1 Tradename

MEKINIST® 0.5 mg and 2 mg film-coated tablets.

2 Description and composition

Pharmaceutical form

0.5 mg film-coated tablets

Yellow, modified oval, biconvex, film-coated tablets with 'GS' debossed on one face and 'TFC' on the opposing face.

Yellow, ovaloid, biconvex, unscored film-coated tablets with beveled edges and with the Novartis logo debossed on one side and 'TT' on the other side.

2 mg film-coated tablets

Pink, round, biconvex, film-coated tablets with 'GS' debossed on one face and 'HMJ' on the opposing face.

Pink, round, biconvex, unscored film-coated tablets with beveled edges and with the Novartis logo debossed on one side and 'LL' on the other side.

Certain dosage strengths and dosage forms may not be available in all countries.

Active substance

0.5 mg film-coated tablets

Each film-coated tablet contains trametinib-dimethylsulfoxide (1:1) equivalent to 0.5 mg trametinib.

2 mg film-coated tablets

Each film-coated tablet contains trametinib-dimethylsulfoxide (1:1) equivalent to 2 mg trametinib.

Excipients

Tablet core: mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (vegetable source), sodium laurylsulfate, colloidal silicon dioxide.

Tablet film coating: hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow (for 0.5 mg tablets), polysorbate 80 and iron oxide red (for 2 mg tablets).

Pharmaceutical formulations may vary between countries.

3 Indications

Unresectable or metastatic melanoma

Trametinib as monotherapy or in combination with dabrafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (*see section 6 Warnings and Precautions and section 12 Clinical studies*).

Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy *(see section 12 Clinical studies)*.

Adjuvant treatment of melanoma

Trametinib in combination with dabrafenib is indicated for the adjuvant treatment of patients with melanoma with BRAF V600 mutation and involvement of lymph node(s), following complete resection.

Advanced non-small cell lung cancer

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

Locally advanced or metastatic anaplastic thyroid cancer

Trametinib in combination with dabrafenib is indicated for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with a BRAF V600 mutation and with no satisfactory locoregional treatment options *(see section 12 Clinical studies).*

4 Dosage regimen and administration

Treatment with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.

Before taking trametinib, patients must have confirmation of BRAF V600 mutation using a validated test.

When Mekinist is used in combination with Tafinlar, please also refer to the full Tafinlar Package Insert.

Dosage regimen

General target population

Adults

Recommended Dosage for Unresectable or Metastatic Melanoma

The recommended dose of trametinib, either used as monotherapy or in combination with dabrafenib, is 2 mg once daily. The recommended dose of dabrafenib, when used in combination with trametinib, is 150 mg twice daily. It is recommended that patients continue treatment with trametinib until patients no longer derive benefit or the development of unacceptable toxicity.

Recommended Dosage for the Adjuvant Treatment of Melanoma

The recommended dose of trametinib in combination with dabrafenib is 2 mg once daily. The recommended dose of dabrafenib, when used in combination with trametinib, is 150 mg twice daily, until disease recurrence or unacceptable toxicity for up to 1 year.

Recommended Dosage for NSCLC

The recommended dose of trametinib in combination with dabrafenib, is 2 mg once daily. The recommended dose of dabrafenib, when used in combination with trametinib, is 150 mg twice daily. It is recommended that patients continue treatment with trametinib until patients no longer derive benefit or the development of unacceptable toxicity.

Recommended Dosage for ATC

The recommended dose of trametinib in combination with dabrafenib, is 2 mg once daily. The recommended dose of dabrafenib, when used in combination with trametinib, is 150 mg twice daily, until 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 adjustments

Mekinist as monotherapy and in combination with Tafinlar

The management of adverse events/ adverse drug reactions may require treatment interruption, dose reduction, or treatment discontinuation.

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

Recommended dose level reductions are provided in Table 4-1. Doses below 1 mg once daily are not recommended.

Table 4-1 Recommended dose level reductions

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

The recommended dose modification schedule is provided in Table 4-2. 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 Mekinist dose should not exceed 2 mg once daily.

Table 4-2 Dose modification schedule based on the grade of any Adverse Events (AE) (excluding pyrexia)

Grade (CTC-AE)*	**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 events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)

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 pyrexia, 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

Pyrexia

Therapy should be interrupted (Mekinist when used as monotherapy, and both Mekinist and Tafinlar when used in combination) if the patient's temperature is ≥38ºC (100.4°F). 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. Patients should be evaluated for signs and symptoms of infection (see section 6 Warnings and precautions). Mekinist, or both Mekinist and Tafinlar when used in combination, should be restarted if 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. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient.

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 Warnings and Precautions)*.

RAS-mutation-positive non-cutaneous malignancies

Consider the benefits and risks 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 below the institution's lower limit of normal (LLN) *(see section Warnings and Precautions)*. 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 Warnings and Precautions*).

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 Warnings and Precautions*).

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 4-3 below for trametinib (*see section Warnings and Precautions*).

Table 4-3 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

Withhold trametinib 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. Permanently discontinue trametinib for 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. Mild or moderate renal impairment had no significant effect on the population pharmacokinetics of Mekinist (*see section Clinical pharmacology, Pharmacokinetics*). There are no clinical data 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. In a population pharmacokinetic analysis, trametinib oral clearance and thus exposure was not significantly different in patients with mild hepatic impairment compared to patients with normal hepatic function. Available data in patients with moderate or severe hepatic impairment from a clinical pharmacology study indicate a limited impact on trametinib exposure (see *section Clinical pharmacology, Pharmacokinetics)*. Trametinib should be used with caution in patients with

moderate or severe hepatic impairment when administered as monotherapy or in combination with dabrafenib.

Non-Caucasian patients

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

Geriatric patients (65 years of age or above)

No dose adjustment is required in patients 65 years of age or older *(see section Clinical pharmacology, Pharmacokinetics)*. More frequent dose adjustments (see Tables 4-1 and 4-2 above) may be required in patients 65 years of age or older (*see section Adverse Drug Reactions*).

Pediatric patients (below 18 years)

The safety and efficacy of trametinib in pediatric patients have not been established. Mekinist is not recommended in this age group. No data are available. Studies in juvenile animals have shown adverse effects of trametinib which had not been observed in adult animals (*see section Non-clinical safety data*).

Method of administration

Trametinib should be taken orally with a full glass of water. Trametinib tablets should not be chewed or crushed. Trametinib should be taken without food, at least 1 hour before or 2 hours after a meal *(see section Clinical pharmacology)*.

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 Package Insert for information on method of administration when given in combination with trametinib.

5 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed.

6 Warnings and precautions

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

<u>BRAF V600 testing</u>

The efficacy and safety of trametinib have not been evaluated in patients whose melanoma, NSCLC or ATC 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 Clinical pharmacology*). 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.

Trametinib in combination with dabrafenib in patients with brain metastases

The safety and efficacy of the combination of trametinib and dabrafenib have not been evaluated in patients with a BRAF V600 mutation-positive melanoma which has metastasised to the brain.

New malignancies

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

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 Package Insert.

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 Package Insert.

Non-cutaneous malignancy

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 Package Insert. 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 Adverse drug reactions)*.

The potential for these events in patients with unstable and/or symptomatic brain metastases or low platelets (<75,000) is not established as patients with these conditions were excluded from

clinical trials. The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy. If haemorrhage occurs, patients should be treated as clinically indicated.

Out of the 559 unresectable or metastatic melanoma patients treated with Mekinist in combination with Tafinlar, there were seven fatal intracranial hemorrhagic cases (1%). Three cases were from study MEK115306 (COMBI-d) and three cases were from study MEK116513 (COMBI-v). During the COMBI-v three year extended follow-up, one fatal intracranial hemorrhage occurred in one additional patient. No fatal hemorrhagic events occurred in the Phase III study in the adjuvant treatment of melanoma. Two out of 93 patients (2%) receiving Mekinist in combination with Tafinlar in a Phase II NSCLC trial had fatal intracranial hemorrhagic events. If patients develop symptoms of hemorrhage they should immediately seek medical care.

LVEF reduction/Left ventricular dysfunction

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

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

Pyrexia was reported in the clinical trials with trametinib as monotherapy and in combination with dabrafenib *(see section Adverse drug reactions)*. The incidence and severity of pyrexia are increased with the combination therapy with dabrafenib (see dabrafenib Package Insert). In patients with unresectable or metastatic melanoma who received the combination dose of Mekinist 2 mg once daily and Tafinlar 150 mg twice daily developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy. About one third of the patients receiving combination therapy who experienced pyrexia had three or more events Pyrexia may be accompanied by severe rigors, dehydration, and hypotension, which in some cases can lead to acute renal insufficiency. Serum creatinine and other evidence of renal function should be monitored during and following severe events of pyrexia. Serious non-infectious febrile events have been observed. These events responded well to dose interruption and/or dose reduction and supportive care in clinical trials.

A cross-study comparison in 1,810 patients treated with combination therapy demonstrated a reduction in the incidence of high-grade pyrexia and other pyrexia-related adverse outcomes when both Mekinist and Tafinlar were interrupted, compared to when only Tafinlar was interrupted. Therefore, interruption of both Mekinist and Tafinlar is recommended if patient's

temperature is ≥38ºC (100.4°F), and in case of recurrence, therapy can also be interrupted at the first symptom of pyrexia (see sections 4 Dosage regimen and administration and 12 Clinical studies)

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 Adverse drug reactions)*. Blood pressure should be measured at baseline and monitored during treatment with trametinib, with control of hypertension by standard therapy as appropriate.

Interstitial lung disease (ILD)/Pneumonitis

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

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 Dosage regimen and administration)*. 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 chorioretinopathy or RPED and RVO, may occur with trametinib as monotherapy and in combination with dabrafenib. Symptoms such as blurred vision, decreased acuity, and other visual phenomena have been reported in the clinical trials with trametinib *(see section Adverse drug reactions)*. In clinical trials uveitis and iridocyclitis have also been reported in patients treated with trametinib in combination with dabrafenib.

Trametinib is not recommended in patients with a history of RVO. A thorough ophthalmological evaluation should be performed at baseline and during treatment with Mekinist, if clinically warranted. 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 visual disturbances, such as diminished central vision, blurred vision or loss of vision at any time while on trametinib therapy, additional ophthalmological evaluation should be undertaken. If a retinal abnormality is noted, treatment with Mekinist should be interrupted immediately and referral to a retinal specialist should be considered. If RPED is diagnosed, the dose modification schedule in Table 4-3 should be followed *(see section Dosage regimen and administration)*; if uveitis is diagnosed, please refer to dabrafenib Package Insert. 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.

Skin Toxicity

Rash

In clinical studies, rash has been observed in about 60% of patients receiving trametinib as monotherapy and 20 to 30% receiving trametinib in combination with dabrafenib *(see section Adverse drug reactions)*. The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions.

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 Mekinist in combination with Tafinlar. 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, Mekinist and Tafinlar should be withdrawn

Rhabdomyolysis

Rhabdomyolysis has been reported in patients taking trametinib as monotherapy or in combination with dabrafenib *(see section Adverse drug reactions)*. 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 Package Insert.

Pancreatitis

Pancreatitis has been reported in patients treated with trametinib in combination with dabrafenib in clinical studies. Please refer to the dabrafenib Package Insert.

Hepatic events

Hepatic adverse events have been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib (*see section Adverse drug reactions*). 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 section Dosage regimen and administration and section Clinical pharmacology, Pharmacokinetics)*.

Venous thromboembolism (VTE)

VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE) can occur on Mekinist monotherapy and when Mekinist is used in combination with Tafinlar. Patients should

be advised to immediately seek medical care if they develop symptoms of VTE (see section Adverse drug reactions).

Colitis and gastrointestinal perforation

Colitis and gastrointestinal perforation, including fatal outcome, have been reported in patients taking trametinib as monotherapy and in combination with dabrafenib *(see section Adverse drug reactions)*. 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 medications with a recognised risk of gastrointestinal perforation.

If patients develop symptoms of colitis and gastrointestinal perforation they should immediately seek medical care.

Hemophagocytic lymphohistiocytosis (HLH)

In post-marketing experience, HLH has been observed with trametinib in combination with dabrafenib. If HLH is suspected, treatment should be interrupted. If HLH is confirmed, treatment should be discontinued and appropriate management of HLH should be initiated.

Tumour Lysis Syndrome (TLS)

Cases of TLS, including fatal cases, have been reported in patients treated with Mekinist in combination with Tafinlar (see section 7 Adverse drug reactions). Risk factors for TLS include rapidly growing tumors, a high tumor burden, renal dysfunction, and dehydration. Patients with risk factors for TLS should be closely monitored, prophylaxis should be considered (e.g., intravenous hydration and treatment of high uric acid levels prior to initiating treatment) and treated as clinically indicated.

7 Adverse drug reactions

Summary of the safety profile

The safety of trametinib monotherapy has been evaluated in the integrated population of 329 patients with BRAF V600 mutant unresectable or metastatic melanoma treated with trametinib 2 mg orally 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 Clinical Studies*). The most common adverse reactions (≥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 641 patients with BRAF V600 mutant unresectable or metastatic melanoma and advanced NSCLC treated with trametinib 2 mg once daily and dabrafenib 150 mg twice daily. Of these patients, 559 were treated with the combination for BRAF V600 mutant melanoma in two randomised Phase III studies, MEK115306 (COMBI-d) and MEK116513 (COMBI-v), and 82 were treated with the combination for BRAF V600 mutant NSCLC in a multi-cohort, non-randomised Phase II study BRF113928 *(see section Clinical Studies)*.

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

The safety profile observed in study BRF117277/DRB436B2204 (COMBI-MB) in metastatic melanoma patients with brain metastases is consistent with the safety profile of Mekinist in combination with Tafinlar in unresectable or metastatic melanoma (see also section Clinical studies).

Tabulated summary of adverse reactions

Adverse reactions are listed below by MedDRA body 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
Not known	(cannot be estimated from the available data)

Categories have been assigned based on absolute frequencies in the clinical trial data. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 7-1 Adverse reactions reported in the integrated safety population of trametinib monotherapy (n=329)

System Organ Class	Frequency category Integrated Safety Data N=329	Adverse Reactions
Infections and infestation	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
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
Vascular disorders	Very common	Hypertension
		Haemorrhage[b]
	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 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] Events include but are not limited to: epistaxis, haematochezia, gingival bleeding, haematuria, and rectal, haemorrhoidal, gastric, vaginal, conjunctival, intracranial and post procedural haemorrhage.		

Table 7-2 Unresectable or metastatic melanoma and Advanced NSCLC Adverse reactions reported in the integrated safety population of trametinib in combination with dabrafenib (n=641)

System Organ Class	Frequency (all grades)	Adverse Reactions
Infections and Infestations	Very common	Urinary tract infection
		Nasopharyngitis
	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
		Acrochordon (skin tags)

Blood and lymphatic system disorders	Very common	Neutropenia
	Common	Anaemia
		Thrombocytopenia
		Leukopenia
Immune system disorders	Uncommon	Hypersensitivity[c]
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Dehydration
		Hyponatraemia
		Hypophosphataemia
		Hyperglycaemia
Nervous system disorders	Very common	Headache
		Dizziness
Eye disorders	Common	Vision blurred
		Visual impairment
	Uncommon	Chorioretinopathy
		Uveitis
		Retinal detachment
		Periorbital oedema
Cardiac disorder	Common	Ejection fraction decreased
	Uncommon	Bradycardia
	Unknown	Myocarditis
Vascular disorders	Very common	Hypertension
		Haemorrhage[d]
	Common	Hypotension
		Lymphoedema
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea
		Pneumonitis
Gastrointestinal disorders	Very common	Abdominal pain
		Constipation
		Diarrhoea
		Nausea
		Vomiting
	Common	Dry mouth
		Stomatitis
	Uncommon	Pancreatitis
		Gastrointestinal perforation
		Colitis

Skin and subcutaneous disorders	Very common	Dry skin
		Pruritus
		Rash
		Erythema
	Common	Dermatitis acneiform
		Actinic keratosis
		Night sweats
		Hyperkeratosis
		Alopecia
		Palmar-plantar erythrodysaesthesia syndrome
		Skin lesion
		Hyperhidrosis
		Panniculitis
		Photosensitivity[e]
		Skin fissures
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Myalgia
		Pain in extremity
		Muscle spasms
Renal and urinary disorders	Common	Renal failure
	Uncommon	Nephritis
General disorders and administration site conditions	Very common	Fatigue
		Chills
		Asthenia
		Oedema peripheral
		Pyrexia
	Common	Mucosal inflammation
		Influenza-like illness
		Face oedema
Investigations	Very common	Alanine aminotransferase increased
		Aspartate aminotransferase increased
	Common	Blood alkaline phosphatase increased
		Gamma-glutamyltransferase increased
		Blood creatine phosphokinase increased

[a] cu SCC: SCC, SCC of the skin, SCC *in situ* (Bowen's disease) and keratoacanthoma
[b] Papilloma, skin papilloma
[c] Includes drug hypersensitivity
[d] Bleeding from various sites, including intracranial bleeding and fatal bleeding
e Photosensitivity cases were also observed in post-marketing experience. All cases reported in the COMBI-d and COMBI-v clinical trials were Grade 1 and no dose modification was required.

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 Package Insert.

Haemorrhage

Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages occurred in patients taking trametinib as monotherapy and in combination with dabrafenib. The majority

of bleeding events were mild. Fatal intracranial haemorrhages occurred in the integrated safety population of trametinib in combination with dabrafenib in 1% (8/641) 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 Warnings and precautions*).

LVEF reduction/Left ventricular dysfunction

Trametinib has been reported to decrease LVEF when used as monotherapy or in combination with dabrafenib. In clinical trials, the median time to first occurrence of left ventricular dysfunction, cardiac failure and LVEF decrease was between 2 to 5 months. In the integrated safety population of trametinib in combination with dabrafenib, decreased LVEF has been reported in 8% (54/641) of patients with most cases being asymptomatic and reversible. Patients with LVEF lower than the institutional lower limit of normal were not included in clinical trials with trametinib. Trametinib should be used with caution in patients with conditions that could impair left ventricular function (see *section Dosage regimen and administration* and *Section Warnings and precautions*).

Pyrexia

Pyrexia has been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib; however, the incidence and severity of pyrexia are increased with the combination therapy. Please refer to *section Warnings and precautions and 7 Adverse drug reaction* of the dabrafenib Package Insert.

Hepatic events

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

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 Warnings and precautions*).

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 *section Dosage regimen and administration and 6*

Warnings and precautions).

Visual impairment

Disorders associated with visual disturbances, including RPED and RVO, have been observed with trametinib. Symptoms such as blurred vision, decreased acuity, and other visual disturbances have been reported in the clinical trials with trametinib (*see section dosage regimen and administration and 6 Warnings and precautions*).

Rash

Rash has been observed in about 60% of patients when given as monotherapy and in about 25% 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 section Dosage regimen and administration and 6 Warnings and precautions*).

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 Warnings and precautions).

Pancreatitis

Pancreatitis has been reported with dabrafenib in combination with trametinib. Please see the dabrafenib Package Insert.

Renal failure

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

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 events (AE) and serious adverse events (SAE) was similar in the subjects aged <65 years and those aged ≥65 years. Patients ≥65 years were more likely to experience AEs 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=641), 180 patients (28%) were ≥65 years of age; 50 patients (8%) were ≥75 years of age. The proportion of patients experiencing AEs was similar in those aged <65 years and those aged ≥65 years in all studies. Patients ≥65 years were more likely to experience SAEs and AEs 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 Pharmacokinetics*). Trametinib should be used with caution in patients with severe renal impairment (*see section Dosage regimen and administration and 6 Warnings and precautions*).

Hepatic impairment

No dosage adjustment is required in patients with mild hepatic impairment (*see section Pharmacokinetics*). Trametinib should be used with caution in patients with moderate or severe hepatic impairment (*see section Dosage regimen and administration and 6 Warnings and precautions*).

Adjuvant treatment of melanoma

Mekinist in combination with Tafinlar

The safety of Mekinist in combination with Tafinlar was evaluated in a Phase III, randomized, double-blind study of Mekinist in combination with Tafinlar versus two placebos in the adjuvant treatment of Stage III BRAF V600 mutation-positive melanoma after surgical resection (see section Clinical studies).

In the Mekinist 2 mg once daily and Tafinlar 150 mg twice daily arm, the most common adverse reactions (≥20%) were pyrexia, fatigue, nausea, headache, rash, chills, diarrhea, vomiting, arthralgia, and myalgia.

Table 7-3 lists the adverse drug reactions in study BRF115532 (COMBI-AD) occurring at an incidence ≥10% for all grade adverse reactions or at an incidence ≥2% for Grade 3 and Grade 4 adverse drugs reactions or adverse events that are medically significant in the Mekinist in combination with Tafinlar arm.

Adverse drug reactions are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent adverse drug reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Table 7-3 Adjuvant treatment of melanoma - Adverse drug reactions for Mekinist in combination with Tafinlar vs. placebo

Adverse drug reactions	Mekinist in combination with Tafinlar N=435		Placebo N=432		Frequency category (combination arm, all grades)
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %	
Infections and infestations					
Nasopharyngitis[1)]	12	<1	12	NR	Very common
Blood and lymphatic system disorders					
Neutropenia[2)]	10	5	<1	NR	Very common
Metabolism and nutrition disorders					
Decreased appetite	11	<1	6	NR	Very common
Nervous system disorders					
Headache[3)]	39	1	24	NR	Very common
Dizziness[4)]	11	<1	10	NR	Very common
Eye disorders					
Uveitis	1	<1	<1	NR	Common
Chorioretinopathy[5)]	1	<1	<1	NR	Common
Retinal detachment[6)]	1	<1	<1	NR	Common
Vascular disorders					

Adverse drug reactions	Mekinist in combination with Tafinlar N=435		Placebo N=432		Frequency category (combination arm, all grades)
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %	
Haemorrhage[7)]	15	<1	4	<1	Very common
Hypertension[8)]	11	6	8	2	Very common
Respiratory, thoracic, and mediastinal disorders					
Cough[9)]	17	NR	8	NR	Very common
Gastrointestinal disorders					
Nausea	40	<1	20	NR	Very common
Diarrhoea	33	<1	15	<1	Very common
Vomiting	28	<1	10	NR	Very common
Abdominal pain[10)]	16	<1	11	<1	Very common
Constipation	12	NR	6	NR	Very common
Skin and subcutaneous tissue disorders					
Rash[11)]	37	<1	16	<1	Very common
Dry skin[12)]	14	NR	9	NR	Very common
Dermatitis acneiform	12	<1	2	NR	Very common
Erythema[13)]	12	NR	3	NR	Very common
Pruritus[14)]	11	<1	10	NR	Very common
Palmar-plantar erythrodysaesthesia syndrome	6	<1	1	<1	Common
Musculoskeletal and connective tissue disorders					
Arthralgia	28	<1	14	NR	Very common
Myalgia[15)]	20	<1	14	NR	Very common
Pain in extremity	14	<1	9	NR	Very common
Muscle spasms[16)]	11	NR	4	NR	Very common
Rhabdomyolysis	<1	<1	NR	NR	Uncommon
Renal and urinary disorders					
Renal failure	<1	NR	NR	NR	Uncommon
General disorders and administration site conditions					
Pyrexia[17)]	63	5	11	<1	Very common
Fatigue[18)]	59	5	37	<1	Very common
Chills	37	1	4	NR	Very common
Oedema peripheral[19)]	16	<1	6	NR	Very common
Influenza-like illness	15	<1	7	NR	Very common
Investigations					
Alanine aminotransferase increased[20)]	17	4	2	<1	Very common
Aspartate aminotransferase increased[21)]	16	4	2	<1	Very common
Alkaline phosphatase increased	7	<1	<1	<1	Common
Ejection fraction decreased	5	NR	2	<1	Common

1) Nasopharyngitis also includes pharyngitis.
2) Neutropenia also includes febrile neutropenia and cases of neutrophil count decreased that met the criteria for neutropenia.
3) Headache also includes tension headache.
4) Dizziness also includes vertigo.
5) Chorioretinopathy also includes chorioretinal disorder.
6) Retinal detachment also includes detachment of macular retinal pigment epithelium and detachment of retinal pigment epithelium.
7) Haemorrhage includes a comprehensive list of hundreds of event terms that capture bleeding events.
8) Hypertension also includes hypertensive crisis.

Adverse drug reactions	Mekinist in combination with Tafinlar N=435		Placebo N=432		Frequency category (combination arm, all grades)
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %	

[9] Cough also includes productive cough.
[10] Abdominal pain also includes abdominal pain upper and abdominal pain lower.
[11] Rash also includes rash maculo-papular, rash macular, rash generalized, rash erythematous, rash papular, rash pruritic, nodular rash, rash vesicular, and rash pustular.
[12] Dry skin also includes xerosis and xeroderma.
[13] Erythema also includes generalized erythema.
[14] Pruritus also includes puritus generalized and pruritus genital.
[15] Myalgia also includes musculoskeletal pain and musculoskeletal chest pain.
[16] Muscle spasms also includes musculoskeletal stiffness.
[17] Pyrexia also includes hyperpyrexia.
[18] Fatigue also includes asthenia and malaise.
[19] Oedema peripheral also includes peripheral swelling.
[20] Alanine aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia.
[21] Aspartate aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia.
NR: not reported

Locally advanced or metastatic anaplastic thyroid cancer

Mekinist in combination with Tafinlar:

The efficacy and safety of Mekinist in combination with Tafinlar was studied in a Phase II, nine-cohort, multicenter, non-randomized, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC *(see section 12 Clinical studies)*.

The 'All Treated Subjects (ATS)' population was the primary safety population for the study and includes all patients who received at least one dose of Mekinist or Tafinlar from all the histologic cohorts. The safety profiles in the ATS population and in the ATC cohort are consistent.

At the time of safety analysis, the most common adverse events (≥20%) reported for Mekinist in combination with Tafinlar in the ATS population were fatigue, pyrexia, rash, nausea, chills, vomiting, cough, and headache.

Table 7-4 lists the adverse drug reactions for Mekinist in combination with Tafinlar occurring at an incidence ≥10% for all grade adverse drug reactions or at an incidence ≥2% for Grade 3 and Grade 4 adverse drug reactions or events which are medically significant in Study BRF117019.

Adverse drug reactions are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent adverse drug reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Table 7-4 Anaplastic Thyroid Cancer - Adverse drug reactions for Mekinist in combination with Tafinlar in the ATS population

Adverse drug reactions	Mekinist in combination with Tafinlar N=100		
	All grades %	Grades 3/4 %	Frequency category
Blood and lymphatic system disorders			
Neutropenia[1)]	15	6	Very common
Anaemia	14	2	Very common
Leukopenia[2)]	13	NR	Very common
Metabolism and nutrition disorders			
Hyperglycaemia	12	3	Very common
Decreased appetite	11	NR	Very common
Hypophosphataemia	6	3	Common
Hyponatremia	3	3	Common
Nervous system disorders			
Headache	20	2	Very common
Dizziness[3)]	13	NR	Very common
Eye disorders			
Detachment of retinal pigment epithelium	1	NR	Common
Vascular disorders			
Haemorrhage[4)]	16	NR	Very common
Hypertension	4	2	Common
Respiratory, thoracic and mediastinal disorders			
Cough[5)]	21	NR	Very common
Gastrointestinal disorders			
Nausea	31	1	Very common
Vomiting	22	1	Very common
Diarrhoea	17	1	Very common
Constipation	15	NR	Very common
Dry mouth	11	NR	Very common
Skin and subcutaneous tissue disorders			
Rash[6)]	31	4	Very common
Musculoskeletal and connective tissue disorders			
Myalgia[7)]	11	1	Very common
Arthralgia	11	NR	Very common
Rhabdomyolysis	1	1	Common
General disorders and administration site conditions			
Fatigue[8)]	45	5	Very common
Pyrexia	35	4	Very common
Chills	25	1	Very common
Oedema[9)]	17	NR	Very common
Investigations			
Alanine aminotransferase increased	13	3	Very common
Aspartate aminotransferase increased	12	2	Very common
Blood alkaline phosphatase increased	11	3	Very common
Ejection fraction decreased	3	1	Common

[1)] *Neutropenia includes neutropenia, neutrophil count decreased and febrile neutropenia. Neutrophil count decreased qualified as a neutropenia event.*

[2)] *Leukopenia includes leukopenia, white blood cell count decreased and lymphopenia.*

[3)] *Dizziness includes dizziness, vertigo and vertigo positional.*

Adverse drug reactions	Mekinist in combination with Tafinlar N=100		
	All grades %	Grades 3/4 %	Frequency category

4) Haemorrhage includes haematuria, purpura, epistaxis, eye contusion, gingival bleeding, haemoptysis, melaena, petechiae, prothrombin time prolonged, rectal haemorrhage, retinal haemorrhage and vaginal haemorrhage.
5) Cough includes cough and productive cough.
6) Rash includes rash, rash maculo-papular, rash generalized and rash papular.
7) Myalgia includes myalgia and musculoskeletal pain.
8) Fatigue includes fatigue, asthenia and malaise.
9.) Oedema includes oedema and peripheral oedema.
NR: not reported

Adverse drug reactions (ADRs) from post-marketing experience and pooled clinical trials

The following ADRs have been derived from post-marketing experience including spontaneous case reports with Mekinist monotherapy or in combination with Tafinlar. Because post-marketing ADRs are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency. Where applicable, these ADR frequencies have been calculated from the pooled clinical trials across indications. ADRs are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 7-5 ADRs from post-marketing experience and pooled clinical trials across indications

Adverse drug reaction	Mekinist in combination with Tafinlar Frequency category	Mekinist monotherapy Frequency category
Immune system disorders		
Sarcoidosis	Uncommon	-
Haemophagocytic lymphohistiocytosis	Not known	-
Metabolism and nutrition disorders		
Tumour lysis syndrome	Not known	-
Nervous system disorders		
Peripheral neuropathy	Common	Common
Cardiac disorders		
Atrioventricular block[1]	Common	Uncommon
Bundle branch block[2]	Uncommon	Uncommon
Vascular disorders		
Venous thrombo-embolism (VTE)[3]	Common	-

1) Atrioventricular block includes atrioventricular block, atrioventricular block first degree, atrioventricular block second degree and atrioventricular block complete.
2) Bundle branch block includes bundle branch block right and bundle branch block left.
3) VTE includes, pulmonary embolism, deep vein thrombosis, embolism and venous thrombosis.

8 Interactions

Monotherapy

As trametinib is metabolised predominantly via deacetylation mediated by hydrolytic enzymes (including carboxylesterases), its pharmacokinetics are unlikely to be affected by other agents

through metabolic interactions. A small, non-clinically relevant, decrease in trametinib bioavailability (16 %) was noted with co-administration with a cytochrome P450 (CYP) 3A4 inducer.

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 trametininb with medicinal products that are strong inhibitors of P-gp (e.g. verapamil, cyclosporine, ritonavir, quinidine, itraconazole).

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 Clinical pharmacology, Pharmacokinetics*). Repeat-dose administration of Mekinist 2 mg once daily had no clinically relevant effect on the single dose C_{max} and AUC of dabrafenib, a CYP2C8/CYP3A4 substrate. 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.

Combination therapy and non-fixed dose combination therapy

Combination with dabrafenib

Co-administration of repeat dosing of Mekinist 2 mg once daily and Tafinlar 150 mg twice daily resulted in a 16% increase in dabrafenib C_{max} and a 23% increase in dabrafenib AUC. A small decrease in trametinib bioavailability, corresponding to a decrease in AUC of 12%, was estimated when Mekinist is administered in combination with Tafinlar using a population pharmacokinetic analysis. These changes in dabrafenib or trametinib C_{max} and AUC are considered not clinically relevant. When trametinib is used in combination with dabrafenib see dabrafenib Package Insert 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 Dosage regimen and administration and section Clinical pharmacology, Pharmacokinetics*).

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

MEKINIST can cause fetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the foetus.

There are no adequate and well-controlled studies of MEKINIST in pregnant women. MEKINIST should not be administered to pregnant women or nursing mothers. Women of childbearing potential should use effective methods of contraception during therapy and for 4 months following discontinuation of MEKINIST. When MEKINIST is used in combination with dabrafenib, patients should use a non-hormonal method of contraception since dabrafenib can render hormonal contraceptives ineffective. If MEKINIST is used during pregnancy, or if the patient becomes pregnant while taking MEKINIST, the patient should be informed of the potential hazard to the foetus.

Reproductive studies in animals (rats and rabbits) with trametinib have demonstrated maternal and developmental toxicity. In embryofetal development studies in rats, maternal and developmental toxicity (decreased foetal weights) were seen following maternal exposure to trametinib at ≥ 0.031 mg/kg/day (approximately 0.3 times the exposure in humans at the highest recommended dose of 2 mg once daily based on AUC). Post implantation loss was increased at 0.125 mg trametinib/kg/day. In pregnant rabbits, maternal and developmental toxicity (decreased foetal body weight and increased incidence of variations in ossification) were seen at ≥ 0.039 mg/kg/day (approximately 0.1 times the exposure in humans at the highest recommended dose of 2 mg once daily based on AUC). Post implantation loss and incidence of skeletal defects were increased at 0.154 mg trametinib/kg/day.

9.2 Lactation

Risk summary

There are no data on the effect of Mekinist on the breast-fed child, or the effect of Mekinist on milk production. Because many drugs are transferred into human milk and because of the potential for adverse reactions in nursing infants from Mekinist, a nursing woman should be advised on the potential risks to the child. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Mekinist and any potential adverse effects on the breast-fed child from Mekinist or from the underlying maternal condition

9.3 Females and males of reproductive potential

Contraception

Females

Females of reproductive potential should be advised that animal studies have been performed showing Mekinist to be harmful to the developing fetus. Sexually-active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1% pregnancy rates) when taking Mekinist and for at least 16 weeks after stopping treatment with Mekinist.

Females of reproductive potential receiving Mekinist in combination with Tafinlar should be advised that Tafinlar may decrease the efficacy of oral or any other systemic hormonal contraceptives and an alternative method of contraception should be used.

Males

Male patients (including those that have had a vasectomy) with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during sexual intercourse while taking Mekinist monotherapy or in combination with Tafinlar and for at least 16 weeks after stopping treatment with Mekinist.

Infertility

There is no information on the effect of Mekinist on human fertility. In animals, no fertility studies have been performed, but adverse effects were seen on female reproductive organs *(see section Non-clinical safety data)*. 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 Package Insert

for further information.

10 Overdosage

No cases of overdose have been reported. There were no cases of Mekinist dose above 4 mg once daily reported from the clinical trials. Doses up to 4 mg orally once daily and loading doses of 10 mg orally once daily, administered on two consecutive days, have been evaluated in clinical trials. Further management should be as clinically indicated or as recommended by the national poisons center, where available. There is no specific treatment for an overdose of Mekinist. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Hemodialysis is not expected to enhance the elimination as trametinib is highly bound to plasma proteins.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Mitogen-activated protein kinase (MEK) inhibitors, ATC code: L01EE01.

Mechanism of action (MOA)

Mekinist Monotherapy – Melanoma, NSCLC and ATC

Trametinib (Mekinist) is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinases 1 (MEK1) and MEK2 activation and kinase activity. MEK proteins are critical components of the extracellular signal-regulated kinase (ERK) pathway. In melanoma and other cancers, this pathway is often activated by mutated forms of BRAF which activate MEK and stimulate tumor cell growth. Trametinib inhibits MEK kinase activity, suppresses growth of BRAF V600 mutant melanoma, non-small cell lung cancer (NSCLC) and ATC cell lines *in vitro* and demonstrates anti-tumour effects in BRAF V600 mutant melanoma xenograft models.

Mekinist in combination with Tafinlar – Melanoma, NSCLC and ATC

Dabrafenib (Tafinlar) is a potent, selective, ATP-competitive inhibitor of the BRAF (both wild-type and V600 variants) and wild type CRAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway and stimulation of tumor cell growth. Because co-treatment with trametinib and dabrafenib results in concomitant inhibition of two kinases in this pathway, BRAF and MEK, the combination provides superior pathway suppression relative to either agent alone. The combination of trametinib with dabrafenib is synergistic/additive in BRAF V600 mutation positive melanoma, NSCLC and ATC cell lines *in vitro*, and delays the emergence of resistance *in vivo* in BRAF V600 mutation positive melanoma xenografts.

Determination of BRAF mutation status

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

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

Subsequently, all patient samples were re-tested using the CE-marked bioMerieux (bMx) THxID BRAF validated assay. The bMx THxID BRAF assay is an allele-specific PCR performed on DNA extracted from FFPE tumour tissue. The assay was designed to detect the BRAF V600E and V600K mutations with high sensitivity (down to 5% V600E and V600K sequence in a background of wild-type sequence using DNA extracted from FFPE tissue). Non-clinical and clinical 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%.

Pharmacodynamics (PD)

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

In patients with BRAF and NRAS mutation positive melanoma, administration of trametinib resulted in dose-dependent changes in tumor 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.

Cardiac electrophysiology

Based on the results of a dedicated QT study, Mekinist does not prolong the QT interval to any clinically relevant extent.

Pharmacokinetics (PK)

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) micro-dose. 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 following a 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 section Dosage regimen and administration and section Interactions*).

Distribution

Binding of trametinib to human plasma proteins is 97.4%. Trametinib has a volume of distribution of 1,060 L determined following administration of a 5 microgram IV micro-dose.

Biotransformation/metabolism

In vitro and *in vivo* studies demonstrated that trametinib is metabolised predominantly via deacetylation alone or in combination or 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, and may also be mediated by other hydrolytic enzymes.

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

Elimination

Trametinib accumulates with repeat daily dosing with a mean accumulation ratio of 6.0 following a 2 mg once-daily dose. Mean terminal half-life is 127 hours (5.3 days) after single dose administration. Steady-state was achieved by Day 15. Trametinib plasma IV clearance is 3.21 L/hr.

Total dose recovery is 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 half-life. Drug-related material was excreted predominantly in the faeces (>81% of recovered radioactivity) and to a small extent in urine (≤19%). Less than 0.1% of the excreted dose was recovered as parent in urine.

In Vitro evaluation of drug interaction potential

Effects of other drugs on trametinib:

In vitro and *in vivo* data suggest that the pharmacokinetics (PK) of trametinib are unlikely to be affected by other drugs. Trametinib is deacetylated via carboxylesterases and possibly other hydrolytic enzymes. There is little evidence from clinical studies for drug interactions mediated by carboxylesterases. CYP enzymes play a minor role in the elimination of trametinib and the compound is not a substrate of the following transporters: breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, OATP2B1, organic cation transporter (OCT) 1, multidrug resistance-associated protein (MRP) 2, and the multidrug and toxin extrusion protein (MATE) 1. Trametinib is an *in vitro* substrate of the efflux transporter P-glycoprotein (Pgp), but is unlikely to be significantly affected by inhibition of this transporter given its high passive permeability and high bioavailability.

Special populations

Hepatic impairment

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

Renal impairment

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

Geriatric patients (65 years of age or above)

Based on the population pharmacokinetics analysis (range 19 to 92 years), age had no relevant clinical effect on trametinib pharmacokinetics.

Race/Ethnicity

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

Pediatric population (below 18 years)

No studies have been conducted to investigate the pharmacokinetics of trametinib in pediatric patients.

Gender/Weight

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, Pgp 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 Interactions*).

Effects of other drugs on trametinib: *In vivo* and *in vitro* data suggest that the pharmacokinetics (PK) of trametinib are unlikely to be affected by other drugs. Trametinib is deacetylated via carboxylesterases and possibly other hydrolytic enzymes. There is little evidence from clinical studies for drug interactions mediated by carboxylesterases. CYP enzymes play a minor role in the elimination of trametinib and the compound is is not a substrate of the following transporters: breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, OATP2B1, organic cation transporter (OCT) 1, multidrug resistance-associated protein (MRP) 2, and the multidrug and toxin extrusion protein (MATE) 1. Trametinib is an *in vitro* substrate of the efflux transporter P-glycoprotein (Pgp), but is unlikely to be significantly affected by inhibition of this transporter given its high passive permeability and high bioavailability. 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 Interactions*).

12 Clinical studies

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 monotherapy***

Treatment naïve patients

Study MEK114267

The efficacy and safety of trametinib in patients with BRAF mutant unresectable or metastatic melanoma (V600E and V600K) were evaluated in a randomized open-label Phase III study (MEK114267 [METRIC]). Measurement of patients' BRAF V600 mutation status was required. Screening included central testing of BRAF mutation (V600E and V600K) using a BRAF mutation assay conducted on the most recent tumor sample available.

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 randomized 2:1 to receive trametinib 2 mg once daily or chemotherapy (dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks). Treatment for all patients continued until disease progression, death or withdrawal.

The primary endpoint of the study was to evaluate the efficacy of trametinib compared to chemotherapy with respect to progression-free survival (PFS) in patients with advanced (unresectable or metastatic) BRAF V600E 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 overall survival (OS), overall response rate (ORR), and duration of response (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 fifty-one (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 (100%). The median age was 54 years (22% were ≥65 years); all patients had an ECOG performance score of 0 or 1; and 11 patients (3%) had history of brain metastases. Most patients (87%) in the ITT population had BRAF V600E mutation and 12% of patients had BRAF V600K mutation. Most patients (66%) had 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 12-1. Kaplan-Meier curves of investigator assessed OS (post-hoc analysis 20 May 2013) is presented in Figure 12-1.

Table 12-1 Investigator assessed efficacy results (ITT population)

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

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

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

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

An additional OS analysis was undertaken based upon the 20 May 2013 data cut, see Table 12-2.

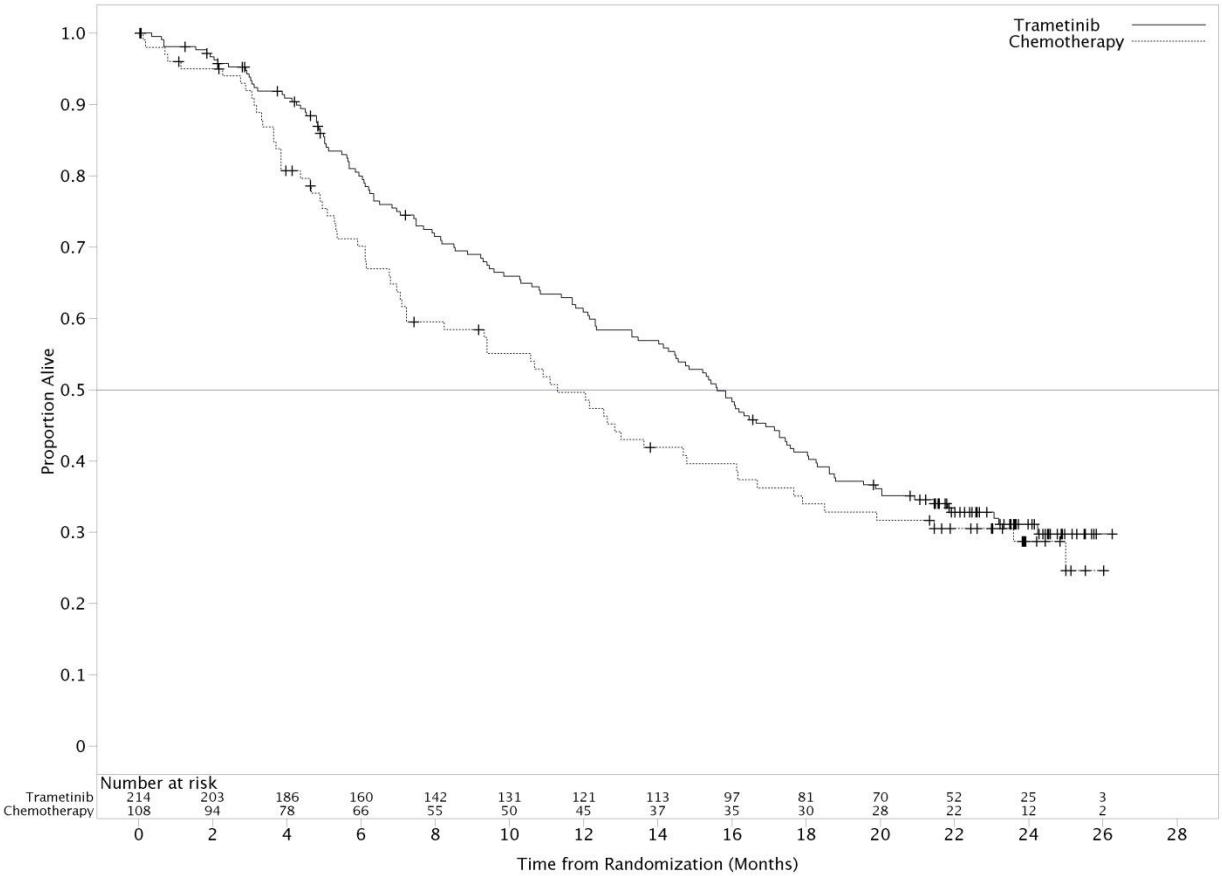
For October 2011, 47% of subjects had crossed over, while for May 2013, 65% of subjects had crossed over.

Table 12-2 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 12-1 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.

- ***<u>Trametinib in combination with dabrafenib</u>***

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 were studied in two pivotal Phase III studies and one supportive Phase I/II study.

MEK115306 (COMBI-d):

MEK115306 (COMBI-d) was a Phase III, randomized, 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 investigator-assessed progression-free survival (PFS), with a key secondary endpoint of overall survival (OS). Patients 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 patients were randomised 1:1 to either the combination therapy arm (Mekinist 2 mg once daily and Tafinlar 150 mg twice daily) (N = 211) or dabrafenib monotherapy arm (150 mg twice daily) (N = 212). Baseline characteristics were balanced between treatment groups. Most patients were Caucasian (>99%) and male (53%), with a median age of 56 years (28% were ≥65 years). The majority of patients 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 patients had a BRAF V600E mutation (85%); the remaining 15% of patients had the BRAF V600K mutation. Patients with brain metastases were not included in the trial.

Median OS and estimated 1-year, 2-year, 3-year, 4 year and 5-year survival rates are presented in Table 12-2. An OS analysis at 5 years demonstrated continued benefit for the combination of dabrafenib and trametinib compared with dabrafenib monotherapy; the median OS for the combination arm was approximately 7 months longer than the median OS for dabrafenib monotherapy (25.8 months versus 18.7 months) with 5-year survival rates of 32% for the combination versus 27% for dabrafenib monotherapy (Table 12-3, Figure 12-2). The Kaplan-Meier OS curve appears to stabilize from 3 to 5 years (see Figure 12-2).

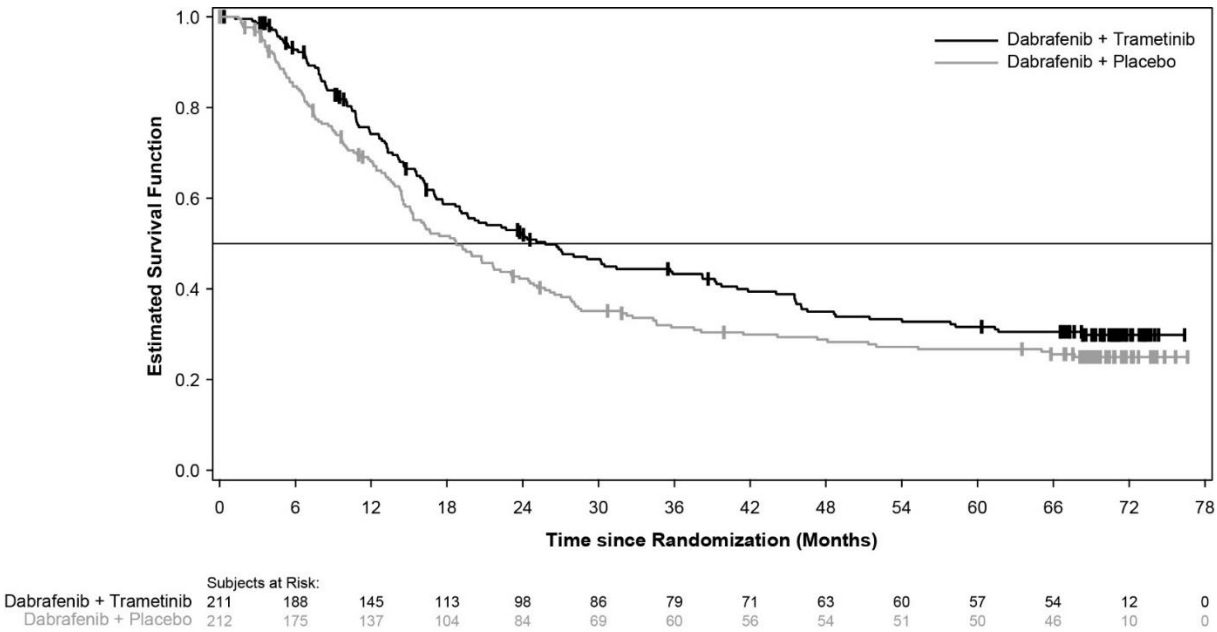
The 5-year overall survival rate was 40% (95% CI: 31.2, 48.4) in the combination arm versus 33% (95% CI: 25.0, 41.0) in the dabrafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 8.4, 26.0) in the combination arm versus 14% (95% CI: 6.8, 23.1) in the dabrafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline.

Table 12-3 COMBI-d - Overall Survival results (ITT population)

	OS analysis*		**3-year OS analysis***		**5-year OS analysis***	
	Dabrafenib + Trametinib (n=211)	**Dabrafenib + Placebo (n=212)**	**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)	114 (54)	139 (66)	135 (64)	151 (71)
Estimates of OS (months)						
Median (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.7)	26.7 (19.0, 38.2)	18.7 (15.2, 23.1)	25.8 (19.2, 38.2)	18.7 (15.2, 23.1)
Hazard ratio (95% CI)	0.71 (0.55, 0.92)		0.75 (0.58, 0.96)		0.80 (0.63, 1.01)	
p-value	0.011		NA		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)
*OS analysis data cut-off: 12-Jan-2015; 3-year OS analysis data cut-off: 15-Feb-2016; 5-year OS analysis data cut-off: 10-Dec-2018 NR = Not reached, NA = Not applicable		

Figure 12-2 COMBI-d - Kaplan-Meier overall survival curves (ITT Population)



Clinically meaningful improvements for the primary endpoint of PFS were sustained over a 5-year timeframe in the combination arm compared to dabrafenib monotherapy. Clinically meaningful 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 12-4).

Table 12-4 Investigator-assessed efficacy results for MEK115306 (COMBI-d) study

Endpoints	Primary Analysis*		Updated Analysis*		3-Year Analysis*		5-Year Analysis*	
	Dabrafenib + Trametinib (n = 211)	Dabrafenib + Placebo (n = 212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)
Investigator Assessed PFS								
Progressive disease or death, n (%)	102 (48)	109 (51)	139 (66)	162 (76)	153 (73)	168[f] (79)	160 (76)	166 (78)

Median, months (95% CI[a])	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 (8.0, 12.8)	7.6 (5.8, 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)		0.71 (0.57, 0.88)		0.73 (0.59, 0.91)	
P value (log-rank test)	0.035		<0.001[g]		NA		NA	
Overall Response Rate[b] (%) (95% CI)	67 (59.9, 73.0)	51 (44.5, 58.4)	69 (61.8, 74.8)	53 (46.3, 60.2)	68 (61.5, 74.5)	55 (47.8, 61.5)	69 (62.5, 75.4)	54 (46.8, 60.6)
Difference in response rate (CR[c] +PR[c]), % 95% CI for difference *P* value	15[d] 5.9, 24.5 0.0015		15[d] 6.0, 24.5 0.0014[g]		NA		NA	
Duration of Response (months)								
Median (95% CI)	9.2[e] (7.4, NR)	10.2[e] (7.5, NR)	12.9 (9.4,19.5)	10.6 (9.1,13.8)	12.0 (9.3, 17.1)	10.6 (8.3, 12.9)	12.9 (9.3, 18.4)	10.2 (8.3, 13.8)

** Primary analysis data cut-off: 26-Aug-2013, Final analysis data cut-off: 12-Jan-2015, 3-year analysis data cut-off: 15-Feb-2016, 5-year analysis data cut-off: 10-Dec-2018*

a - Confidence interval

b - Overall Response Rate = Complete Response + Partial Response

c - CR: Complete Response, PR: Partial Response

d - ORR difference calculated based on the ORR result not rounded

e - At the time of the reporting the majority (≥59%) of investigator-assessed responses were still ongoing

f - Two patients were counted as progressed or died in the 3-year analysis but had an extended time without adequate assessment prior to the events, meaning they were censored in the 5-year analysis.

g - 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 two-arm, randomized, 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. Patients 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 patients were randomized 1:1 to either combination therapy arm (Mekinist 2mg once daily and Tafinlar 150mg twice daily) or vemurafenib monotherapy arm (960mg twice daily). Most patients were Caucasian (>96%) and male (55%), with a median age of 55 years (24% were ≥65 years). The majority of patients had Stage IV M1c disease (61%). 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 patients had BRAF V600E mutation-positive melanoma (89%). Subjects with brain metastases were not included in the trial.

An OS analysis at 5 years demonstrated continued benefit for the combination of dabrafenib and trametinib compared with vemurafenib monotherapy; 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 12-5, Figure 12-3). The Kaplan-Meier OS curve appears to stabilize from 3 years to 5 years (see Figure 12-3). 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 12-5 Overall Survival results for Study MEK116513 (COMBI-v)

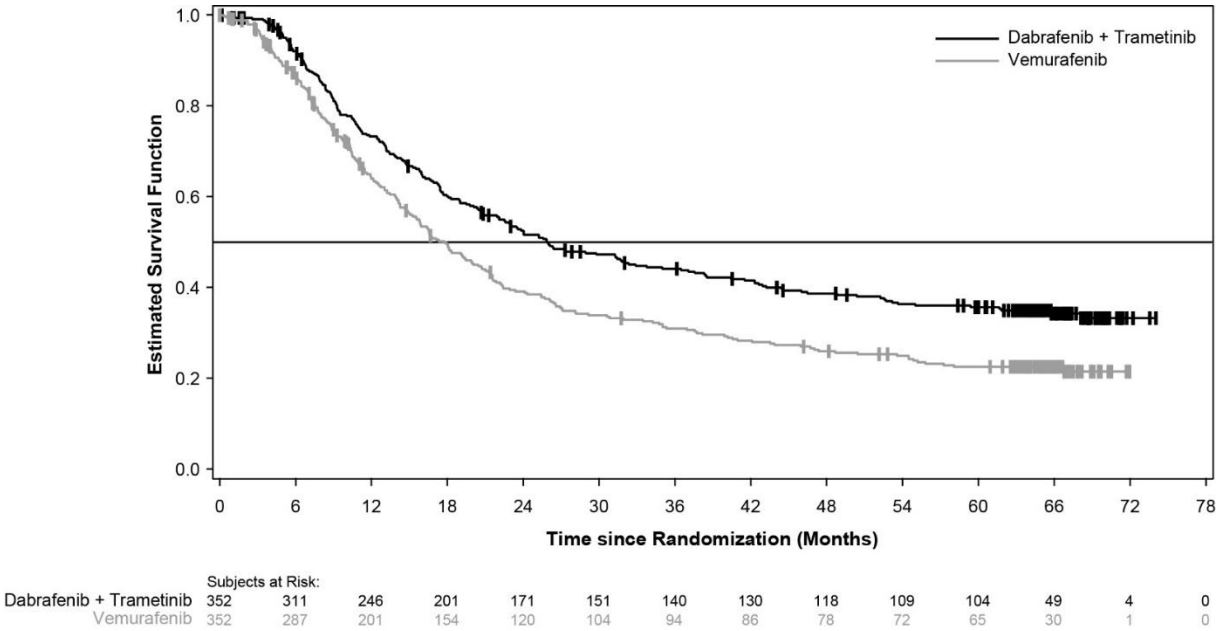
	OS analysis*		**3-year OS analysis***		**5-year OS analysis***	
	Dabrafenib + Trametinib (n=352)	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
Number of patients						
Died (event), n (%)	100 (28)	122 (35)	190 (54)	224 (64)	216 (61)	246 (70)
Estimates of OS (months)						
Median (95% CI)	NR (18.3, NR)	17.2 (16.4, NR)	26.1 (22.6, 35.1)	17.8 (15.6, 20.7)	26.0 (22.1, 33.8)	17.8 (15.6, 20.7)
Adjusted hazard ratio (95% CI)	0.69 (0.53, 0.89)		0.68 (0.56, 0.83)		0.70 (0.58, 0.84)	
p-value	0.005		NA		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

***** *Primary OS analysis data cut-off: 17-Apr-2014, 3-year OS analysis data cut-off: 15-Jul-2016, 5-year data cut-off: 8-Oct-2018*

Figure 12-3 COMBI-v - Kaplan-Meier overall survival curves (ITT Population)



Clinically meaningful improvements for the secondary endpoint of PFS were sustained over a 5-year timeframe in the combination arm compared to vemurafenib monotherapy. Clinically meaningful improvements were also observed for overall response rate (ORR) and a longer duration of response (DoR) was observed in the combination arm compared to vemurafenib monotherapy (Table 12-6).

Table 12-6 Investigator-assessed efficacy results for MEK116513 (COMBI-v) study

Endpoint	Primary Analysis*		3-year analysis*		5-year analysis*	
	Dabrafenib + Trametinib (n=352)	Vemurafenib (n=352)	Dabrafenib + Trametinib (n=352)	Vemurafenib (n=352)	Dabrafenib + Trametinib (n=352)	Vemurafenib (n=352)
Investigator Assessed PFS						
Progressive disease or death, n (%)	166 (47)	217 (62)	250 (71)	257 (73)	257 (73)	259 (74)
Median, months (95% CI)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)	12.1 (9.7, 14.7)	7.3 (5.7, 7.8)	12.1 (9.7, 14.7)	7.3 (6.0, 8.1)
Hazard Ratio (95% CI)	0.56 (0.46, 0.69)		0.61 (0.51, 0.73)		0.62 (0.52, 0.74)	
P value	<0.001		NA		NA	
Overall Response Rate(%) (95% CI)	64 (59.1, 69.4)	51 (46.1, 56.8)	67 (61.9, 71.9)	53 (47.8, 58.4)	67 (62.2, 72.2)	53 (47.2, 57.9)
Difference in response rate (CR+PR), % (95% CI for difference)	13 (5.7, 20.2)		NA		NA	
P value	0.0005		NA		NA	
Duration of Response (months)						

Endpoint	Primary Analysis*		3-year analysis*		5-year analysis*	
	Dabrafenib + Trametinib (n=352)	Vemurafenib (n=352)	Dabrafenib + Trametinib (n=352)	Vemurafenib (n=352)	Dabrafenib + Trametinib (n=352)	Vemurafenib (n=352)
Median (95% CI)	13.8 (11.0, NR)	7.5 (7.3, 9.3)	13.8 (11.3, 17.7)	7.9 (7.4, 9.3)	13.8 (11.3, 18.6)	8.5 (7.4, 9.3)

Primary analysis data cut-off: 17-Apr-2014, 3-year analysis data cut-off: 15-Feb-2016, 5-year analysis data cut-off: 8-Oct-2018
PFS = Progression Free Survival; NR = Not reached; NA=Not applicable

BRF117277 / DRB436B2204 (COMBI-MB) – Metastatic melanoma patients with brain metastases

The efficacy and safety of Mekinist in combination with Tafinlar in patients with BRAF mutant-positive melanoma that has metastasized to the brain was studied in a non-randomized, open-label, multi-center, 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 Tumours (RECIST) version 1.1. Efficacy results are summarised in Table 12-5. Secondary endpoints were duration of intracranial response, ORR, PFS and OS. Efficacy results are summarized in Table 12-7. Due to small sample size reflected by wide 95% CIs, the results in cohorts B, C, and D should be interpreted with caution". BRAF V600K was the predominant mutation in cohort C and BRAF V600E was the predominant mutation in cohort D; and there were no BRAF V600D mutations observed.

Table 12-7 COMBI-MB - Efficacy data by investigator assessment

	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)
ORR, % (95% CI)				
	59% (47.3, 70.4)	56% (29.9, 80.2)	44% (19.8, 70.1)	65% (38.3, 85.8)
PFS, 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)
OS, median, months (95% CI)				
Median, months	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 Reported*				

- In cohort A, 3 patients were found to have the BRAF V600K mutation upon central confirmation.
- In cohort C, 14 patients had the BRAF V600K mutation, and 2 patients had the BRAF V600R mutation.
- In cohort D, 15 patients had the BRAF V600E mutation, 1 patient had the BRAF V600K mutation and 1 patient had the BRAF V600R mutation.

Adjuvant treatment of melanoma

Study BRF115532 / DRB436F2301 (COMBI-AD)

The efficacy and safety of Mekinist in combination with Tafinlar was studied in a Phase III, multicenter, randomized, double-blind, placebo-controlled study in patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

Patients were randomized 1:1 to receive either dabrafenib and trametinib combination therapy (Mekinist 2 mg once daily and Tafinlar 150 mg twice daily) or two placebos for a period of 12 months. Enrollment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomization. Any prior systemic anticancer 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 or V600K) and stage of disease prior to surgery (by Stage III sub-stage, indicating different levels of lymph node involvement and primary tumor size and ulceration). The primary endpoint was investigator-assessed relapse-free survival (RFS), defined as the time from randomization to disease recurrence or death from any cause. Radiological tumor 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) and distant metastasis-free survival (DMFS).

A total of 870 patients were randomized 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 tumor ulceration. The majority of patients had a BRAF V600E mutation (91%). At the time of the primary analysis, the median duration of follow-up (time from randomization to last contact or death) was 2.83 years in the dabrafenib and trametinib combination arm and 2.75 years in the placebo arm.

Results for the primary analysis of RFS are presented in Table 12-8. The study showed a statistically significant difference for the primary outcome of RFS between treatment arms, with an estimated 53% risk reduction in the dabrafenib and trametinib combination arm as compared to the placebo arm (HR=0.47; 95% CI: 0.39, 0.58; $p=1.53\times10^{-14}$). Results were consistent across subgroups, including stratification factors for disease stage and BRAF V600 mutation type. Median RFS was 16.6 months for the placebo arm, and was not reached for the combination arm at the time of the primary analysis.

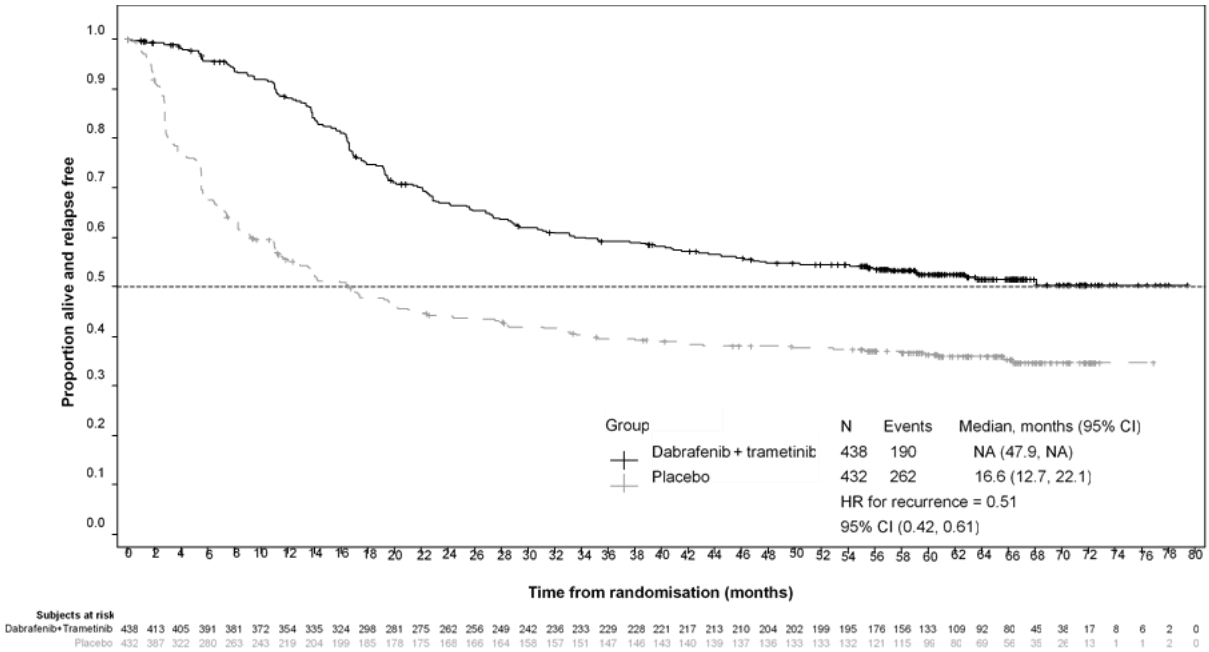
Table 12-8 COMBI-AD primary analysis – Relapse-free survival results

	Dabrafenib + Trametinib	**Placebo**
RFS parameter	**N=438**	**N=432**
Number of events, n (%) Recurrence Relapsed with distant metastasis Death	166 (38%) 163 (37%) 103 (24%) 3 (<1%)	248 (57%) 247 (57%) 133 (31%) 1 (<1%)
Median (months) (95% CI)	NE (44.5, NE)	16.6 (12.7, 22.1)
Hazard ratio[1] (95% CI) p-value[2]	0.47 (0.39, 0.58) 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

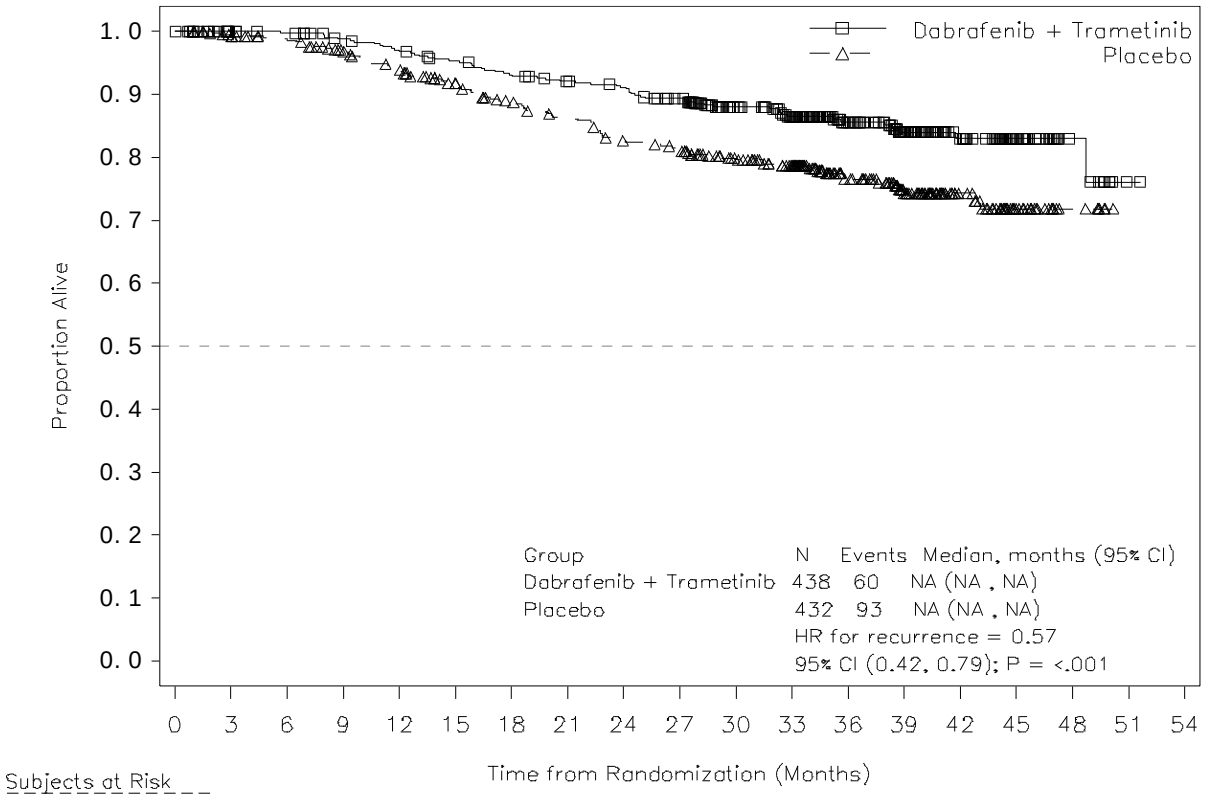
Based on updated data with an additional 29 months of follow-up compared to the primary analysis (minimum follow-up of 59 months), the RFS benefit was maintained with an estimated HR of 0.51 (95% CI: (0.42, 0.61) (Figure 12-4). The 5-year RFS rate was 52% (95% CI: 48, 58) in the combination arm compared to 36% (95% CI: 32, 41) in the placebo arm.

Figure 12-4 COMBI-AD - Relapse-free survival Kaplan-Meier curves (ITT Population)



Based on 153 events (60 (14%) in the combination arm and 93 (22%) in the placebo arm) corresponding to a 26% information fraction of the total target of 597 OS events, the estimated hazard ratio for OS was 0.57 (95% CI: 0.42, 0.79; p=0.0006). These results did not meet the pre-specified boundary to claim statistical significance at this first OS interim analysis (HR=0.50; p=0.000019). Survival estimates at 1 and 2 years from randomization were 97% and 91% in the combination arm and 94% and 83% in the placebo arm, respectively. The Kaplan-Meier curve for this OS interim analysis is shown in Figure 12-5.

Figure 12-5 COMBI-AD – Overall survival Kaplan-Meier curves (ITT Population)



Advanced NSCLC

Study E2201 (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 the investigator-assessed overall response rate (ORR) using the 'Response Evaluation Criteria In Solid Tumors' (RECIST 1.1 assessed by the investigator). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (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 (see package insert for Tafinlar on results from Cohort A).
- Cohort B (n=57): Combination therapy (dabrafenib 150 mg twice daily and trametinib 2 mg once daily), 59 patients enrolled. 57 patients had one to three lines of previous systemic treatment for their metastatic disease. Two patients did not have any previous systemic treatment and were included in the analysis for patients enrolled in Cohort C.
- Cohort C (n=36): Combination therapy (dabrafenib 150 mg twice daily and trametinib 2 mg once daily), 34 patients. (note: the two patients from Cohort B that did not have any previous systemic treatment were included in the analysis for patients enrolled in Cohort C for a total of 36 patients). All patients received study medication as first-line treatment for metastatic disease.

Among the total of 93 patients who were enrolled in the combination therapy in Cohorts B and C, most patients were Caucasian (n = 79, 85%). There was a similar female to male ratio (54% versus 46%). The median age was 64 years in patients who had at least one prior therapy and 68 years in patients who were treatment naïve for their advanced disease. Most patients (n=87, 94%) enrolled in the combination therapy treated Cohorts had an ECOG performance status of 0 or 1. Twenty-six (26) patients (28%) had never smoked. Ninety-one (91) patients (97.8%) had a non-squamous histology. In the pre-treated population, 38 patients (67%) had one line of systemic anti-cancer therapy for metastatic disease.

At the time of the primary analysis, the investigator-assessed ORR was 61.1% (95% CI, 43.5%, 76.9%) in the first-line population and 66.7% (95% CI, 52.9%, 78.6%) in the previously treated population. These results met the statistical significance to reject the null hypothesis that the ORR of trametinib in combination with dabrafenib for both NSCLC populations was less than or equal to 30%. The ORR results assessed by IRC were consistent with the investigator assessment (Table 12-9). The final analysis of efficacy performed 5 years after last subject first dose is presented in Table 12-9.

Table 12-9 Efficacy Results in Patients with BRAF V600E NSCLC

Endpoint	Analysis	Combination First Line N=36	Combination Second Line Plus N=57
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)

Locally advanced or metastatic anaplastic thyroid cancer

Study BRF117019 / CDRB436X2201

The efficacy and safety of Mekinist in combination with Tafinlar was studied in a Phase II, nine-cohort, multicenter, non-randomized, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic anaplastic thyroid cancer (ATC).

The study had pre-specified interim analyses that were performed approximately every 12 weeks. Patients received Mekinist 2 mg once daily and Tafinlar 150 mg twice daily. The primary endpoint was the investigator-assessed overall response rate (ORR) using the 'Response Evaluation Criteria In Solid Tumors' (RECIST 1.1 assessed by the investigator).

Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. ORR, DoR, and PFS were also assessed by an Independent Review Committee (IRC).

Thirty-six patients were enrolled and were evaluable for response in the ATC cohort. The median age was 71 years (range: 47 to 85); 44% were male, 50% white, 44% Asian; and 94% had ECOG performance status of 0 or 1. Prior anti-cancer treatments included surgery (n=30, 83%), external beam radiotherapy (n=30, 83%), and systemic therapy (n=24, 67%) for ATC. Central laboratory testing confirmed the BRAF V600E mutation in 23 patients (92%).

For the primary endpoint, the investigator-assessed ORR was 56% (95% CI: 38.1, 72.1) in the ATC cohort. The ORR results assessed by IRC and investigator-assessment were consistent (Table 12-8).

Responses were durable with a median DoR in the ATC cohort of 14.4 months (95% CI: 7.4, 43.6) by investigator assessment, and a median PFS of 6.7 months (95% CI: 4.7, 13.8).

For ATC subjects, the median OS was 14.5 months (95% CI: 6.8, 23.2). Kaplan-Meier estimate of overall survival at 12 months for ATC patients was 51.7% (95% CI: 33.6, 67.1).

Table 12-10 Efficacy Results in Patients with BRAF V600E ATC

Endpoint	Analysis By Investigator[1] ATC Cohort N= 36	Analysis By IRC ATC Cohort N= 36
Overall confirmed response n (%) (95% CI)	20 (56%) (38.1, 72.1)	19 (53%)(35.5, 69.6)
Median DoR, months (95% CI)	14.4 (7.4, 43.6)	13.6 (3.8, NE[2])
Median PFS, months (95% CI)	6.7 (4.7, 13.8)	5.5 (3.7, 12.9)
Median OS, months (95% CI)	14.5 (6.8, 23.2)	

[1] *Data cut-off:* 14-Sep-2020
[2] *NE: Not Estimable*

Other studies

Pyrexia Management Analysis

Pyrexia is observed in patients treated with Mekinist and Tafinlar 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 Tafinlar in case of pyrexia. 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 Mekinist and Tafilnar when patient's temperature was ≥38°C (100.4°F) (COMBI-Aplus) or at the first symptom of pyrexia (COMBI-i; COMBI-Aplus for recurrent pyrexia), resulted in improved pyrexia-related outcomes without impacting efficacy:

- Unresectable or metastatic melanoma setting (COMBI-d/v vs COMBI-i):
  - grade 3/4 pyrexia reduced from 6.6% to 3.4%
  - hospitalization due to pyrexia reduced from 12.3% to 6.1%
  - pyrexia with complications (dehydration, hypotension, renal dysfunction, syncope, severe chills) reduced from 6.4 % to 1.9%
  - treatment discontinuation rates due to pyrexia were comparable, 1.1% versus 1.9%

- Adjuvant melanoma setting (COMBI-AD vs COMBI-Aplus):
  - grade 3/4 pyrexia reduced from 5.7% to 4.3%
  - hospitalization due to pyrexia reduced from 11.0% to 5.1%
  - pyrexia with complications (dehydration, hypotension, renal dysfunction, syncope, severe chills) reduced from 6.0% to 2.2%
  - treatment discontinuation due to pyrexia reduced from 6.2% to 2.5%

13 Non-clinical safety data

Carcinogenicity and mutagenicity

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.

Reproductive toxicity

Embryofetal development and fertility

Trametinib may impair female fertility in humans. In adult and juvenile rat repeat-dose studies with trametinib, alterations in follicular maturation, consisting of increases in cystic follicles and decreases in cystic corpora lutea, were observed at ≥0.016 mg/kg/day (approximately 0.3 times 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.

Juvenile animal studies

In a juvenile rat toxicity study, the principal toxicities in juvenile rats were on growth (bodyweight and long bone length), adverse microscopic findings included changes in the bone, mineralization and/or degeneration in various organs, primarily stomach at all doses. Adverse findings at the higher doses included in eye, kidney, aortic arch and/or nasal cavity/sinuses, heart, liver and in skin, and higher heart weights and the delay in a physical landmark of sexual maturity in females (vaginal opening).

The majority of findings are reversible with the exception of the bone, serum phosphorus and soft tissue mineralization which progressed/worsened during the off-drug period. Also, kidney tubular basophilia and higher heart weights were still present at end of recovery period.

With the exception of corneal mineralization/dystrophy and increased heart weight, similar

effects have been observed in adult animals given trametinib. At the lowest combined dose level evaluated, the systemic exposure is approximately 0.3 times the human exposure at clinical dose of 2 mg/day based on AUC.

Safety pharmacology and repeat-dose toxicity

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 three weeks. In adult rats, myocardial mineralisation and necrosis of multiple organs was associated with increased serum phosphorus were seen at doses ≥1 mg/kg/day (approximately 12 times human clinical exposure based on AUC) 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 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 clinical exposures (IC_{50} at 2.92 µg/ml, ≥130 times the clinical exposure based on C_{max}), indicating that there is low risk for phototoxicity to patients taking trametinib.

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).

Non-fixed dose combination therapy

Trametinib in combination with dabrafenib: Dogs given trametinib and dabrafenib in combination for 4 weeks demonstrated similar toxicities to those in comparable monotherapy studies. Refer to the full package insert for Tafinlar.

14 Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

See folding box.

Store in a refrigerator 2 to 8°C. Store in the original package to protect from light and moisture. Keep the bottle tightly closed. Contains desiccant, do not remove or eat.

Mekinist should not be used after the date marked “EXP” on the pack.

Mekinist must be kept out of the reach and sight of children.

Instructions for use and handling

There are no special requirements for use or handling of this product.

Presentation

Opaque, white high density polyethylene (HDPE) bottles (40cc), containing 7 tablets or 30 tablets, closed with plastic screw closures (with desiccant).

Not all presentations may be available locally.

Manufacturer:

See folding box.

Country Specific Package Leaflet

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