not breast-feed while you are taking Mekinist. You and your doctor will decide whether you will take Mekinist or breast-feed.

Fertility – both men and women
Mekinist may impair fertility in both men and women.

Taking Mekinist with dabrafenib: Dabrafenib may permanently reduce male fertility. In addition, men who are taking dabrafenib may have a reduced sperm count, and their sperm count may not return to normal levels after they stop taking this medicine.

Prior to starting treatment with dabrafenib, talk to your doctor about options to improve your chances to have children in the future.

If you have any further questions on the effect of this medicine on fertility, ask your doctor, pharmacist or nurse.

Driving and using machines
Mekinist can have side effects that may affect your ability to drive or use machines. Avoid driving or using machines if you feel tired or weak, if you have problems with your vision or if your energy levels are low.
Descriptions of these effects can be found in other sections (see sections 2 and 4). Read all the information in this leaflet for guidance.
Discuss with your doctor, pharmacist or nurse if you are unsure about anything. Your disease symptoms and treatment situation may also affect your ability to drive or use machines.

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

3. How to take Mekinist

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take

Adults
- The usual dose of Mekinist is one 2 mg tablet once a day regardless of body weight.

Adolescents (12 to less than 18 years of age)
- Your doctor will decide on the correct dose of Mekinist for you based on your body weight.

Your doctor may decide to lower the dose if you get side effects.

Don't take more Mekinist than your doctor has recommended, since this may increase the risk of side effects.

How to take it
Swallow the tablet whole, with a full glass of water.
Take Mekinist once a day, on an empty stomach (at least 1 hour before a meal or 2 hours after a meal). This means that:
- after taking Mekinist, you must wait at least 1 hour before eating.
- after eating, you must wait at least 2 hours before taking Mekinist.

Take Mekinist at about the same time each day.

If you take more Mekinist than you should
If you take too many tablets of Mekinist, contact your doctor, pharmacist or nurse for advice. If possible, show them the Mekinist pack and this leaflet.

If you forget to take Mekinist
If the missed dose is less than 12 hours late, take it as soon as you remember.
If the missed dose is more than 12 hours late, skip that dose and take your next dose at the usual time. Then carry on taking your tablets at regular times as usual.
Do not take a double dose to make up for a forgotten dose.

If you stop taking Mekinist
Take Mekinist for as long as your doctor recommends. Do not stop unless your doctor advises you to.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

How should you take Mekinist in combination with dabrafenib
- Take Mekinist in combination with dabrafenib exactly as your doctor, pharmacist or nurse tells you. Do not change your dose or stop Mekinist or dabrafenib unless your doctor, pharmacist or nurse tells you to.
- Take **Mekinist once daily** and take **dabrafenib twice daily**. It may be good for you to get into the habit of taking both medicines at the same times each day. Mekinist should be taken with **either** the morning dose of dabrafenib **or** the evening dose of dabrafenib. The dabrafenib doses should be about 12 hours apart.
- Take Mekinist and dabrafenib on an empty stomach, at least one hour before or two hours after a meal. Take whole with a full glass of water.
- If you miss a dose of Mekinist or dabrafenib, take it as soon as you remember: Do not make up for missed doses and just take your next dose at your regular time:
    - If it is less than 12 hours to your next scheduled dose of Mekinist, which is taken once daily.
    - If it is less than 6 hours to your next scheduled dose of dabrafenib, which is taken twice daily.
- If you take too much Mekinist or dabrafenib, immediately contact your doctor, pharmacist or nurse. Take Mekinist tablets and dabrafenib capsules with you when possible. If possible, show them the Mekinist and dabrafenib pack with each leaflet.
- If you get side effects your doctor may decide that you should take lower doses of Mekinist and dabrafenib. Take the doses of Mekinist and dabrafenib exactly as your doctor, pharmacist or nurse tells you.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Possible serious side effects

Heart conditions
Mekinist can affect how well your heart pumps blood. It is more likely to affect people who have an existing heart problem. You will be checked for any heart problems while you are taking Mekinist. Signs and symptoms of heart problems include:
- feeling like your heart is pounding, racing, or beating irregularly
- dizziness
- tiredness
- feeling lightheaded
- shortness of breath
- swelling in the legs

Tell your doctor as soon as possible if you get any of these symptoms, either for the first time or if they get worse.

High blood pressure
Mekinist can cause new or worsening high blood pressure (hypertension). Your doctor or nurse should check your blood pressure during treatment with Mekinist. Call your doctor or nurse right away if you develop high blood pressure, your blood pressure worsens, or you have severe headache, light-headedness, or dizziness.

Bleeding problems
Mekinist can cause serious bleeding problems, especially in your brain or stomach. Call your doctor or nurse and get medical help right away if you have any unusual signs of bleeding, including:
- headaches, dizziness, or weakness
- coughing up of blood or blood clots
- vomit containing blood or that looks like "coffee grounds"
- red or black stools that look like tar

Eye (vision) problems
Mekinist can cause eye problems. Mekinist is not recommended if you have ever had a blockage of the vein draining the eye (retinal vein occlusion). Your doctor may advise an eye examination before you take Mekinist and while you are taking it. Your doctor may ask you to stop taking Mekinist or refer you to a specialist, if you develop signs and symptoms in your vision that include:
- loss of vision
- eye redness and irritation
- coloured dots in your vision
- halo (seeing a blurred outline around objects)
- blurred vision

Changes in your skin
Serious skin reactions have been reported in people taking Mekinist in combination with dabrafenib (frequency not known). If you notice any of the following:
- reddish patches on the trunk that are circular or target-shaped, with central blisters. Skin peeling. Ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome).
- widespread rash, fever, and enlarged lymph nodes (DRESS-syndrome or drug hypersensitivity syndrome).

  ➔ **stop using the medicine and seek medical attention immediately**

Up to 3 in 100 people taking Mekinist in combination with dabrafenib may develop a different type of skin cancer called *cutaneous squamous cell carcinoma (cuSCC)*. Others may develop a type of skin cancer called *basal cell carcinoma (BCC).* Usually, these skin changes remain local and can be removed with surgery and treatment with Mekinist and dabrafenib can be continued without interruption.

Some people taking Mekinist in combination with dabrafenib may also notice that new melanomas have appeared. These melanomas are usually removed by surgery and treatment with Mekinist and dabrafenib can be continued without interruption.

Your doctor will check your skin before you start taking dabrafenib, then check it again every month while you are taking dabrafenib and for 6 months after you stop taking it. This is to look for any new skin cancers.

Your doctor will also check your head, neck, mouth and lymph glands and you will have scans of your chest and stomach area (called CT scans) regularly. You may also have blood tests. These checks are to detect if any other cancer, including squamous cell carcinoma, develops inside your body. Pelvic examinations (for women) and anal examinations are also recommended before and at the end of your treatment.

Mekinist as monotherapy or in combination with dabrafenib can cause rash or acne-like rash. Follow your doctor's instructions for what to do to help prevent rash. Tell your doctor or nurse as soon as possible if you get any of these symptoms for the first time or if they get worse.
Contact your doctor immediately if you get a severe skin rash with any of the following symptoms: blisters on your skin, blisters or sores in your mouth, peeling of your skin, fever, redness or swelling of your face, or soles of your feet.

Tell your doctor or nurse as soon as possible if you get any skin rash, or if you have a rash that gets worse.

Muscle pain
Mekinist can result in the breakdown of muscle (rhabdomyolysis). Tell your doctor or nurse if you have any new or worsening symptoms, including:
- muscle pain
- dark urine due to kidney damage

Lung or breathing problems
Mekinist can cause inflammation of the lung (pneumonitis or interstitial lung disease). Tell your doctor or nurse if you have any new or worsening symptoms of lung or breathing problems, including:
- shortness of breath
- cough
- fatigue

Immune system disorders
If you experience multiple symptoms such as fever, swollen lymph glands, bruising or skin rash, at the same time, tell your doctor immediately. These may be signs of a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (haemophagocytic lymphohistiocytosis), see section 2 (frequency rare).

Tumour lysis syndrome
Tell your doctor immediately if you experience the following symptoms: nausea, shortness of breath, irregular heartbeat, muscular cramps, seizures, clouding of urine, decrease in urine output and tiredness. These may be signs of a condition resulting from a rapid breakdown of cancer cells which in some people may be fatal (tumour lysis syndrome or TLS), see section 2 (frequency not known).

Possible side effects in patients taking Mekinist alone

The side effects that you may see when you take Mekinist alone are as follows:

Very common side effects (may affect more than 1 in 10 people):
- High blood pressure (hypertension)
- Bleeding, at various sites in the body, which may be mild or serious
- Cough
- Shortness of breath
- Diarrhoea
- Feeling sick (nausea), being sick (vomiting)
- Constipation
- Stomach ache
- Dry mouth

- Skin rash, acne-like rash, redness of the face, dry or itching skin (see also "Changes in your skin" earlier in section 4)
- Unusual hair loss or thinning
- Lack of energy or feeling weak or tired
- Swelling of the hands or feet (oedema peripheral)
- Fever

Very common side effects that may show up in your blood tests
- Abnormal blood test results related to the liver

Common side effects (may affect up to 1 in 10 people):
- Inflammation of hair follicles in the skin
- Nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles
- Infection of the skin (cellulitis)
- Skin rash with pus-filled blisters (see also "Changes in your skin" earlier in section 4)
- Allergic reaction (hypersensitivity)
- Dehydration (low levels of water or fluid)
- Blurred vision
- Swelling around the eyes
- Eyesight problems (see also "Eye (vision) problems" earlier in section 4)
- Changes in how the heart pumps blood (left ventricular dysfunction) (see also "Heart conditions" earlier in section 4)
- Heart rate that is lower than the normal range and/or a decrease in heart rate
- Localised tissue swelling
- Inflammation of the lung (pneumonitis or interstitial lung disease)
- Sore mouth or mouth ulcers, inflammation of mucous membranes
- Reddening, chapping or cracking of the skin
- Red, painful hands and feet
- Swelling of the face
- Inflammation of the mucosa
- Feeling weak
- Problem with the nerves that can produce pain, loss of sensation or tingling in hands and feet and/or muscle weakness (peripheral neuropathy)

Common side effects that may show up in your blood tests:
- Decreased red blood cells (anaemia), abnormal test related to creatine phosphokinase, an enzyme found mainly in heart, brain, and skeletal muscle

Uncommon side effects (may affect up to 1 in 100 people):
- Swelling in the eye caused by fluid leakage (chorioretinopathy) (see also "Eye (vision) problems" earlier in section 4)
- Swelling of nerves at the back of the eye (papilloedema) (see also "Eye (vision) problems" earlier in section 4)
- Separation of the light-sensitive membrane in the back of the eye (the retina) from its supporting layers (retinal detachment) (see also "Eye (vision) problems" earlier in section 4).
- Blockage of the vein draining the eye (retinal vein occlusion) (see also "Eye (vision) problems" earlier in section 4)
- Heart pumping less efficiently, causing shortness of breath, extreme tiredness and swelling in ankles and legs (heart failure)
- A hole (perforation) in the stomach or intestines
- Inflammation of the intestines (colitis)
- Breakdown of muscle which can cause muscle pain and kidney damage (rhabdomyolysis)

Not known (frequency cannot be estimated from the available data):
- Irregular heartbeat (atrioventricular block)

Side effects when Mekinist and dabrafenib are taken together

When you take Mekinist and dabrafenib together you may get any of the side effects given in the lists above, although the frequency may change (increase or decrease).

You may also get **additional side effects due to taking dabrafenib** at the same time as Mekinist in the list below.

Tell your doctor as soon as possible if you get any of these symptoms, either for the first time or if they get worse.

Please read the dabrafenib Package Leaflet for details of the side effects you may get when taking this medicine.

The side effects that you may see when you take Mekinist in combination with dabrafenib are as follows:

Very common side effects (may affect more than 1 in 10 people):
- Nasal and throat inflammation
- Urinary tract infection
- Decreased appetite
- Headache
- Dizziness
- High blood pressure (hypertension)
- Bleeding, at various sites in the body, which may be mild or serious (haemorrhage)
- Cough
- Stomach ache
- Constipation
- Diarrhoea
- Feeling sick (nausea), being sick (vomiting)
- Rash, dry skin, itching, skin reddening
- Acne-like problems (dermatitis acneiform)
- Joint pain, muscle pain, or pain in the hands or feet
- Muscle spasms
- Lack of energy, feeling weak
- Chills
- Swelling of the hands or feet (oedema peripheral)
- Fever
- Flu-like illness

Very common side effects that may show up in your blood tests
- Abnormal blood test results related to the liver
- Low levels of white blood cells (neutropenia)
- Decrease in number of red blood cells (anaemia)

Common side effects (may affect up to 1 in 10 people):
- Skin effects including infection of the skin (cellulitis), inflammation of hair follicles in the skin, nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles, skin rash with pus-filled blisters, cutaneous squamous cell carcinoma (a type of skin cancer), papilloma (a type of skin tumour which is usually not harmful), wart-like growths, increased sensitivity of the skin to sun (see also “Changes in your skin” earlier in section 4)
- Dehydration (low levels of water or fluid)
- Blurred vision, eyesight problems, inflammation of the eye (uveitis)
- Heart pumping less efficiently

- Heart rate that is lower than the normal range and/or a decrease in heart rate (bradycardia)
- Low blood pressure (hypotension)
- Localised tissue swelling
- Inflammation of the lung (pneumonitis)
- Shortness of breath
- Dry mouth
- Sore mouth or mouth ulcers, inflammation of mucous membranes
- Inflamed, flaky skin (exfoliative dermatitis)
- Thickening of the outer layer of the skin (hyperkeratosis), patches of thick, scaly, or crusty skin (actinic keratosis), chapping or cracking of the skin
- Increased sweating, night sweats
- Unusual hair loss or thinning
- Red, painful hands and feet
- Inflammation of the fatty layer under the skin (panniculitis)
- Kidney failure (renal failure)
- Severely decreased urine output (acute kidney injury)
- Inflammation of the mucosa
- Swelling of the face
- Problem with the nerves that can produce pain, loss of sensation or tingling in hands and feet and/or muscle weakness (peripheral neuropathy)

Common side effects that may show up in your blood tests
- Decrease in blood platelets (cells that help blood to clot) and a type of white blood cells (leukopenia)
- Low levels of sodium (hyponatraemia) or phosphate (hypophosphataemia) in the blood
- Increase in blood sugar level
- Increase in creatine phosphokinase, an enzyme found mainly in heart, brain, and skeletal muscle
- Increase in some substances (enzymes) produced by the liver

Uncommon side effects (may affect up to 1 in 100 people):
- Appearance of new skin cancer (melanoma)
- Skin tags
- Allergic reactions (hypersensitivity)
- Eye changes including swelling in the eye caused by fluid leakage (chorioretinopathy), separation of the light-sensitive membrane in the back of the eye (the retina) from its supporting layers (retinal detachment) and swelling around the eyes
- Breathlessness, difficulty breathing when lying down, swelling of the feet or legs as signs of heart muscle not pumping blood as well as it should (cardiac failure)
- Fatigue, feeling full or bloated, heart palpitations, loss of appetite, nausea, reduced ability to exercise, shortness of breath, swelling as signs of changes in the way that the heart pumps (left ventricular dysfunction)
- Irregular heartbeat (atrioventricular block)
- A hole (perforation) in the stomach or intestines (gastrointestinal perforation)
- Inflammation of pancreas
- Inflammation of the intestines (colitis)
- Inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes (sarcoidosis)
- Raised, painful, red to dark reddish-purple skin patches or sores that appear mainly on the arms, legs, face and neck, with a fever (signs of acute febrile neutrophilic dermatosis)
- Abnormal breakdown of muscle causing pain, fever, red-brown urine (rhabdomyolysis)

Rare side effects (may affect up to 1 in 1 000 people)
- Cough, difficulty breathing, painful breathing (interstitial lung disease)
- Inflammation of the kidneys (nephritis)

Not known (frequency cannot be estimated from the available data):
- Inflammation of the heart muscle (myocarditis) which can result in breathlessness, fever, palpitations and chest pain.
- Skin reactions localised in tattoos

Additional side effects in adolescents

Very common side effects (may affect more than 1 in 10 people)
- Increase in weight (abnormal weight gain)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Mekinist

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and carton after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light and moisture.
Keep the bottle tightly closed with the dessicant inside (small cylinder-shaped container).

Before opening: This medicine does not require any special temperature storage conditions.
After opening: Store at not more than 30°C. Use within 30 days of opening.

Do not throw away medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Mekinist contains
- The active substance is trametinib. Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 0.5 mg or 2 mg of trametinib.
- The other ingredients are
  - Tablet: mannitol (E421), microcrystalline cellulose (E460), hypromellose (E464), croscarmellose sodium (E468), magnesium stearate (E470b), sodium laurilsulfate and colloidal silicon dioxide (E551).
  - Film coating: hypromellose (E464), titanium dioxide (E171), polyethylene glycol, iron oxide yellow (E172) (for 0.5 mg tablets), polysorbate 80 (E433) and iron oxide red (E172) (for 2 mg tablets).

What Mekinist looks like and contents of the pack
The Mekinist 0.5 mg film-coated tablets are yellow, modified oval, biconvex, with the company logo debossed on one face and “TT” on the opposing face.

The Mekinist 2 mg film-coated tablets are pink, round, biconvex, with the company logo debossed on one face and “LL” on the opposing face.

The film-coated tablets are supplied in opaque white plastic bottles with threaded plastic closures. One bottle contains either 7 or 30 tablets.

The bottles also include a silica gel desiccant in a small cylinder-shaped container. The desiccant must be kept inside the bottle and must not be eaten.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.