NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Mekinist 0.5 mg film coated tablet

Mekinist 2 mg film coated tablet

Mekinist 0.05 mg/mL powder for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mekinist 0.5 mg film coated tablet

Each film coated tablet contains trametinib dimethyl sulfoxide equivalent to trametinib 500 microgram.

Mekinist 2 mg film coated tablet

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

Mekinist 0.05 mg/mL powder for oral solution

Each bottle contains 5.3 mg trametinib dimethylsulfoxide equivalent to 4.7 mg of trametinib. Each mL of the constituted solution contains 0.05 mg of trametinib.

Excipients
For the full list of excipients, see section 6.1.

Excipients with known effect

Mekinist powder for oral solution contains sucralose, sorbates and benzoates.

Note: Mekinist tablets and powder for oral solution are not fully interchangeable.

3. PHARMACEUTICAL FORM

Film-coated tablet

Mekinist 0.5 mg film coated tablet

Yellow, ovaloid, biconvex, unscored, film-coated tablets with ⏻ (Novartis logo) on one side and TT on the other side.

Mekinist 2 mg film coated tablet

Pink, round, biconvex, unscored, film-coated tablets with ⏻ (Novartis logo) on one side and LL on the other side.

Mekinist 0.05 mg/mL powder for oral solution

White or almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Unresectable or metastatic melanoma

Trametinib in combination with dabrafenib is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.

Trametinib as a monotherapy is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma and in whom either there is intolerance to BRAF inhibitors or BRAF inhibitors cannot be used.

Trametinib as monotherapy has not demonstrated clinical activity in patients who have progressed on BRAF inhibitor therapy (see section 5.1).

Adjuvant treatment of melanoma

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

Anaplastic thyroid cancer (ATC)

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.

Non-small cell lung cancer (NSCLC)

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

Low-grade glioma

Trametinib in combination with dabrafenib is indicated for the treatment of paediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy (see section 5.1 Pharmacodynamic properties).

High-grade glioma

Trametinib in combination with dabrafenib is indicated for the treatment of paediatric patients 1 year of age and older with high-grade glioma (HGG) with a BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options (see section 5.1 Pharmacodynamic properties).

4.2 Dose and method of administration

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

Confirmation of BRAF V600 mutation using an approved/validated test is required, for selection of patients appropriate for trametinib monotherapy and in combination with dabrafenib (see section 5.1).

When trametinib is used in combination with dabrafenib, refer to section 4.2 Dose and Administration in the full dabrafenib Data Sheet for dabrafenib dosing instructions.

The efficacy and safety of trametinib have not been established in patients with wild-type BRAF tumours (see section 5.1 Pharmacodynamic properties). Trametinib should not be used in patients with BRAF wild-type tumours (see section 4.4 Special Warnings and Precautions for Use).

Note: Mekinist tablets and powder for oral solution are not fully bioequivalent/interchangeable; caution is advised when consideration is given to changing formulations due to any difficulty in swallowing solid forms and frequent switching between formulations is discouraged.

Duration of treatment

The recommended duration of treatment for patients with unresectable or metastatic melanoma, metastatic NSCLC, or locally advanced or metastatic anaplastic thyroid cancer is until disease progression or unacceptable toxicity.

In the adjuvant melanoma setting, the treatment duration is limited to a maximum of 1 year.

The recommended duration of treatment for paediatric patients with glioma is until disease progression or until unacceptable toxicity. There are limited data in patients older than 18 years

of age with glioma who require first systemic therapy. Therefore, continued treatment into adulthood should be based on benefits and risks to the individual patient as assessed by the physician.

Recommended dosage

Trametinib is available in two dosage forms, film coated tablets and powder for oral solution.

Adult patients.

The recommended dose of trametinib used as monotherapy or in combination with dabrafenib is 2 mg given orally once daily independent of body weight.

Dose modifications

Monotherapy and in combination with dabrafenib

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

Recommended dose level reductions are provided in Table 1. Doses below 1 mg once daily are not recommended, whether used as monotherapy or in combination with dabrafenib.

Table 1 Recommended trametinib dose level reductions for trametinib tablets in adult patients

Dose Level	Trametinib dose
Starting dose	2 mg orally once daily
1st dose reduction	1.5 mg orally once daily
2nd dose reduction	1 mg orally once daily

Permanently discontinue if unable to tolerate trametinib 1 mg orally once daily.

The recommended dose modification schedule is provided in Tables 2 and 3. When adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The trametinib dose should not exceed 2 mg once daily.

Table 2 Trametinib dose modification schedule (excluding pyrexia)

Grade (CTC-AE)*	Dose Modifications
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 0-1 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 with the exceptions shown below.

Exceptions where dose modifications are necessary for only trametinib:

- Left ventricular ejection fraction (LVEF) reduction
- Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED)
- Interstitial lung disease (ILD)/Pneumonitis

Detailed dosing modifications for selected adverse reactions

New Primary Malignancies

For new primary cutaneous malignancies no dose modifications are required. For new primary non-cutaneous malignancies no dose modifications are required for trametinib. If used in combination with dabrafenib, permanently discontinue dabrafenib in patients who develop RAS mutation-positive non-cutaneous malignancies.

Haemorrhagic events

Permanently discontinue trametinib, and also permanently discontinue dabrafenib if administered in combination, for all Grade 4 haemorrhagic events and for any Grade 3 haemorrhagic events that do not improve. Withhold trametinib for up to 3 weeks for Grade 3 haemorrhagic events; if improved resume at a lower dose level. Withhold dabrafenib for Grade 3 haemorrhagic events; if improved resume at a lower dose level.

Pyrexia Management

Therapy should be interrupted (trametinib when used as monotherapy, and both trametinib and dabrafenib when used in combination) if the patient's temperature is ≥38°C or at the first symptom of pyrexia/pyrexia syndrome. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia/pyrexia syndrome. 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 4.4 Special warnings and precautions for use).

Trametinib, or both trametinib and dabrafenib 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.

Table 3 Recommended trametinib dose modifications in pyrexia management

Patient's temperature	Trametinib monotherapy	Trametinib combination therapy with dabrafenib
Fever of 38.0ºC - 40ºC	Withhold trametinib if patient's temperature is 38.0ºC - 40ºC or at the first sign of pyrexia/pyrexia syndrome (i.e. chills, rigors, night sweats, or flu-like symptoms). trametinib should be restarted if patient is symptom free for at least 24 hours either at the same dose level, or reduced by one dose level, if pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration,	Withhold trametinib and dabrafenib if patient's temperature is 38.0ºC - 40ºC or at the first sign of pyrexia/pyrexia syndrome (i.e. chills, rigors, night sweats, or flu-like symptoms). trametinib and dabrafenib should be restarted if patient is symptom free for at least 24 hours either at the same dose level, or reduced by one dose level, if pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure.

Patient's temperature	Trametinib monotherapy	Trametinib combination therapy with dabrafenib
	hypotension or renal failure.	
Fever of > 40ºC or Fever is complicated by rigors, hypotension, dehydration, or renal failure	Withhold trametinib if patient's temperature is >40ºC or at the first sign of pyrexia/pyrexia syndrome (i.e. chills, rigors, night sweats, or flu-like symptoms). trametinib should be restarted if patient is symptom free for at least 24 hours either at the same or lower dose level, or permanently discontinue.	Withhold trametinib and dabrafenib if patient's temperature is >40ºC or at the first sign of pyrexia/pyrexia syndrome (i.e. chills, rigors, night sweats, or flu-like symptoms). trametinib and dabrafenib should be restarted if patient is symptom free for at least 24 hours either at the same or lower dose level, or permanently discontinue.

LVEF Reduction/Left Ventricular Dysfunction management

Trametinib should be interrupted in patients who have an asymptomatic, absolute decrease of ≥10 % in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN) (see section 4.4 Special warnings and precautions for use). If trametinib is being used in combination with dabrafenib then therapy with dabrafenib may be continued at the same dose. If the LVEF recovers, treatment with trametinib may be restarted, but reduce dose by one dose level with careful monitoring.

Permanently discontinue trametinib with Grade 3 or 4 left ventricular cardiac dysfunction or if LVEF reduction does not recover. If trametinib is being used in combination with dabrafenib then therapy with dabrafenib should be withheld and resumed at the same dose upon recovery of cardiac function.

Retinal Vein Occlusion (RVO) and Retinal Pigment Epithelial Detachment (RPED) management

If patients report new visual disturbances such as diminished central vision, blurry vision, or loss of vision at any time while on trametinib therapy, a prompt ophthalmological assessment is recommended. In patients who are diagnosed with retinal vein occlusion (RVO), treatment with trametinib, whether given as monotherapy or in combination with dabrafenib, should be permanently discontinued. Dabrafenib treatment can continue at the same dose.

If retinal pigment epithelial detachment (RPED) is diagnosed, follow the dose modification schedule in Table 4 for trametinib and continue dabrafenib at the same dose (see section 4.4).

Table 4 Recommended dose modifications for trametinib for retinal pigment epithelial detachments (RPED)

Grade	Recommended dose modifications for trametinib
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 management

Follow the dose modification guidelines in Table 2 for trametinib.

If trametinib is used in combination with dabrafenib, do not modify the dose of dabrafenib. Refer to the full Data Sheet of dabrafenib for dose modification guidelines (see section 4.2 Dose and method of administration).

Serious Skin Toxicity

For dosing instructions for intolerable or severe skin toxicity for trametinib and trametinib in combination with dabrafenib see Table 5. Dose reduction, interruption or discontinuation should be applied to both treatments.

Table 5 Guidelines for Cutaneous toxicity

Severity of Adverse Reaction	**Trametinib**	**Dabrafenib (When Used in Combination)**
• Intolerable Grade 2 skin toxicity • Grade 3 or 4 skin toxicity	Withhold trametinib for up to 3 weeks. • If improved, resume at a lower dose level. • If not improved, permanently discontinue.	Withhold dabrafenib for up to 3 weeks. • If improved, resume at a lower dose level. • If not improved, permanently discontinue.

The following rash management guidance should be considered whether trametinib is given as monotherapy or in combination with dabrafenib, and if dose reduction, interruption or discontinuation is necessary it should be applied to both treatments.

Treatment of rash has not been formally studied and should be based on rash severity. The following guidelines were used in clinical studies with trametinib as monotherapy or in combination with dabrafenib and can be used to manage rash (see Table 6).

Table 6 Supportive Care Guidelines for Rash

Step	**Rash Grade**	**Rash severity**	**Management of Rash**
1	Mild	Localised Minimally symptomatic No impact on ADL No sign of superinfection	Initiate prophylactic regimen[a] if not already started. Reassess after two weeks; if rash worsens or does not improve, proceed to step 2
2	Moderate	Generalised Mild symptoms (e.g. pruritus, tenderness) Minimal impact on ADL No sign of superinfection	Initiate prophylactic regimen[a] if not already started, using moderate strength topical steroids. Reassess after two weeks; if rash worsens or does not improve, proceed to step 3
3	Severe	Generalised	Initiate prophylactic regimen[a] if not already started, using moderate strength

Step	Rash Grade	Rash severity	Management of Rash
		Severe symptoms (e.g. pruritus, tenderness) Significant impact on ADL Sign of or potential for superinfection	topical steroids PLUS systemic corticosteroids. Manage rash per dermatologist's recommendation.

[a] broad-spectrum sunscreen (skin protection factor ≥ 15), alcohol-free emollient cream, mild-strength topical steroid, and oral antibiotics for first 2-3 weeks

ADL= Activity of Daily Living

Paediatric patients

Film-coated tablets

The recommended dosage for trametinib tablets in paediatric patients who weigh at least 26 kg, is based on body weight (Table 7). A recommended dose for patients who weigh less than 26 kg has not been established.

Table 7 Recommended weight-based dosing for trametinib tablets in paediatric patients

Body weight	Recommended starting dosage
26 to 37 kg	1 mg orally once daily
38 to 50 kg	1.5 mg orally once daily
51 kg or greater	2 mg orally once daily

Recommended dose level reductions for trametinib tablets in paediatric patients are provided in Table 8.

Table 8 Recommended dose level reductions for trametinib tablets in paediatric patients

Dose level reduction	Recommended starting dosage		
	1 mg orally once daily	**1.5 mg orally once daily**	**2 mg orally once daily**
First dose reduction	0.5 mg orally once daily	1 mg orally once daily	1.5 mg orally once daily
Second dose reduction	-	0.5 mg orally once daily	1 mg orally once daily

Permanently discontinue if unable to tolerate a maximum of two dose reductions

Powder for Oral Solution

The recommended dosage and dose level reductions for trametinib powder for oral solution are based on body weight (Table 9).

Table 9 Recommended weight-based dosing and dose reductions for trametinib powder for oral solution

Body weight (kg)	Recommended dose total volume of oral solution once daily (trametinib content)	Dose Level Reductions	
		First dose reduction (once daily)	Second dose reduction (once daily)

8 kg	6 mL (0.3 mg)	5 mL	3 mL
9 kg	7 mL (0.35 mg)	5 mL	4 mL
10 kg	7 mL (0.35 mg)	5 mL	4 mL
11 kg	8 mL (0.4 mg)	6 mL	4 mL
12 to 13 kg	9 mL (0.45 mg)	7 mL	5 mL
14 to 17 kg	11 mL (0.55 mg)	8 mL	6 mL
18 to 21 kg	14 mL (0.7 mg)	11 mL	7 mL
22 to 25 kg	17 mL (0.85 mg)	13 mL	9 mL
26 to 29 kg	18 mL (0.9 mg)	14 mL	9 mL
30 to 33 kg	20 mL (1 mg)	15 mL	10 mL
34 to 37 kg	23 mL (1.15 mg)	17 mL	12 mL
38 to 41 kg	25 mL (1.25 mg)	19 mL	13 mL
42 to 45 kg	28 mL (1.4 mg)	21 mL	14 mL
46 to 50 kg	32 mL (1.6 mg)	24 mL	16 mL
≥51 kg	40 mL (2 mg)	30 mL	20 mL
Permanently discontinue if unable to tolerate a maximum of two dose reductions.			

Special populations

Paediatric patients (< 18 years of age)
The safety and efficacy of trametinib in combination with dabrafenib have not been established in paediatric patients younger than 1 year of age with LGG/HGG with BRAF V600E mutation. The safety and effectiveness of trametinib as a single agent in paediatric patients has not been established.

Patients > 65 years of age
No dose adjustments are required in patients over 65 years (see section 5.2).

Renal impairment
No dosage adjustment required in patients with mild or moderate renal impairment. Mild or moderate renal impairment had no significant effect on the population pharmacokinetics of trametinib (see section 5.2). There are no clinical data with trametinib in patients with severe renal impairment; therefore, the potential need for starting dose adjustment cannot be determined. Trametinib should be used with caution in patients with severe renal impairment.

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 5.2, Pharmacokinetic properties).

Trametinib should be used with caution in patients with moderate or severe hepatic impairment.

Administration

Film-coated tablets

Trametinib should be taken without food, at least one hour before or two hours after a meal (see section 5.2 – Pharmacokinetic properties).

When trametinib and dabrafenib are taken in combination, the dose of trametinib should be taken at the same time each day with either the morning dose or the evening dose of dabrafenib.

Swallow the trametinib tablet whole with a full glass of water.

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

Powder for oral solution

When using trametinib powder for oral solution, physicians should review and discuss with the patient or caregiver(s) the Consumer Medicine Information and instructions for mixing and administering trametinib. Physicians should confirm that the patients or caregiver(s) understand how to mix trametinib powder for oral solution with water and administer the correct daily dose. For instructions on reconstitution of the medicine before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

BRAF V600 testing

Confirmation of BRAF V600 mutation using an approved/validated test is required for selection of patients appropriate for trametinib monotherapy and in combination with dabrafenib. Patients enrolled in the melanoma clinical studies were required to have BRAF V600 mutation status measured. The safety and efficacy of trametinib have not been evaluated in patients whose melanoma tested negative for the BRAF V600 mutation.

New primary malignancies

New primary malignancies can occur when trametinib is used in combination with dabrafenib and with dabrafenib as a single agent [refer to Full Data Sheet for dabrafenib].

Based on its mechanism of action, dabrafenib may promote growth and development of malignancies with activation of RAS through mutation or other mechanisms (refer to the Product Information for dabrafenib).

Non-Cutaneous secondary/ recurrent malignancies

In patients receiving trametinib in combination with dabrafenib, four cases of non-cutaneous malignancies were identified: KRAS mutation-positive pancreatic adenocarcinoma (n = 1), recurrent NRAS mutation-positive colorectal carcinoma (n = 1), head and neck carcinoma (n = 1), and glioblastoma (n = 1). Monitor patients receiving the combination closely for signs or symptoms of non-cutaneous malignancies. If used in combination with dabrafenib, no dose modification is required for trametinib in patients who develop non-cutaneous malignancies. Permanently discontinue dabrafenib in patients who develop RAS mutation-positive non-cutaneous malignancies (see section 4.2).

Haemorrhage

Haemorrhagic events, including major haemorrhages, defined as symptomatic bleeding in a critical area or organ, have occurred in patients taking trametinib as monotherapy and in combination with dabrafenib (see section 4.8).

Out of the 559 unresectable or metastatic melanoma patients receiving trametinib in combination with dabrafenib in phase III trials, there were six fatal intracranial haemorrhagic events (1 %). No fatal haemorrhagic events occurred in the Phase III study in the adjuvant treatment of melanoma. Two out of 93 patients (2%) receiving trametinib in combination with dabrafenib in a Phase II NSCLC trial had fatal intracranial haemorrhagic events. If patients develop symptoms of haemorrhage they should immediately seek medical care.

Three cases were from study MEK115306 (COMBI-d) and three cases were from study MEK116513 (COMBI-v). If patients develop symptoms of haemorrhage they should immediately seek medical care.

In Study BRF113220, treatment with trametinib in combination with dabrafenib resulted in an increased incidence and severity of any haemorrhagic event: 16% (9/55) of patients treated with trametinib in combination with dabrafenib compared with 2% (1/53) of patients treated with dabrafenib as a single agent. The major haemorrhagic events of intracranial or gastric haemorrhage occurred in 5% (3/55) of patients treated with trametinib in combination with dabrafenib compared with none of the 53 patients treated with dabrafenib as a single agent. Intracranial haemorrhage was fatal in two (4%) patients receiving the combination of trametinib and dabrafenib.

Permanently discontinue trametinib, and also permanently discontinue dabrafenib if administered in combination, for all Grade 4 haemorrhagic events and for any Grade 3 haemorrhagic events that do not improve. Withhold trametinib for up to 3 weeks for Grade 3 haemorrhagic events; if improved resume at a lower dose level. Withhold dabrafenib for Grade 3 haemorrhagic events; if improved resume at a lower dose level (see section 4.2).

Cardiac effects

Left ventricular ejection fraction (LVEF) reduction/Left Ventricular dysfunction

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

Across clinical trials of trametinib at the recommended dose (N = 329), 11% of patients developed evidence of cardiomyopathy (decrease in left ventricular ejection fraction, or LVEF, below institutional lower limits of normal with an absolute decrease in LVEF ≥ 10% below baseline) and 5% demonstrated a decrease in LVEF below institutional lower limits of normal with an absolute decrease in LVEF of ≥ 20% below baseline.

Trametinib should be used with caution in patients with conditions that could impair left ventricular function. LVEF should be evaluated by echocardiogram or multigated acquisition (MUGA) scan in all patients prior to initiation of treatment with trametinib, one month after initiation of therapy, and then at approximately 3 monthly intervals, as clinically appropriate, while on treatment (see section 4.2).

Trametinib should be interrupted in patients who have an asymptomatic, absolute decrease of ≥ 10 % in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN). If trametinib is being used in combination with dabrafenib then therapy with dabrafenib may be continued at the same dose. If the LVEF recovers, treatment with trametinib may be restarted, but the dose should be reduced by one dose level with careful monitoring.

With Grade 3 or 4 left ventricular cardiac dysfunction or if LVEF does not recover trametinib should be permanently discontinued. If trametinib is being used in combination with dabrafenib then therapy with dabrafenib should be withheld and resumed at the same dose upon recovery of cardiac function (see section 4.2).

QT Prolongation

Based on the results of a dedicated Phase I QT study (MEK114655), trametinib does not prolong the QT interval to any clinically relevant extent.

Visual impairment

A thorough ophthalmological evaluation should be performed at baseline and during treatment with trametinib, if clinically warranted. If a retinal abnormality is noted, treatment with trametinib should be interrupted immediately and referral to a retinal specialist should be considered.

The data from clinical trials demonstrates that when all reported ocular events are pooled, there was a higher reported rate in the subjects treated with combination therapy than monotherapy (20% vs 13%, respectively). The median exposure time for combination therapy was substantially longer than trametinib monotherapy (6.41 vs. 3.84 months, respectively).

Disorders associated with visual disturbance, including retinal pigment chorioretinopathy or epithelial detachment (RPED) and retinal vein occlusion (RVO), have been observed with trametinib as monotherapy and in combination with dabrafenib. Symptoms such as blurred vision, decreased acuity, and other visual phenomena have been reported in the clinical trials with trametinib (see section 4.8). If patients report new visual disturbances such as diminished central vision, blurry vision, or loss of vision at any time while on trametinib therapy, a prompt ophthalmological assessment is recommended.

Retinal Pigment Epithelial Detachment (RPED)

Retinal pigment epithelial detachments (RPED) can occur during treatment with trametinib. Across all clinical trials of trametinib, the incidence of RPED was 0.8% (14/1749). Retinal detachments were often bilateral and multifocal, occurring in the macular region of the retina. RPED led to reduction in visual acuity that resolved after a median of 11.5 days (range: 3 to 71 days) following the interruption of dosing with trametinib, although Ocular Coherence Tomography (OCT) abnormalities persisted beyond a month in at least several cases.

If RPED is diagnosed, follow the dose modification schedule in Table 1 (see section 4.2).

Retinal Vein Occlusion (RVO)

Trametinib is not recommended in patients with a history of RVO. Across all clinical trials of trametinib, the incidence of RVO was 0.2% (4/1749). An RVO may lead to macular oedema, decreased visual function, neovascularisation, and glaucoma.

Urgently (within 24 hours) perform ophthalmological evaluation for patient-reported loss of vision or other visual disturbances. Permanently discontinue trametinib in patients who experience RVO.

Interstitial lung disease (ILD)/Pneumonitis

Any diagnosis of ILD or pneumonitis warrants immediate discontinuation of trametinib.

In a Phase 3 trial, 2% (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).

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. If trametinib is used in combination with dabrafenib, do not modify the dose of dabrafenib.

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

DVT and PE can occur on trametinib monotherapy and when trametinib is used in combination with dabrafenib. If patients develop symptoms of pulmonary embolism or deep vein thrombosis they should immediately seek medical care.

Pyrexia and serious non-infectious febrile events

Pyrexia was reported in the clinical trials with trametinib. The incidence and severity of pyrexia are increased when trametinib is used in combination with dabrafenib (see section 4.8). In

patients with melanoma who received the combination dose of dabrafenib 150 mg twice daily and trametinib 2 mg once daily and 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 3 or more events. Pyrexia may be accompanied by severe rigors, dehydration, and hypotension which in some cases can lead to acute renal insufficiency. Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia. Renal failure was reported in 7% of patients who received the combination dose of dabrafenib 150 mg twice daily and trametinib 2 mg once daily, a higher frequency than observed in dabrafenib monotherapy patients (<1%), and was often seen in the context of pyrexia and dehydration.

Monitor serum creatinine and other evidence of renal function 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 trametinib and dabrafenib were interrupted, compared to when only dabrafenib was interrupted.

Therapy with trametinib (trametinib when used in monotherapy, or both trametinib and dabrafenib when used in combination) should be interrupted if the patient's temperature is ≥ 38.0 ºC or at the first symptom of pyrexia/pyrexia syndrome. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia/pyrexia syndrome. 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 4.4 Special warnings and precautions for use).

Trametinib (or both trametinib and dabrafenib) 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.

For management of pyrexia see Section 4.2 Dose and Method of Administration.

For the management of pyrexia please see section 4.2 in full Data Sheet for dabrafenib.

Serious Skin Toxicity

Serious skin toxicity can occur when trametinib is administered as a single agent or when used in combination with dabrafenib. Serious skin toxicity can also occur with dabrafenib as a single agent (refer to Product Information for dabrafenib).

In MEK114267, the overall incidence of any skin toxicity, the most common of which were rash (see section 4.8 – Rash), dermatitis acneiform rash, palmar-plantar erythrodysesthesia syndrome, and erythema, was 87% in patients treated with trametinib and 13% in chemotherapy-treated patients. Severe skin toxicity occurred in 12% of patients treated with trametinib. Skin toxicity requiring hospitalisation occurred in 6% of patients treated with trametinib, most commonly for secondary infections of the skin requiring intravenous antibiotics or severe skin toxicity without secondary infection. In comparison, no patients treated with chemotherapy required hospitalisation for severe skin toxicity or infections of the skin. The median time to onset of skin toxicity in patients treated with trametinib was 15 days (range: 1 to 221 days) and median time to resolution of skin toxicity was 48 days (range: 1 to 282 days). Reductions in the dose of trametinib were required in 12% and permanent discontinuation of trametinib was required in 1% of patients with skin toxicity.

In BRF113220, the incidence of any skin toxicity was similar for patients receiving trametinib in combination with dabrafenib (65% [36/55]) compared with patients receiving dabrafenib as a

single agent (68% [36/53]). The median time to onset of skin toxicity in patients treated with trametinib in combination with dabrafenib was 37 days (range: 1 to 225 days) and median time to resolution of skin toxicity was 33 days (range: 3 to 421 days). No patient required dose reduction or permanent discontinuation of trametinib or dabrafenib for skin toxicity.

Across clinical trials of trametinib administered in combination with dabrafenib (n = 202), severe skin toxicity and secondary infection of the skin requiring hospitalisation occurred in 2.5% (5/202) of patients treated with trametinib in combination with dabrafenib.

Withhold trametinib, and dabrafenib if used in combination, for intolerable or severe skin toxicity until further assessment (see section 4.2). Trametinib and dabrafenib may be resumed at a lower dose level in patients with improvement or recovery from skin toxicity within three weeks.

Rash

In clinical studies with trametinib, rash has been observed in about 60 % of patients as monotherapy and 30 % in combination with dabrafenib (see section 4.2). 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 trametinib in combination with dabrafenib. 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, trametinib and dabrafenib should be withdrawn.

Venous thromboembolism (VTE)

VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), can occur with trametinib monotherapy and with trametinib used in combination with dabrafenib. If patients develop symptoms of VTE they should advised to immediately seek medical care (see section 4.8).

Hepatic Events

Hepatic adverse events (including increased transaminases, and hepatic failure) have been reported with trametinib as monotherapy and in combination with dabrafenib. 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 (see section 4.8).

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 4.8). Treatment with trametinib monotherapy or in combination with dabrafenib should be used with caution in patients with risk factors for gastrointestinal perforation, including a 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.

Haemophagocytic 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 trametinib in combination with dabrafenib (see section 4.8 Undesirable effects). Risk factors for TLS include rapidly growing tumours, a high tumour 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.

Use in paediatrics (< 18 years of age)

The safety and efficacy of trametinib in combination with dabrafenib have not been yet established in paediatric patients younger than 1 year of age with LGG/HGG with BRAF V600E mutation. For information of paediatric patients aged 1 to 18 years, refer to sections 4.1 – Therapeutic indications, 4.2 – Dose and method of administration, 4.8 – Undesirable effects, 5.1 – Pharmacodynamic properties and 5.2 – Pharmacokinetic properties. The safety and effectiveness of trametinib as a single agent in paediatric patients have not been established.

Use in patients ≥ 65 years of age

No initial dose adjustments are required in patients over 65 years of age (see section 5.2).

More frequent dose adjustments (see Table 10 and Table 11) may be required in patients over 65 years of age (see section 4.8). Across clinical trials of trametinib administered in combination with dabrafenib (n = 202), adverse events resulting in dose interruption were reported for 71% of those aged ≥65 years as compared to 60% of those <65 years, while adverse events resulting in dose reduction occurred in 64% of those aged ≥65 years as compared to 44% of those <65 years.

Clinical trials of trametinib administered as a single agent or in combination with dabrafenib did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In MEK114267, 49 patients (23%) were 65 years of age and older, and 9 patients (4%) were 75 years of age and older. Across clinical trials of trametinib administered in combination with dabrafenib (n = 202), 42 patients (21%) were 65 years of age and older, and 12 patients (6%) were 75 years of age and older.

4.5 Interactions with other medicines and other forms of interaction

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. Trametinib repeat-dose exposure was not affected by co-administration with a cytochrome P450 (CYP) 3A4 inducer.

Based on in vitro and in vivo data, trametinib is unlikely to significantly affect the pharmacokinetics of other medicinal products via interactions with CYP enzymes or transporters. Repeat dose administration of trametinib 2 mg once daily had no clinically relevant effect on the single dose Cmax and AUC of dabrafenib, a CYP2C8/CYP3A4 substrate.

Combination trametinib with dabrafenib

Co-administration of repeat dosing of dabrafenib 150 mg twice daily and trametinib 2 mg once daily resulted in a 16 % increase in dabrafenib Cmax and a 23 % increase in dabrafenib AUC. A small decrease in trametinib bioavailability, corresponding to a decrease in AUC of 12 %, was estimated when dabrafenib is administered in combination with trametinib using a population pharmacokinetic analysis. These changes in dabrafenib or trametinib Cmax and AUC are considered not clinically relevant.

In vitro evaluation of drug interaction potential

Effects of Other Drugs on trametinib

In vivo and in vitro data suggest that the 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, 1B3, 2B1, 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 (P-gp), but is unlikely to be significantly affected by inhibition of this transporter given its high passive permeability and high bioavailability.

Effects of trametinib on Drug Metabolising Enzymes and Transporters

In vitro and in vivo data suggest that trametinib is unlikely to affect the PK of other drugs. Based on in vitro studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP3A4. Trametinib was found to be an in vitro inhibitor of CYP2C8, CYP2C9 and CYP2C19, an inducer of CYP3A4 and an inhibitor of the transporters OAT1, OAT3, OCT2, MATE1, OATP1B1, OATP1B3, P-gp and BCRP. However, based on the low dose and low clinical systemic exposure relative to the in vitro potency of inhibition or induction, trametinib is not considered to be an in vivo inhibitor or inducer of these enzymes or transporters. Repeat dose administration of once-daily 2 mg trametinib had no effect on the single dose Cmax and AUC of dabrafenib, a CYP2C8/CYP3A4 substrate, while a small increase in exposure was noted with repeat dose dabrafenib.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Female patients

Females of reproductive potential should be advised to use effective contraception (methods that result in less than 1% pregnancy rates) when taking trametinib and for at least sixteen weeks after stopping treatment with trametinib.

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

Male patients

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 trametinib monotherapy or in combination with dabrafenib and for at least 16 weeks after stopping treatment with trametinib.

Pregnancy (Category D)

Trametinib can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of trametinib in pregnant women. Pregnant women should be advised of the potential risk to the foetus.

Trametinib should not be administered to pregnant women or nursing mothers (see Lactation). Women of childbearing potential should use effective methods of contraception during therapy and for 4 months following discontinuation of trametinib. If trametinib is used alone or in combination with dabrafenib, women of child bearing potential should use a non-hormonal method of contraception since dabrafenib can render hormonal contraceptives ineffective. If trametinib is used during pregnancy, or if the patient becomes pregnant while taking trametinib, the patient should be informed of the potential hazard to the foetus.

Reproductive studies in animals (rats and rabbits) have demonstrated that trametinib induced maternal and developmental toxicity. In rats, decreased foetal weights and incidences of post implantation loss were observed following maternal exposure to trametinib at concentrations 0.3 and 0.8 times the exposure in humans at the highest recommended dose of 2 mg once daily. In rabbits, decreased fetal weight and increased incidence of variations in ossification and post implantation loss were observed following maternal exposure to trametinib at concentrations 0.09 and 0.3 times the exposure in humans at the highest recommended dose of 2 mg once daily.

In embryo-fetal development studies, rats and rabbits received oral doses of trametinib up to 0.125 mg/kg/day and 0.31 mg/kg/day, respectively, during the period of organogenesis. In rats at ≥ 0.031 mg/kg/day and 0.125 mg/kg/day, maternal systemic exposures (AUC) were 110 ng*h/mL and 684 ng*h/mL, respectively, corresponding to approximately 0.3 and 1.8 times the exposure in humans at the highest recommended dose of 2 mg once daily. At doses ≥ 0.031 mg/kg/day developmental toxicity consisted of decreased fetal weights. At a dose of 0.125 mg/kg/day there was maternal toxicity and increases in post implantation loss. In rabbits at ≥ 0.039 mg/kg/day and 0.15 mg/kg/day, maternal systemic exposures (AUC) were 31.9 ng*h/mL and 127 ng*h/mL, respectively corresponding to approximately 0.09 and 0.3 times the exposures in humans at the highest recommended dose of 2 mg once daily. At doses ≥ 0.039 mg/kg/day developmental toxicity consisted in decreased fetal body weight and increased incidence of variations in ossification. At doses 0.15 mg/kg/day there were increases in post-implantation loss, including total loss of pregnancy, compared with control animals.

Lactation

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

Fertility

Trametinib monotherapy

There is no information on the effect of trametinib on human fertility. In animals, no fertility studies have been performed, but adverse effects were seen on female reproductive organs. trametinib may impair fertility in humans.

In adult and juvenile rat repeat dose studies with trametinib, alterations in follicular maturation, consisting of increases in ovarian cystic follicles and decrease in corpora lutea were observed in female rats ≥ 0.016 mg/kg/day (0.3 times the clinical exposure based on AUC. Trametinib may impair female fertility in humans. However, in rat and dog toxicity studies up to 13 weeks in duration, there were no treatment-related effects observed on male reproductive tissues.

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-related effects observed on male reproductive tissues.

Males taking trametinib in combination with dabrafenib

Male fertility studies in animals with the trametinib/dabrafenib combination have not been conducted. Effects on spermatogenesis have been observed in animals given dabrafenib. Male patients should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. See Data Sheet information for dabrafenib for more detail.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of trametinib on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of trametinib. The clinical status of the patient and the adverse event profile of trametinib should be borne in mind when considering the patient's ability to perform tasks that require judgment, motor and cognitive skills.

4.8 Undesirable effects

Clinical trial data

Unresectable or metastatic melanoma

Monotherapy

The safety of trametinib monotherapy has been evaluated in an integrated population of 329 patients with metastatic melanoma treated with trametinib 2 mg orally once daily in studies MEK114267, MEK113583, and MEK111054. Of these patients, 211 patients were treated with trametinib for BRAF mutant melanoma in the randomised open label study MEK114267 (see section 5.1). The most common adverse reactions (≥ 20%) for trametinib include rash, diarrhoea, fatigue, oedema peripheral, nausea, and dermatitis acneiform. In clinical trials with trametinib, adverse reactions of diarrhoea and rash were managed with appropriate supportive care *(*see section 4.2).

Adverse reactions are listed in Table 10 and Table 11 by MedDRA body system organ class. Table 11 lists the very common adverse events (≥ 10%) reported in patients receiving trametinib.

The following convention has been utilised for the classification of frequency:

Very common	≥ 1 in 10
Common	≥ 1 in 100 and < 1 in 10
Uncommon	≥ 1 in 1,000 and < 1 in 100

Categories have been assigned based on absolute frequencies in the clinical trial data.

Table 10 Unresectable or metastatic melanoma - adverse reactions with trametinib monotherapy (N = 329)

Infections and Infestations	
Common	Folliculitis, paronychia, cellulitis, rash pustular
Blood and lymphatic system disorders	
Common	Anaemia
Immune system disorders	
Common	Hypersensitivity[b]
Metabolism and Nutrition Disorders	
Common	Dehydration
Eye disorders	
Common	Vision blurred, periorbital oedema, visual impairment
Uncommon	Chorioretinopathy, retinal vein occlusion, papilloedema, retinal detachment
Cardiac disorders	
Common	Left ventricular dysfunction, ejection fraction decreased, bradycardia
Uncommon	Cardiac failure
Vascular Disorders	
Very common	Hypertension, haemorrhage[a]

Common	Lymphoedema
Respiratory, thoracic and mediastinal disorders	
Very common	Cough, dyspnoea
Common	Epistaxis, pneumonitis
Uncommon	Interstitial lung disease
Gastrointestinal disorders	
Very common	Diarrhoea, nausea, vomiting, constipation, abdominal pain, dry mouth
Common	Stomatitis
Uncommon	Gastrointestinal perforation, colitis
Investigations	
Common	Aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased
Skin and Subcutaneous Tissue Disorders	
Very common	Rash, dermatitis acneiform, dry skin, pruritus, alopecia
Common	Skin chapped, erythema, palmar-plantar erythrodysaesthesia syndrome, skin fissures
Musculoskeletal and connective tissue disorder	
Common	Blood creatine phosphokinase increased
Uncommon	Rhabdomyolysis
General disorders	
Very common	Fatigue, oedema peripheral, pyrexia
Common	Face oedema, mucosal inflammation, asthenia

[a] Events include: epistaxis, haematochezia, gingival bleeding, haematuria, melaena and rectal, haemorrhoidal, gastric, vaginal, conjunctival, and post procedural haemorrhage. The majority of bleeding events were mild; major events, defined as symptomatic bleeding in a critical area or organ, and fatal intracranial haemorrhages have been reported.

[b] May present with symptoms such as fever, rash, increased liver function tests, and visual disturbances

Table 11 Adverse Events (%) occurring in ≥ 10 % of patients treated with trametinib

	Trametinib (N = 211)			Chemotherapy (N = 99)		
Events	**All Grades[a]**	**Grade 3**	**Grade 4**	**All Grades[a]**	**Grade 3**	**Grade 4**
Skin and subcutaneous tissue disorders						
Rash	57	7	<1	10	0	0
Dermatitis acneiform	19	<1	0	1	0	0
Alopecia	17	<1	0	19	0	0
Dry skin	11	0	0	0	0	0
Pruritus	10	2	0	1	0	0
Gastrointestinal disorders						
Diarrhoea	43	0	0	16	1	1
Nausea	18	<1	0	37	1	0
Constipation	14	0	0	23	1	0
Vomiting	13	<1	0	19	2	0
General disorders and administrative site conditions						
Fatigue	26	4	0	27	3	0
Edema peripheral	26	<1	0	3	0	0
Vascular disorders						
Hypertension	15	12	0	7	3	0
Haemorrhage[b]	13	<1	0	0	0	0
Infections and infestations						
Paronychia	10	0	0	1	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.
[b] Events include: epistaxis, haematochezia, gingival bleeding, haematuria, melaena, and rectal, haemorrhoidal, and conjunctival haemorrhage

Combination of trametinib with dabrafenib

The safety of trametinib and dabrafenib combination therapy has been evaluated in 2 randomised Phase III studies of patients with BRAF mutant unresectable or metastatic melanoma treated with trametinib 2 mg orally once daily and dabrafenib 150 mg orally twice daily (see section 5.1). The most common adverse reactions (≥ 20 %) for trametinib and dabrafenib combination therapy include pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, vomiting, peripheral oedema, and cough.

Table 12 lists adverse reactions when trametinib was used in combination with dabrafenib from the randomised double-blind Phase III study MEK115306 (N=209), and integrated safety data from MEK115306 (N=209) and from the randomised open-label Phase III study MEK 116513 (N=350).

The following convention has been utilised for the classification of frequency:
Very common: ≥ 1/10
Common: ≥ 1/100 and < 1/10

Note: As patient numbers are small the frequencies of uncommon or rare events could not be determined.

Table 12 Unresectable or metastatic melanoma - Adverse reactions for trametinib in combination with dabrafenib from the randomised double-blind phase III combination study MEK115306, and integrated safety data from two randomised phase III combination studies, MEK115306 and MEK116513

Adverse event	Frequency classification COMBI-d N=209	COMBI-d and COMBI-v N=559
Infections and Infestations		
Urinary tract infection	Very common	Common
Nasopharyngitis	Very common	Very common
Cellulitis	Common	Common
Folliculitis	Common	Common
Paronychia	Common	Common
Rash pustular	Common	Common
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma	Common	Common
Papilloma including skin papilloma	Common	Common
Seborrhoeic keratosis	Common	Common
Acrochordon (skin tags)	Common	Uncommon
New primary melanoma	Uncommon	Uncommon
Blood and lymphatic system disorders		
Neutropenia	Very Common	Common
Anaemia	Common	Common
Thrombocytopenia	Common	Common
Leukopenia	Common	Common
Immune system disorders		
Hypersensitivity	Uncommon	Uncommon

Adverse event	Frequency classification COMBI-d N=209	COMBI-d and COMBI-v N=559
Metabolic and nutrition disorders		
Decreased appetite	Very common	Very common
Dehydration	Common	Common
Hyperglycaemia	Common	Common
Hyponatraemia	Common	Common
Hypophosphataemia	Common	Common
Nervous system disorders		
Headache	Very common	Very common
Dizziness	Very common	Very common
Eye disorders		
Vision blurred	Common	Common
Visual impairment	Common	Common
Chorioretinopathy	Uncommon	Uncommon
Uveitis	Uncommon	Uncommon
Retinal detachment	Uncommon	Uncommon
Periorbital oedema	Uncommon	Uncommon
Cardiac disorders		
Ejection fraction decreased	Common	Common
Bradycardia	Common	Common
Left ventricular dysfunction	NR	Uncommon
Cardiac failure	NR	Uncommon
Vascular disorders		
Hypertension	Very common	Very common
Haemorrhage*	Very common	Very common
Hypotension	Common	Common
Lymphoedema	Uncommon	Common
Respiratory, thoracic and mediastinal disorders		
Cough	Very common	Very common
Dyspnoea	Common	Common
Pneumonitis	Uncommon	Uncommon
Interstitial lung disease	NR	Uncommon
Gastrointestinal disorders		
Abdominal pain	Very common	Very common
Constipation	Very common	Very common
Diarrhoea	Very common	Very common
Nausea	Very common	Very common
Vomiting	Very common	Very common
Dry mouth	Common	Common
Stomatitis	Common	Common
Pancreatitis	Uncommon	Uncommon
Gastrointestinal perforation	NR	Uncommon
Colitis	Uncommon	Uncommon
Investigations		
Alanine aminotransferase increased	Very common	Very common
Aspartate aminotransferase increased	Very common	Very common
Blood alkaline phosphatase increased	Common	Common
Gamma-glutamyltransferase increased	Common	Common
Skin and subcutaneous tissue disorders		
Dry skin	Very common	Very common

Adverse event	Frequency classification COMBI-d N=209	Frequency classification COMBI-d and COMBI-v N=559
Pruritus	Very common	Very common
Rash	Very common	Very common
Dermatitis acneiform	Very common	Common
Erythema	Common	Common
Actinic keratosis	Common	Common
Night sweats	Common	Common
Hyperkeratosis	Common	Common
Alopecia	Common	Common
Palmar-plantar erythrodysaesthesia syndrome	Common	Common
Skin lesion	Common	Common
Hyperhidrosis	Common	Common
Skin fissures	Common	Common
Panniculitis	Common	Common
**Photosensitivity	Common	Common
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Very common
Myalgia	Very common	Very common
Pain in extremity	Very common	Very common
Muscle spasms	Common	Common
Blood creatine phosphokinase increased	Common	Common
Rhabdomyolysis	NR	Uncommon
Renal disorders		
Renal failure	Uncommon	Common
Nephritis	Uncommon	Uncommon
Renal failure acute	NR	Uncommon
General disorders and administration site disorders		
Fatigue	Very common	Very common
Oedema peripheral	Very common	Very common
Pyrexia	Very common	Very common
Chills	Very common	Very common
Asthenia	Very common	Very common
Mucosal inflammation	Common	Common
Influenza-like illness	Common	Common
Face oedema	Common	Common

NR = Not reported

* The majority of bleeding events were mild. Major events, defined as symptomatic bleeding in a critical area or organ, and fatal intracranial haemorrhages have been reported

** 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

Table 13 Treatment Emergent Abnormalities in Liver Function Tests Occurring in Patients Treated With trametinib in Combination with dabrafenib in unresectable or metastatic melanoma

	Dabrafenib 150 mg BID Monotherapy (N = 53)	Trametinib 1mg QD Combination (N = 54)	Trametinib 2mg QD Combination (N = 55)
Test	Grade	Grade	Grade

	All grades[a]	3	4	All grades[a]	3	4	All grades[a]	3	4
Increased ALP	26	2	0	67	6	0	60	2	0
Increased AST	15	0	0	54	0	0	60	5	0
Increased ALT	11	0	0	35	4	0	42	4	0
Hyperbilirubinemia	0	0	0	7	4	0	15	0	0

[a] No Grade 4 events were reported in dabrafenib arm.

ALP = alkaline phosphatase; AST= aspartate transaminase; ALT = alanine transaminase

Metastatic melanoma patients with brain metastases

The safety profile observed in study BRF117277/DRB436B2204 (COMBI-MB) in metastatic melanoma patients with brain metastases is consistent with the safety profile of trametinib in combination with dabrafenib in unresectable or metastatic melanoma (see also section 5.1, Pharmacodynamic Properties - Clinical Trials).

Adjuvant treatment of melanoma

Trametinib in combination with dabrafenib

The safety of trametinib in combination with dabrafenib was evaluated in a Phase III, randomised, double-blind study of trametinib in combination with dabrafenib versus two placebos in the adjuvant treatment of Stage III BRAF V600 mutation-positive melanoma after surgical resection (see section 5.1).

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

Table 14 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 trametinib in combination with dabrafenib 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 in 10
Common	≥ 1 in 100 and < 1 in 10
Uncommon	≥ 1 in 1,000 and < 1 in 100
Rare	≥ 1/10,000 to < 1/1,000
Very rare	< 1/10,000

Table 14 Adjuvant treatment of melanoma - Adverse drug reactions for trametinib in combination with dabrafenib **versus placebo**

Adverse drug reactions	Trametinib in combination with dabrafenib 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					
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

Adverse drug reactions	Trametinib in combination with dabrafenib N=435 %		Placebo N=432 %		Frequency category (combination arm, all grades)
	All Grades	Grade 3/4	All Grades	Grade 3/4	
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*
[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 generalised, 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 generalised erythema*
[14] *Pruritus also includes puritus generalised 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

Trametinib in combination with dabrafenib

The efficacy and safety of trametinib in combination with dabrafenib was studied in a Phase II, nine-cohort, multicentre, non-randomised, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC (see section 5.1 Clinical Trials).

The 'All Treated Patients (ATS)' population was the primary safety population for the study and includes all patients who received at least one dose of trametinib or dabrafenib 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 trametinib in combination with dabrafenib in the ATS population were fatigue, pyrexia, rash, nausea, chills,

vomiting, cough, and headache.

Table 15 lists the adverse drug reactions for trametinib in combination with dabrafenib 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 in 10
Common	≥ 1 in 100 and < 1 in 10
Uncommon	≥ 1 in 1,000 and < 1 in 100
Rare	≥ 1/10,000 to < 1/1,000
Very rare	< 1/10,000.

Table 15 Anaplastic Thyroid Cancer - Adverse drug reactions for trametinib in combination with dabrafenib **in the All Treated Patients (ATS) population**

Adverse drug reactions	Trametinib in combination with dabrafenib		
	All grades n = 100 %	Grades 3/4 n = 100 %	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

Adverse drug reactions	Trametinib in combination with dabrafenib		
	All grades n = 100 %	Grades 3/4 n = 100 %	Frequency category
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.

[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 generalised 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

Advanced non-small cell lung cancer

Trametinib in combination with dabrafenib

The safety of trametinib in combination with dabrafenib was evaluated in a Phase II, multicentre, multi-cohort, non-randomised, open-label study of patients with BRAF V600E mutation positive metastatic NSCLC (see section 5.1).

In the trametinib 2 mg orally once daily and dabrafenib 150 mg orally twice daily arms (Cohorts B and C) the most common adverse events (≥ 20%) reported for trametinib and dabrafenib combination therapy were pyrexia, nausea, vomiting, peripheral oedema, diarrhoea, decreased appetite, asthenia, dry skin, chills, cough, fatigue, rash, and dyspnoea.

Table 16 lists the adverse drug reactions for trametinib in combination with dabrafenib occurring at an incidence ≥ 10% for all adverse drug reactions or at an incidence ≥ 2% for Grade 3 and Grade 4 adverse drug reactions or events which are medically significant in Cohorts B and C of study BRF113928.

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 16 Advanced NSCLC - Adverse drug reactions for trametinib in combination with dabrafenib

Adverse drug reactions	Trametinib in combination with dabrafenib		
	All grades n = 93 %	Grades 3/4 n = 93 %	Frequency category
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Cutaneous squamous cell carcinoma	3	2	Common
Blood and lymphatic system disorders			
Neutropenia[1)]	15	8	Very common
Leukopenia	6	2	Common
Metabolism and nutrition disorders			
Hyponatraemia	14	9	Very common
Dehydration	8	3	Common
Eye disorders			
Detachment of retina/retinal pigment epithelium	2	NR	Common
Nervous system disorders			
Headache	16	NR	Very common
Dizziness	14	NR	Very common
Cardiac disorders			
Ejection fraction decreased	9	4	Common
Vascular disorders			
Haemorrhage[2)]	26	3	Very common
Hypotension	15	2	Very common
Hypertension	8	6	Common
Pulmonary embolism	4	2	Common
Gastrointestinal disorders			
Nausea	46	NR	Very common
Vomiting	37	3	Very common
Diarrhoea	33	2	Very common
Decreased appetite	28	NR	Very common
Constipation	16	NR	Very common
Pancreatitis acute	1	NR	Common
Skin and subcutaneous tissue disorders			
Erythema	10	NR	Very common
Dry skin	32	1	Very common
Rash[3)]	31	3	Very common
Pruritus[4)]	15	2	Very common
Hyperkeratosis[5)]	13	1	Very common
Musculoskeletal and connective tissue disorders			
Muscle spasms	10	NR	Very common
Arthralgia	16	NR	Very common
Myalgia	13	NR	Very common
Renal and urinary disorders			
Renal failure	3	1	Common
Tubulointerstitial nephritis	2	2	Common
General disorders and administration site disorders			
Pyrexia	55	5	Very common
Asthenia[6)]	47	6	Very common
Oedema[7)]	35	NR	Very common

Adverse drug reactions	Trametinib in combination with dabrafenib		
	All grades n = 93 %	Grades 3/4 n = 93 %	Frequency category
Chills	24	1	Very common
Investigations			
Blood alkaline phosphatase increased	12	NR	Very common
Aspartate aminotransferase increased	11	2	Very common
Alanine aminotransferase increased	10	4	Very common

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

2.) *Haemorrhage includes cases of haemoptysis, haematoma, epistaxis, purpura, haematuria, subarachnoid haemorrhage, gastric haemorrhage, urinary bladder haemorrhage, contusion, haematochezia, injection site haemorrhage, melaena, and pulmonary and retroperitoneal haemorrhage.*

3) *Rash includes rash, rash generalised, rash papular, rash macular, rash maculo-papular, and rash pustular.*

4) *Pruritus includes pruritus, pruritus generalised, and eye pruritus.*

5) *Hyperkeratosis includes hyperkeratosis, actinic keratosis, seborrhoeic keratosis, and keratosis pilaris.*

6) *Asthenia also includes fatigue and malaise.*

7) *Oedema includes generalised oedema and peripheral oedema.*

NR: Not Reported

Post-marketing experience and pooled clinical trials

The following adverse reactions have been derived from post-marketing experience including spontaneous case reports with trametinib monotherapy or in combination with dabrafenib. Because post-marketing adverse reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency. Where applicable, these frequencies have been calculated from the pooled clinical trials across indications. Adverse reactions are listed according to system organ classes in MedDRA.

Table 17 Adverse reactions from post-marketing experience and pooled clinical trials across indications

Adverse reaction	Trametinib in combination with dabrafenib frequency	Trametinib monotherapy frequency
Cardiac disorders		
Atrioventricular block[1]	Common	Uncommon
Bundle branch block[2]	Uncommon	Uncommon
Vascular disorders		
Venous thrombo-embolism (VTE)[3]	Common	-
Skin and subcutaneous tissue disorders		
Acute febrile neutrophilic dermatosis (Sweet's syndrome)	Not known	-
Tattoo associated skin reaction	Not known	-
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
Guillain-Barré syndrome	Uncommon	-

[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.

Special Populations

Patients ≥ 65 years of age
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 study drug, dose reduction and dose interruption than those < 65 years.

In the phase I/II study of trametinib in combination with dabrafenib in patients with unresectable or metastatic melanoma (n = 202), 42 patients (21%) were ≥ 65 years of age, and 12 patients (6%) were ≥ 75 years of age. The proportion of subjects experiencing AEs was similar in the subjects aged < 65 years and those aged ≥ 65 years. Patients ≥ 65 years were more likely to experience SAEs, fatal SAEs and AEs leading to permanent discontinuation of study drug, dose reduction and dose interruption than those < 65 years.

Paediatric patients

Trametinib in combination with dabrafenib
The safety of trametinib in combination with dabrafenib was studied in 171 paediatric patients across two studies (G2201 and X2101) with BRAF V600E mutation-positive advanced solid tumours, of which 4 (2.3%) patients were 1 to <2 years of age, 39 (22.8%) patients were 2 to <6

years of age, 54 (31.6%) patients were 6 to <12 years of age, and 74 (43.3%) patients were 12 to <18 years of age. The mean treatment duration was 2.3 years.

The overall safety profile in the paediatric population was similar to the safety profile observed in adults. The most frequently reported adverse drug reactions (≥20%) were pyrexia, rash, headache, vomiting, fatigue, dry skin, diarrhoea, haemorrhage, nausea, dermatitis acneiform, abdominal pain, neutropenia, cough and transaminases increased.

An adverse drug reaction of weight increased was identified in the paediatric safety pool with a frequency of 16% (very common). Sixty-one out of 171 patients (36%) had an increase from baseline of ≥2 BMI-for-age- percentile categories.

Adverse drug reactions occurring at a higher frequency category in paediatric patients compared to adult patients were neutropenia, dermatitis acneiform, paronychia, anaemia, leukopenia, skin papilloma (very common), dermatitis exfoliative generalised, hypersensitivity and pancreatitis (common).

Table 18 Most frequent Grade 3/4 Adverse drug reactions (≥2%) for trametinib in combination with dabrafenib in paediatric patients

Adverse drug reactions	**Trametinib in combination with dabrafenib N=171**
	Grade 3/4 n (%)
Neutropenia[1]	25 (15)
Pyrexia	19 (11)
Transaminases increased[2]	11 (6)
Weight Increased	9 (5)
Headache	5 (3)
Vomiting	5 (3)
Hypotension	4 (2)
Rash[3]	4 (2)
Blood alkaline phosphatase increased	4 (2)

1. *Neutropenia includes, neutrophil count decreased, neutropenia, and febrile neutropenia.*
2. *Transaminases increased includes aspartate aminotransferase increased, alanine aminotransferase increased, hypertransaminasaemia, and transaminases increased*
3. *Rash includes rash, rash maculo-papular, rash pustular, rash erythematous, rash papular, and rash macular.*

Reporting of suspected adverse reactions

The reporting suspected adverse reactions after the authorisation of the medicine is important. It allows for continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to Medsafe via the following web site: https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

There were no cases of trametinib dose above 4 mg once daily reported from the clinical trials. Doses of 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.

Treatment
There is no specific treatment for an overdose of trametinib. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Haemodialysis is not expected to enhance the elimination as trametinib is highly bound to plasma proteins. Further management should be as clinically indicated.

For risk assessment and advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mitogen-activated protein kinase (MEK) inhibitors
Anatomical Therapeutic Chemical (ATC) code: L01EE01

Mechanism of Action

Trametinib monotherapy

Trametinib (trametinib) is a reversible allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and 2 (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 activates MEK and stimulates tumour cell growth. Trametinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity. Trametinib inhibits growth of BRAF V600 mutant melanoma, ATC, and NSCLC cell lines *in vitro* and demonstrates anti-tumour effects in BRAF V600 mutant melanoma xenograft models.

Trametinib in combination with dabrafenib

Dabrafenib is an ATP-competitive inhibitor of BRAF V600 mutant kinases and wild type BRAF and CRAF kinases. Mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway and stimulation of tumour cell growth. Dabrafenib and trametinib inhibit two critical kinases in this pathway, BRAF and MEK, and the combination provides concomitant inhibition of the pathway. Combination of dabrafenib with trametinib is synergistic in BRAF V600 mutation positive melanoma, ATC, and NSCLC cell lines *in vitro* and delays the emergence of resistance *in vivo* in BRAF V600 mutation positive melanoma xenografts.

Pharmacodynamic Effects

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

In patients with BRAF mutant melanoma, administration of trametinib resulted in dose-dependent changes in tumour biomarkers including inhibition of phosphorylated ERK, inhibition of Ki67 (a marker of cell proliferation), and increases in p27 (a marker of apoptosis). The mean trametinib concentrations observed following repeat dose administration of 2 mg once daily exceeds the preclinical target concentration over the 24-hour dosing interval, thereby providing sustained inhibition of the MEK pathway.

CLINICAL TRIALS

Determination of BRAF mutation status

In the Phase II and III clinical trials, screening for eligibility required central testing for BRAF V600 mutation using a BRAF mutation assay conducted on the most recent tumour sample available. Primary tumour or tumour from a metastatic site was tested with an investigational use only assay (IUO) developed by Response Genetics Inc. (RGI). The RGI IUO is an allele-specific polymerase chain reaction (PCR) assay performed on DNA extracted from formalin-fixed paraffin-embedded (FFPE) tumour tissue. The assay was specifically designed to differentiate between the V600E and V600K mutations.

Only subjects with BRAF V600E or V600K mutation positive tumours were eligible for study participation.

Unresectable or metastatic melanoma

Trametinib monotherapy

Open Label Studies

MEK114267

The efficacy and safety of trametinib in patients with BRAF mutant unresectable or metastatic melanoma (V600E and V600K) were evaluated in this randomised open label study. 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 tumour 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 randomised 2:1 to receive trametinib 2 mg once daily or chemotherapy (dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks). Treatment for all patients continued until disease progression, death or withdrawal.

The primary endpoint of the study was to evaluate the efficacy of trametinib compared to chemotherapy with respect to 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 (see Figure 1). The secondary endpoints were progression-free survival in the ITT population and overall survival (OS), overall response rate (ORR), and duration of response 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. A total of 51 (47%) of patients with confirmed disease progression in the chemotherapy arm, 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, the majority of patients were male (54%) and all were Caucasian (100%). The median age was 54 years (22% were ≥65 years), most patients (64%) had ECOG performance status of 0, 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. Most patients (66%) received no prior chemotherapy for advanced or metastatic disease.

The efficacy results in the primary efficacy population were consistent with those in the ITT population; therefore, only the efficacy data for the ITT population are presented in Table 19. At the time of the data cut off, 51 patients (47%) on the chemotherapy arm had crossed over to the trametinib arm after disease progression. These patients are included in the OS analysis.

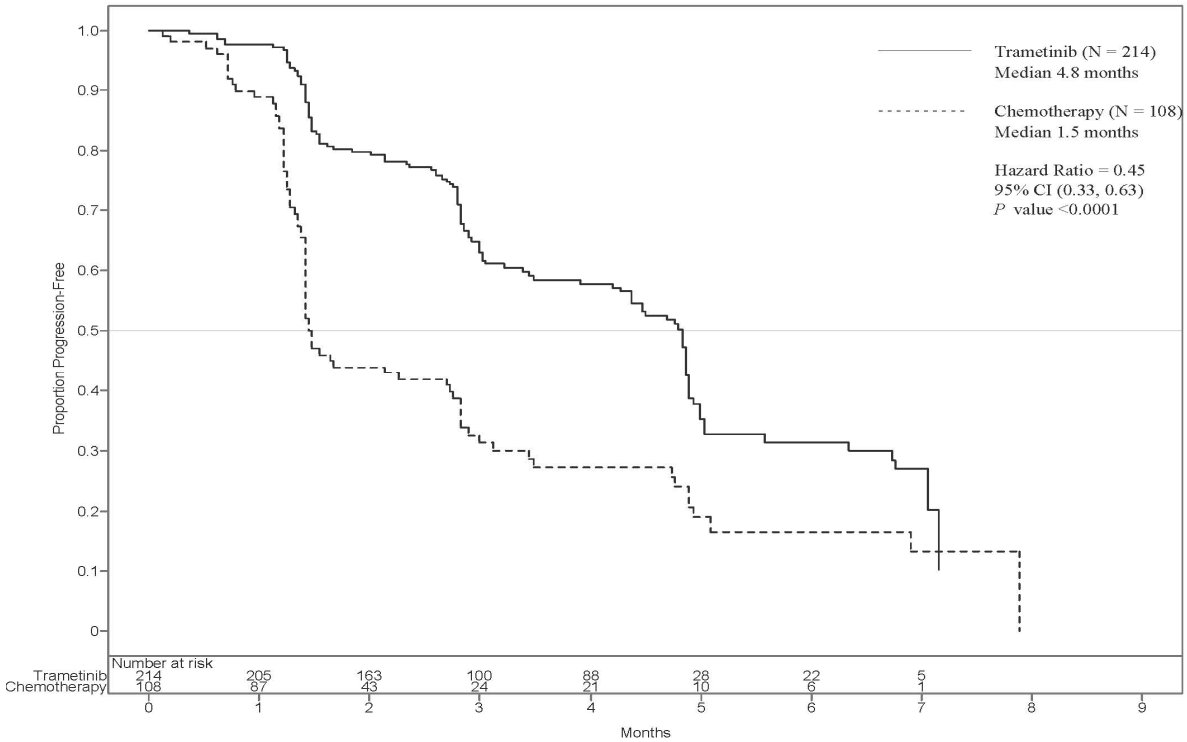
Table 19 MEK114267 - Investigator-Assessed Efficacy Results (ITT Population)

Endpoint Progression-Free Survival (PFS)	Trametinib (N = 214)	Chemotherapy[a] (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 Survival		
Died, n (%)	35 (16)	29 (27)
Hazard Ratio (95% CI) *P* value	0.54 (0.32, 0.92) 0.0136	
Survival at 6 months (%) (95% CI)	81 (73, 86)	67 (55, 77)
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.

Figure 1 MEK114267 Investigator-Assessed Progression-Free Survival (ITT population)



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).

MEK113583 – Phase II BRAF inhibitor pre-treatment study

In single arm, multicentre, Phase II Study MEK113583, evaluated the objective response rate, safety and PK following oral daily dosing of trametinib at 2 mg QD in patients with BRAF V600E, V600K, or V600D mutation-positive metastatic melanoma, previously treated with or without a BRAF inhibitor (BRAFi). Patients were enrolled into two separate cohorts, defined by therapy received prior to trametinib: Cohort A- patients (n=40) had received prior treatment with a BRAF inhibitor (BRAFi). Cohort B- patients (n=57) were BRAFi-naïve and had received at least 1 prior chemotherapy or immunotherapy.

Trametinib did not demonstrate clinical activity in Cohort A (patients who progressed on a prior BRAF inhibitor therapy in one of the cohorts, see section 4.1).

Trametinib in combination with dabrafenib

The efficacy and safety of the recommended dose of trametinib (2 mg once daily) in combination with dabrafenib (dabrafenib 150 mg twice daily) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation was studied in two pivotal Phase III studies, MEK116513 and MEK115306.

MEK116513 (COMBI-v)

Study MEK116513 was a 2-arm, randomised, open-label, Phase III study comparing trametinib and dabrafenib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive unresectable or metastatic melanoma. The primary endpoint of the study was overall survival (Figure 2), and the key secondary endpoint was PFS. Other secondary objectives included ORR, DoR, and safety. 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 randomised 1:1 to either the combination therapy arm (trametinib 2 mg once daily and dabrafenib 150 mg twice daily) or the vemurafenib monotherapy arm (960 mg twice daily). Most patients were white (>96%) and male (55%), with a median age of 55 years (24% were ≥ 65 years). The majority of subjects had Stage IV M1c disease (61%). 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 a BRAF V600E mutation (89%).

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 20, Figure 2). The Kaplan-Meier OS curve appears to stabilise from 3 years to 5 years (see Figure 2). The 5-year overall survival rate was 46% (95% CI: 38.8, 52.0) in the combination arm versus 28% (95% CI: 22.5, 34.6) in the vemurafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 9.3, 23.3) in the combination arm versus 10% (95% CI: 5.1, 17.4) in the vemurafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline.

Table 20 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*

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 21).

Figure 2 COMBI-v Kaplan-Meier Overall Survival Curves (ITT Population)

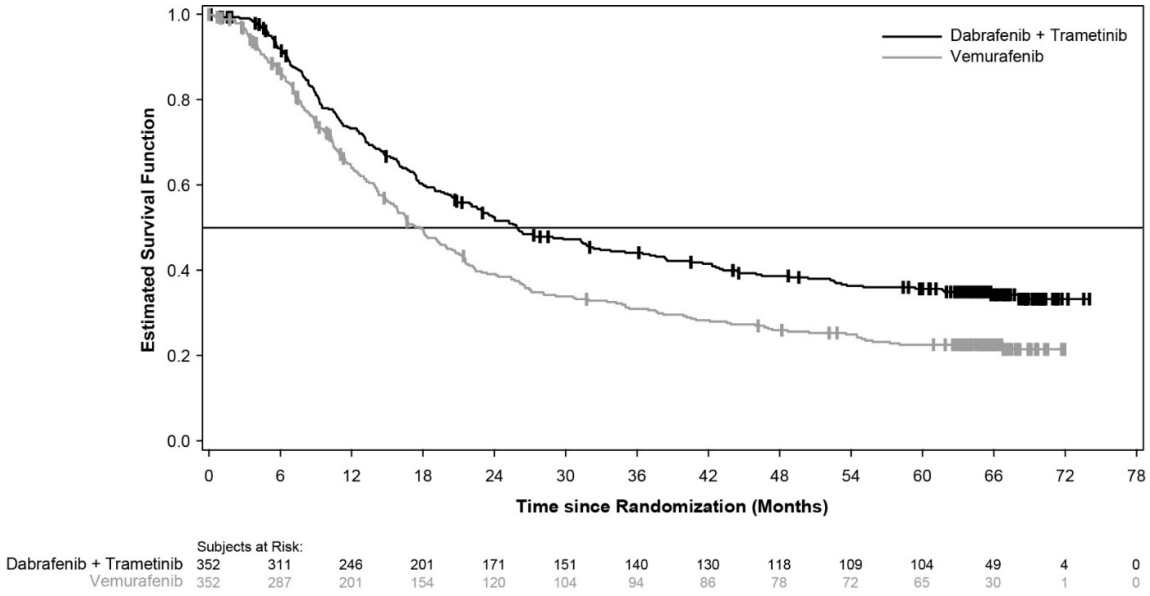


Table 21 Investigator-assessed efficacy results for MEK116513 (COMBI-v) study

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)						
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

Randomised double-blind study

Trametinib with dabrafenib combination therapy study - MEK115306 (COMBI-d)

MEK115306 (COMBI-d) was a Phase III, randomised, double-blind study comparing the combination of trametinib and dabrafenib to dabrafenib and placebo as 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) (Figure 3). 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 subjects were randomised 1:1 to either the combination therapy arm (trametinib 2 mg once daily and dabrafenib 150 mg twice daily) (N = 211) or dabrafenib monotherapy arm (150 mg twice daily) (N = 212). Baseline characteristics were balanced between treatment groups. Males constituted 53 % of patients and the median age was 56 years; Majority of patients had an ECOG performance score of 0 (72 %) and had Stage IVM1c disease (66 %). Most patients had the 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 18. 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 22, Figure 3). The Kaplan-Meier OS curve appears to stabilise from 3 to 5 years (see Figure 3).

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 22 - COMBI-d - Overall Survival results (ITT population)

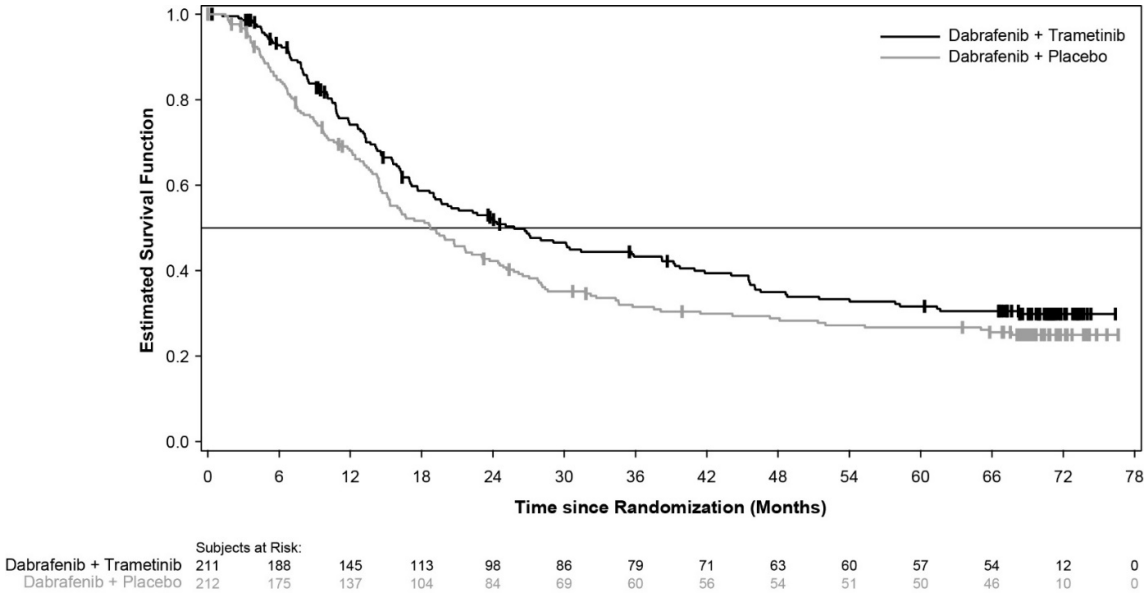
	OS analysis*		3-year OS analysis*		5-year OS analysis*	
	Dabrafenib + trametinib (n=211)	**Dabrafenib + placebo (n=212)**	**Dabrafenib + trametinib (n=211)**	**Dabrafenib + placebo (n=212)**	**Dabrafenib + trametinib (n=211)**	**Dabrafenib + placebo (n=212)**
Number of Patients						
Died (event), n (%)	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 3 Kaplan-Meier Overall Survival Curves (ITT Population) for MEK115306 (COMBI-d) study (Primary Data Cut and Final Data Cut) (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 23)

Table 23 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

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

The efficacy and safety of trametinib in combination with dabrafenib in patients with BRAF mutant-positive melanoma that has metastasised to the brain was studied in a non-randomised open-label, multi-center Phase II study (COMBI-MB study).

A total of 125 patients were enrolled into four cohorts:

- Cohort A: patients with BRAFV600E mutant melanoma with asymptomatic brain metastases without prior local brain-directed therapy and ECOG performance status of 0 or 1.
- Cohort B: patients with BRAFV600E mutant melanoma with asymptomatic brain metastases with prior local brain-directed therapy and ECOG performance status of 0 or 1.
- Cohort C: patients with BRAFV600D/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 BRAFV600D/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 24. Secondary endpoints were duration of intracranial response, ORR, PFS and OS. Efficacy results are summarised in Table 24.

Table 24 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*				

Adjuvant treatment of melanoma

Trametinib in combination with dabrafenib

Randomised double-blind study

Study BRF115532 / DRB436F2301 (COMBI-AD)

The efficacy and safety of trametinib in combination with dabrafenib was studied in a Phase III, multicentre, randomised, double blind, placebo-controlled study in patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

Patients were randomised 1:1 to receive either dabrafenib and trametinib combination therapy (trametinib 2 mg once daily and dabrafenib 150 mg twice daily) or two placebos for a period of 12 months. Enrolment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomisation. 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 tumour size and ulceration). The primary endpoint was investigator-assessed relapse-free survival (RFS), defined as the time from randomisation to disease recurrence or death from any cause. Radiological tumour assessment was conducted every 3 months for the first two years and every 6 months thereafter, until first relapse was observed. Secondary endpoints include overall survival (OS; key secondary endpoint) and distant metastasis-free survival (DMFS).

A total of 870 patients were randomised to the combination therapy (n=438) and placebo (n=432) arms. Most patients were Caucasian (99%) and male (55%), with a median age of 51 years (18% were ≥65 years). The study included patients with all sub-stages of Stage III disease prior to resection; 18% of these patients had lymph node involvement only identifiable by microscope and no primary tumour ulceration. The majority of patients had a BRAF V600E mutation (91%).

The median duration of follow-up at the time of the primary analysis was 2.83 years in the dabrafenib and trametinib combination arm and 2.75 years in the placebo arm.

Results for the primary analysis of RFS are presented in Table 25. The study showed a statistically significant difference for the primary outcome of investigator-assessed 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=1.53×10-14). 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 25 COMBI-AD primary analysis – Relapse-free survival results

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

[1] Hazard ratio is obtained from the stratified Pike model.

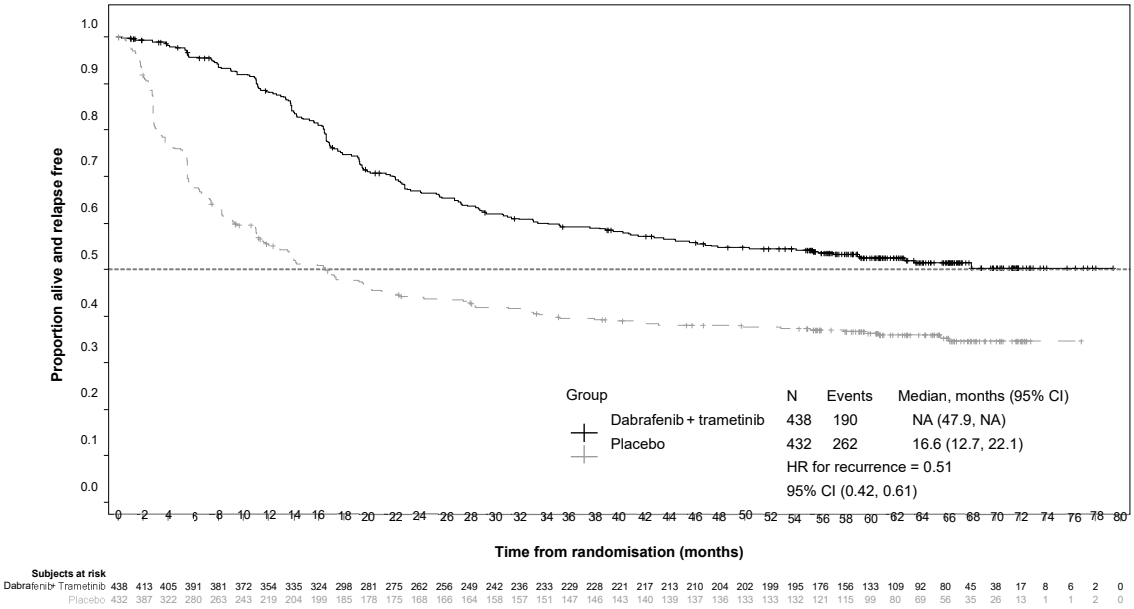
[2] P-value is obtained from the two-sided stratified log-rank test (stratification factors were disease stage – IIIA vs. IIIB vs. IIIC – and BRAF V600 mutation type – V600E vs. V600K)

NE = not estimable

Based on updated data with an additional 29 months of follow-up compared to the primary analysis (minimum follow-up of 59 months), the RFS benefit was maintained with an estimated HR of 0.51

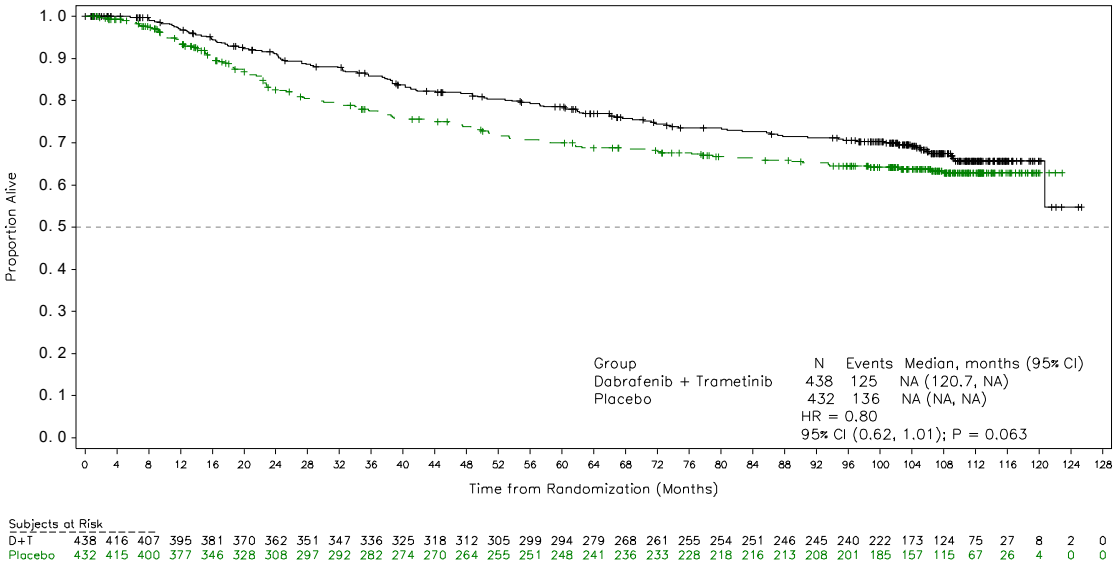
(95% CI: (0.42, 0.61) (Figure 4). The 5-year RFS rate was 52% (95% CI: 48, 58) in the combination arm compared to 36% (95% CI: 32, 41) in the placebo arm.

Figure 4 COMBI-AD Investigator-assessed relapse-free survival Kaplan-Meier curves (ITT Population)



The median duration of follow up at the time of the final overall survival analysis was 8.3 years in the combination arm and 6.9 years in the placebo arm. The estimated hazard ratio for overall survival was 0.80 (95% CI: 0.62, 1.01; p=0.063) with 125 events (29%) in the combination arm and 136 events (31%) in the placebo arm. Estimated 5-year overall survival rates were 79% in the combination arm and 70% in the placebo arm, and estimated 10-year overall survival rates were 66% in the combination arm and 63% in the placebo arm. In patients who went on to receive subsequent anti cancer therapies after study treatment, therapies included targeted therapy in 21% in the combination arm and 37% in the placebo arm, and immunotherapy in 29% in the combination arm and 29% in the placebo arm. The Kaplan-Meier curves for the final overall survival analysis are shown in Figure 5.

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



Locally advanced or metastatic anaplastic thyroid cancer

Trametinib in combination with dabrafenib

Non-randomised open label study

Study BRF117019 (CDRB436X2201)

The efficacy and safety of trametinib in combination with dabrafenib was studied in a Phase II, nine-cohort, multicentre, non-randomised, 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 trametinib 2 mg once daily and dabrafenib 150 mg twice daily. The primary endpoint was the investigator-assessed ORR using the 'Response Evaluation Criteria In Solid Tumours' (RECIST 1.1 assessed by the investigator). Secondary endpoints included DoR, PFS, 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 33 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 26).

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 patients, 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 26 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*

Advanced NSCLC

Trametinib in combination with dabrafenib

Non-randomised open label studies

BRF113928 (Study E2201)

The efficacy and safety of trametinib in combination with dabrafenib was studied in a Phase II, three-cohort, multicentre, non-randomised, open-label study enrolling patients with Stage IV BRAF V600E mutant NSCLC.

The primary endpoint was the investigator-assessed ORR using the 'Response Evaluation Criteria In Solid Tumours' (RECIST 1.1 assessed by the investigator). Secondary endpoints included DoR, PFS, OS, safety and population pharmacokinetics. ORR, DoR and PFS were also assessed by an Independent Review Committee (IRC) as a sensitivity analysis.

Cohorts were enrolled sequentially:

- Cohort A: Monotherapy (dabrafenib 150 mg twice daily): 84 patients enrolled. 78 patients had previous systemic treatment for their metastatic disease (see Product information for dabrafenib on results from Cohort A).
- Cohort B (n=57): Combination therapy (trametinib 2 mg once daily and dabrafenib 150 mg twice daily): 59 patients enrolled. 57 patients had previously received one to three lines of 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 (trametinib 2 mg once daily and dabrafenib 150 mg twice daily): 34 patients enrolled (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 Caucasians (n = 79, 85 %). There was a similar female to male ratio (54 % vs 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.

Primary analysis

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 to the investigator assessment.

The final analysis of efficacy performed 5 years after last subject first dose is presented in Table 27.

Table 27 Efficacy results in patients with BRAF V600E NSCLC

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

Low-grade glioma (LGG) and High-grade glioma (HGG)

Study DRB436G2201

The clinical efficacy and safety of trametinib plus dabrafenib combination therapy in paediatric patients aged 1 to <18 years of age with BRAF V600E mutation-positive glioma was evaluated in the multi-centre, open-label, Phase II clinical trial CDRB436G2201. Patients with low-grade glioma (WHO 2016 grades 1 and 2) who required first systemic therapy were randomised in a 2:1 ratio to trametinib plus dabrafenib (D+T) or carboplatin plus vincristine (C+V), and patients with relapsed or refractory high-grade glioma (WHO 2016 grades 3 and 4) were enrolled into a single arm trametinib plus dabrafenib cohort.

BRAF mutation status was identified prospectively via a local test, or a central laboratory real-time polymerase chain reaction (PCR) test when a local test was not available. In addition, retrospective

testing of available tumour samples by the central laboratory was performed to confirm the BRAF V600E mutation.

Dabrafenib and trametinib dosing was age and weight dependent, with dabrafenib dosed orally at 2.625 mg/kg twice daily for ages <12 years and at 2.25 mg/kg twice daily for ages 12 years and older; trametinib was dosed orally at 0.032 mg/kg once daily for ages <6 years and at 0.025 mg/kg once daily for ages 6 years and older. Dabrafenib doses were capped at 150 mg twice daily and trametinib doses at 2 mg once daily. Carboplatin and vincristine were dosed based on age and body surface area at doses of 175 mg/m^2 and 1.5 mg/m^2, respectively as one 10-week induction course followed by eight 6-week cycles of maintenance therapy.

The primary efficacy endpoint in both cohorts was Overall Response Rate (ORR, sum of confirmed complete/CR and partial responses/PR) by independent review based on RANO criteria (RANO 2017 for LGG, and RANO 2010 for HGG). The primary analysis was performed when all patients in both cohorts had completed at least 32 weeks of therapy. The final analysis was performed 2 years after completion of enrolment in both cohorts.

BRAF mutation-positive paediatric low-grade glioma (WHO grades 1 and 2)

In the low-grade glioma (LGG) cohort of study G2201, 110 patients were randomised to D+T (n=73) or C+V (n=37). Median age was 9.5 years, with 34 patients (30.9%) aged 12 months to <6 years, 36 patients (32.7%) aged 6 to <12 years and 40 patients (36.4%) aged 12 to <18 years; 60% were female.

At the time of the primary analysis, the ORR in the D+T arm (46.6%) showed a statistically significant improvement over C+V arm (10.8%), with an odds ratio of 7.19 and 1-sided p-value <0.001 (Table 28). The subsequent hierarchical testing also demonstrated improved progression-free survival (PFS) over chemotherapy, with an estimated 69% risk reduction in progression/death (HR 0.31; 1-sided log-rank p-value <0.001).

Table 28 Response and progression-free survival based on independent review in Study G2201 (LGG cohort, primary analysis)

	Dabrafenib + trametinib N=73	Carboplatin plus vincristine N=37
Best overall response		
Complete response (CR), n (%)	2 (2.7)	1 (2.7)
Partial response (PR), n (%)	32 (43.8)	3 (8.1)
Stable disease (SD), n (%)	30 (41.1)	15 (40.5)
Progressive disease (PD), n (%)	8 (11.0)	12 (32.4)
Unknown, n (%)	1 (1.4)	6 (16.2)[1]
Overall Response Rate		
ORR (CR+PR) (95% CI)[2], p-value	46.6% (34.8 - 58.6%), p<0.001	10.8% (3.0 - 25.4%)
Odds ratio[3] (95% CI)	7.19 (2.3 - 22.4)	
Clinical Benefit Rate		
CBR (CR+PR+SD), (95% CI)	86.3% (76.2 – 93.2%)	45.9% (29.5 – 63.1%)
Odds ratio (95% CI)	7.41 (2.9 – 18.8)	
Progression-free survival		
Median (months) (95% CI)[4]	20.1 (12.8, NE)	7.4 (3.6, 11.8)
Hazard ratio (95% CI)[5], p-value	0.31 (0.17-0.55), p<0.001	

CBR=clinical benefit rate; CI=confidence interval; CR=complete response; NE=not estimable; ORR=overall response rate; PD=progressive disease; PR=partial response; SD=stable disease.

[1] *4 patients randomised to C+V discontinued prior to receiving treatment.*

[2] *Based on Clopper-Pearson exact confidence interval.*

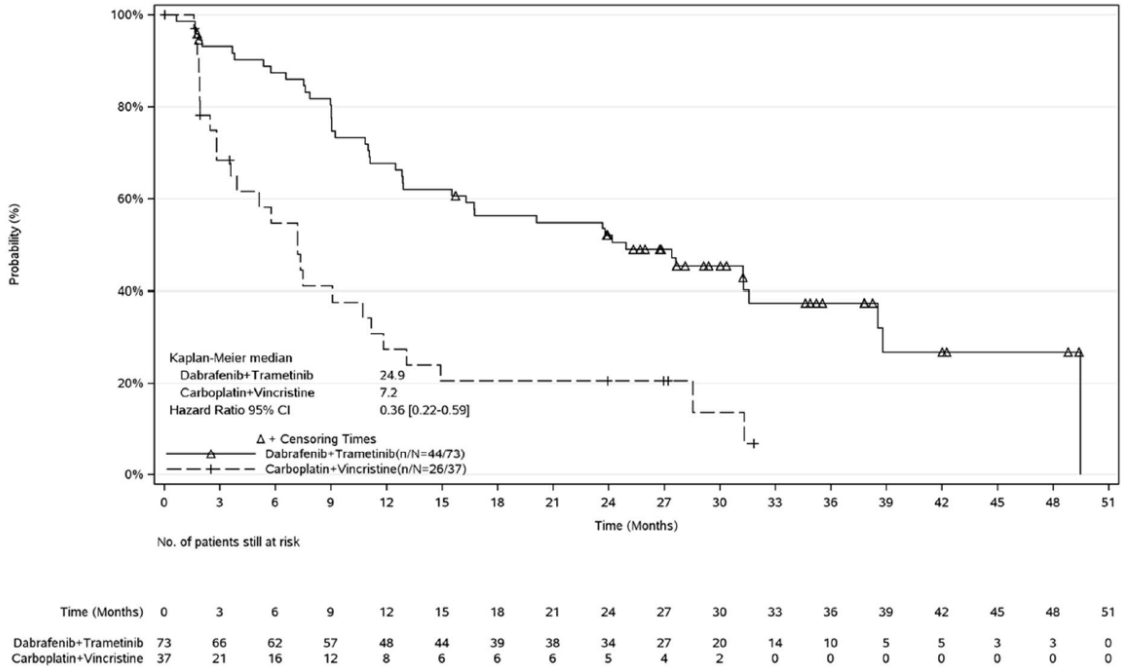
[3] *Odds ratio (D+T vs C+V) and 95% CI are from a logistic regression with treatment as the only covariate, i.e. it is the odds of observing a response in the D+T arm compared to the odds of observing a response in the C+V arm. Odds ratio >1 favours D+T.*

[4] *Based on Kaplan-Meier method.*

[5] *Based on proportional hazards model.*

At the time of the final analysis (median duration of follow-up: 39.0 months), the ORR based on independent review was 54.8% in the D+T arm and 16.2% in the C+V arm with an odds ratio of 6.26. The analysis also confirmed improved PFS over chemotherapy based on independent review with an estimated 64% risk reduction in progression/death (HR 0.36). The median PFS was 24.9 months in the D+T arm and 7.2 months in the C+V arm. No additional deaths were reported in either arm at the time of the final analysis.

Figure 6 Kaplan-Meier progression-free survival curves for Study G2201 based on independent review (LGG cohort, final analysis)



BRAF mutation-positive paediatric high-grade glioma (WHO grades 3 and 4)

In the single-arm high-grade glioma (HGG) cohort of Study G2201, 41 patients with relapsed or refractory HGG were enrolled and treated with trametinib plus dabrafenib. Median age was 13.0 years, with 5 patients (12.2%) aged 12 months to <6 years, 10 patients (24.4%) aged 6 to <12 years and 26 patients (63.4%) aged 12 to <18 years; 56% were female.

At the time of the final analysis (median duration of follow-up: 45.2 months), the ORR based on independent review was 56.1% (23/41), (95% CI: 39.7, 71.5): CR in 14 patients (34.1%) and PR in 9 patients (22.0%). The median duration of response (DoR) was 27.4 months (95% CI: 9.2, NE). The Kaplan-Meier estimate of progression-free survival at 12 months was 45.5% (95% CI: 29.4, 60.3). The estimated 1-year, 2-year and 3-year survival rates were 77.0%, 61.0% and 55.1%, respectively.

Other studies

Pyrexia Management Analysis

Pyrexia is observed in patients treated with trametinib and dabrafenib combination therapy. The initial registration studies for the combination therapy in the unresectable or metastatic melanoma setting (COMBI-d and COMBI-v; total N=559) and in the adjuvant melanoma setting (COMBI-AD, N=435) recommended to interrupt only dabrafenib in case of pyrexia. 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 trametinib and dabrafenib when patient's temperature was ≥38°C (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%
  - hospitalisation 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%
  - hospitalisation 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%

5.2 Pharmacokinetic properties

Absorption

Trametinib is absorbed orally with median time to achieve peak concentrations of 1.5 hours post-dose. The mean absolute bioavailability of a single 2 mg tablet dose is 72% relative to an intravenous (IV) microdose. The increase in exposure (C_{max} and AUC) was dose-proportional following repeat dosing. Following administration of 2 mg daily, geometric mean C_{max}, $AUC_{(0-t)}$ 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 was low (<28%).

Effect of food on trametinib

Administration of a single dose of trametinib tablet with a high-fat, high-calorie meal resulted in a 70% and 10% decrease in C_{max} and AUC, respectively compared to fasted conditions. Trametinib tablets and powder for oral solution are immediate-release formulations that are expected to have similar food effects on PK (see section 4.2 dose and method of administration).

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 microdose.

Biotransformation/ metabolism

In vitro and *in vivo* studies demonstrated that trametinib is metabolised predominantly via deacetylation alone or in combination with mono-oxygenation. The deacetylated metabolite was further metabolised by glucuronidation. The deacetylation is mediated by the carboxyl-esterases 1b, 1c and 2 and may also be mediated by other hydrolytic enzymes carboxyl-esterases.

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 5.3 days (range 3.4-9.0) after single dose administration. Steady-state is generally 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.

Special Patient Populations

Hepatic Impairment

Population pharmacokinetic analyses and data from a clinical pharmacology study in patients with normal hepatic function or with mild, moderate or severe bilirubin and/or AST elevations (based on National Cancer Institute [NCI] classification) indicate that hepatic function does not significantly affect trametinib oral clearance (Section 4.2, dose and method of administration.

Renal Impairment

Renal impairment is unlikely to have a clinically relevant effect on trametinib pharmacokinetics given

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

Patients ≥ 65 years of age

Based on the population pharmacokinetics analysis, age had no relevant clinical effect on trametinib pharmacokinetics.

Paediatric population (< 18 years of age)

The pharmacokinetics of trametinib in glioma and other solid tumours were evaluated in 244 paediatric patients (1 to <18 years old) following single or repeat weight-adjusted dosing. Pharmacokinetic characteristics (drug absorption rate and drug clearance) of trametinib in paediatric patients are comparable to those of adults. Weight was found to influence trametinib oral clearance. The pharmacokinetic exposures of trametinib at the recommended weight-adjusted dosage in paediatric patients were within range of those observed in adults.

5.3 Preclinical safety data

Genotoxicity

Trametinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells and micronuclei in the bone marrow of rats.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Carcinogenicity
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Film-coated tablets:

Mekinist 0.5 mg film-coated tablets

Mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (vegetable source), sodium lauryl sulfate, colloidal anhydrous silica, titanium dioxide, polyethylene glycol, iron oxide yellow.

Mekinist 2 mg film-coated tablets

Mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (vegetable source), sodium lauryl sulfate, colloidal anhydrous silica, titanium dioxide, polyethylene glycol, polysorbate 80 and iron oxide red.

Powder for oral solution:
Sulfobutyl betadex sodium, sucralose, citric acid monohydrate, dibasic sodium phosphate, potassium sorbate, methyl hydroxybenzoate, flavour strawberry (Proprietary ingredient: 05-9-47).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Film-coated tablets

24 months (unopened bottle); 1 month (opened bottle when stored up to 30°C).

Powder for oral solution

24 months (unopened bottle) when stored in a refrigerator at 2°C to 8°C; After reconstitution, stable for 35 days when stored below 25°C.

6.4 Special precautions for storage

Film-coated tablets

Store at 2°C to 8°C (Refrigerate). Protect from light and moisture. Do not remove the desiccant. Store in original container. Keep the bottle tightly closed.

Powder for oral solution

Store in a refrigerator at 2°C to 8°C until reconstitution.

Store in the original package to protect from light and moisture. Keep the bottle tightly closed.
After reconstitution, store the reconstituted solution below 25°C and do not freeze. Discard any unused solution 35 days after reconstitution.

6.5 Nature and contents of container

Mekinist tablets are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures, containing 7* or 30 tablets. The bottle contains a desiccant.

Mekinist powder for oral solution is supplied in 180 mL amber glass (type III) bottle with child-resistant, high-density polyethylene/polypropylene (HDPE/PP) closure, press-in bottle adaptor and dosing syringe, containing 5.3 mg powder.

*Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Film-coated tablets

Any unused product should not be disposed of in household waste or wastewater. Return it to a pharmacist for safe disposal.

Powder for Oral Solution

Mekinist powder for oral solution is reconstituted before use with water. To prepare Mekinist for oral solution, tap the bottle to loosen powder. When prepared in a pharmacy, add 90 mL distilled or purified water to the powder in the bottle and invert or gently shake the bottle with re-attached cap for up to 5 minutes until powder is fully dissolved yielding a clear solution. Separate the dosing adapter from the oral syringe. Insert dosing adapter into bottle neck after reconstitution of the solution. Write the discard after date. Refer to the Instruction for use for detailed reconstitution instructions. Discard any unused solution 35 days after reconstitution. Administer Mekinist for oral solution from oral dosing syringe or feeding tube.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Novartis New Zealand Limited
PO Box 99102, Newmarket Auckland 1149 New Zealand
Telephone: 0800 354 335
Fax number: (09) 361 8181
E-mail: medinfo.phauno@novartis.com

9. DATE OF FIRST APPROVAL

The date of consent to distribute these medicines were published in the New Zealand Gazette on: 26 March 2015 (film coated tablets)

0.05 mg/mL powder for oral solution: 8th December 2025

10. DATE OF REVISION OF THE TEXT

15 December 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Safety updates for special populations – paediatric patients, based on the final analysis of study G2201 in paediatric glioma.
5.1	Efficacy updates for paediatric glioma (LGG, HGG) following final analysis from study G2201. Efficacy updates for COMBI-AD (DRB436F2301) following final analysis.