NOVARTIS

Regulatory Affairs

MEKINIST® (trametinib)

0.5 mg and 2 mg Film-coated tablets

National Package Leaflet

CDS Version 3.8

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Mekinist

Protein kinase inhibitor.

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Trametinib 0.5 mg film-coated tablets - yellow, ovaloid, biconvex, unscored film-coated tablets with beveled edges and with "GSK" on one side and "TT" on the other side.

Trametinib 2 mg film-coated tablets - pink, round, biconvex, unscored film-coated tablets with beveled edges and with "GSK" on one side and "LL" on the other side.

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

Active substance

0.5 mg film-coated tablets

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

2 mg film-coated tablets

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

Excipients

Tablet core

Mannitol

Microcrystalline cellulose

Hypromellose

Croscarmellose sodium

Magnesium stearate (vegetable source)

Sodium laurylsulfate

Colloidal silicon dioxide

Tablet film-coating

Hypromellose

Titanium dioxide

Polyethylene glycol

Iron oxide yellow (for 0.5 mg tablets)

Polysorbate 80 and Iron oxide red (for 2 mg tablets)

Pharmaceutical formulations may vary between countries

INDICATIONS

Unresectable or metastatic melanoma

Mekinist in combination with Dabrafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see CLINICAL STUDIES).

Mekinist as a monotherapy is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see CLINICAL STUDIES).

Mekinist as monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (see CLINICAL STUDIES).

Adjuvant treatment of melanoma

Mekinist in combination with Dabrafenib, is indicated for the adjuvant treatment of patients with Stage III melanoma with a BRAF V600E or V600K mutation, and involvement of lymph node(s), following complete resection.

Advanced non-small cell lung cancer

Mekinist 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

Mekinist in combination with Dabrafenib is indicated for the treatment of pediatric patients 6 years of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy (see CLINICAL STUDIES).

Unresectable or metastatic solid tumors

Mekinist in combination with Dabrafenib is indicated for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options (see CLINICAL STUDIES)

DOSAGE REGIMEN AND ADMINISTRATION

Treatment with Mekinist should be initiated by a physician experienced in the use of anticancer therapies.

Mekinist in combination with dabrafenib is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition. (see CLINICAL PHARMACOLOGY).

Confirmation of BRAF V600 (e.g., V600E, V600K, or country specific requirement) mutation status using an approved/validated test is required for selection of patients appropriate for treatment with Mekinist as monotherapy and in combination with dabrafenib (see CLINICAL STUDIES).

When Mekinist is used in combination with dabrafenib, please also refer to the full dabrafenib prescribing information.

Dosage regimen

General target population

Adult patients

The recommended dosage for Mekinist tablets in adult patients (either as monotherapy or in combination with dabrafenib) is 2 mg given orally once daily, independent of body weight.

Recommended dose level reductions for Mekinist tablets in adult patients are provided in Table 1.

Table 1 Recommended dosage level reductions for Mekinist tablets in adult patients

Dose Level Reductions	**Recommended Starting Dosage**
Starting dose	2 mg orally once daily
First dose reduction	1.5 mg orally once daily
Second dose reduction	1 mg orally once daily
Permanently discontinue if unable to tolerate Mekinist 1 mg orally once daily	

Pediatric patients

The recommended dosage for Mekinist tablets in pediatric patients who weigh at least 26 kg, is based on body weight (Table 2). A recommended dose for patients who weigh less than 26 kg has not been established.

Table 2 Recommended weight-based dosing for Mekinist tablets in pediatric 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 Mekinist tablets in pediatric patients are provided in Table 3.

Table 3 Recommended dose level reductions for Mekinist tablets in pediatric 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			

Duration of treatment

The recommended duration of treatment for patients with unresectable or metastatic melanoma or solid tumors, or metastatic NSCLC 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 pediatric patients with LGG is until loss of clinical benefit or until unacceptable toxicity. There are limited data in patients older than 18 years of age with LGG 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.

Missed dose

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

Dose adjustments

Mekinist as Monotherapy and in combination with dabrafenib

The management of adverse events/adverse drug reactions may require treatment interruption, dose reduction, or treatment discontinuation.
The recommended dose modification schedule is provided in Table 4. When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The Mekinist dose should not exceed 2 mg once daily.

Table 4: Mekinist 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 to 1 and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy.

** The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)*

Pyrexia management: Therapy should be interrupted (Mekinist when used as monotherapy, and both Mekinist and Dabrafenib when used in combination) if the patient's temperature is ≥38^{o}C (100.4°F). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. Patients should be evaluated for signs and symptoms of infection (see WARNINGS AND PRECAUTIONS). Mekinist, or both Mekinist 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.

If treatment-related toxicities occur when Mekinist 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 Mekinist only:

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

LVEF Reduction/Left Ventricular Dysfunction management:

Mekinist should be interrupted in patients who have an asymptomatic, absolute decrease of >10% in LVEF compared to baseline and the ejection fraction below the institution's lower

limit of normal (LLN) (see WARNINGS AND PRECAUTIONS). If Mekinist is being used in combination with dabrafenib then therapy with dabrafenib may be continued at the same dose. If the LVEF recovers, treatment with Mekinist may be restarted, but the dose should be reduced by one dose level with careful monitoring. Mekinist should be permanently discontinued with Grade 3 or 4 left ventricular cardiac dysfunction or if repeatedly reduced LVEF does not recover.

Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED) management:

If RPED is diagnosed, the dose modification schedule (intolerable) in Table 4 above for Mekinist should be followed and, if Mekinist is being used in combination with dabrafenib, dabrafenib should be continued at the same dose. In patients who experience RVO, treatment with Mekinist should be permanently discontinued (see WARNINGS AND PRECAUTIONS).

Pneumonitis and Interstitial Lung Disease (ILD) management:

For events of pneumonitis, follow dose modification guidelines in Table 4 for Mekinist only; no modification of dabrafenib is required when taken in combination with Mekinist.

Special populations

Renal impairment

No dosage adjustment is required in patients with mild or moderate renal impairment. Mild or moderate renal impairment had no significant effect on the population pharmacokinetics of Mekinist (see CLINICAL PHARMACOLOGY, PHARMACOKINETICS). There are no clinical data in patients with severe renal impairment; therefore, the potential need for starting dose adjustment cannot be determined. Mekinist 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 CLINICAL PHARMACOLOGY, Pharmacokinetics). Mekinist should be used with caution in patients with moderate or severe hepatic impairment.

Pediatric patients (below 18 years)

The safety and efficacy of Mekinist tablets in pediatric patients <6 year of age have not been established. Mekinist is not recommended in this age group.

Geriatric patients (65 years of age or above)

No dosage adjustment is required in patients over 65 years of age (see CLINICAL PHARMACOLOGY, PHARMACOKINETICS).

Method of administration

Mekinist should be taken without food, at least one hour before or two hours after a meal with a full glass of water (see CLINICAL PHARMACOLOGY).

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

CONTRAINDICATIONS

Trametinib is contraindicated in patients with hypersensitivity to any of the ingredients.

WARNINGS AND PRECAUTIONS

When Mekinist is used together with dabrafenib read the full prescribing information for dabrafenib section WARNINGS AND PRECAUTIONS.

LVEF Reduction/Left Ventricular Dysfunction

Mekinist has been reported to decrease LVEF (see ADVERSE DRUG REACTIONS). 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 Mekinist as monotherapy or in combination with dabrafenib was between two to five months. Mekinist should be used with caution in patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment with Mekinist with a recommendation of periodic follow-up within eight weeks of initiating therapy, as clinically appropriate. LVEF should continue to be evaluated during treatment with Mekinist as clinically appropriate (see DOSAGE REGIMEN AND ADMINISTRATION).

Hemorrhage

Hemorrhagic events, including major hemorrhagic events have occurred in patients taking Mekinist as monotherapy and in combination with dabrafenib (see ADVERSE DRUG REACTIONS). Out of the 559 unresectable or metastatic melanoma patients treated with Mekinist in combination with dabrafenib, there were six fatal intracranial hemorrhagic cases (1%). Three cases were from study MEK115306 (COMBI-d) and three cases were from study MEK116513 (COMBI-v). No fatal hemorrhagic events occurred in the Phase III study in the adjuvant treatment of melanoma. Two out of 93 patients (2%) receiving Mekinist in combination with dabrafenib in a Phase II NSCLC trial had fatal hemorrhagic events. If patients develop symptoms of hemorrhage, they should immediately seek medical care.

Visual impairment

Disorders associated with visual disturbances, including chorioretinopathy or retinal pigment epithelial detachment (RPED) and Retinal Vein Occlusion (RVO) have been observed with Mekinist. Symptoms such as blurred vision, decreased acuity, and other visual phenomena have been reported in the clinical trials with Mekinist (see ADVERSE DRUG REACTIONS). Mekinist is not recommended in patients with a history of RVO. A thorough ophthalmological evaluation should be performed at baseline and during treatment with Mekinist, if clinically warranted. If patients report visual disturbances at any time while on Mekinist therapy, additional ophthalmological evaluation should be undertaken. If a retinal abnormality is noted, treatment with Mekinist should be interrupted immediately and referral to a retinal specialist should be considered. If RPED is diagnosed, the dose modification schedule (intolerable) in Table 4 should be followed (see DOSAGE REGIMEN AND ADMINISTRATION). In patients who experience RVO, treatment with Mekinist should be permanently discontinued.

Skin toxicity

Rash

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

Severe cutaneous adverse reactions

Cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with Mekinist in combination with 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, Mekinist and Dabrafenib should be withdrawn.

Venous thromboembolism (VTE)

VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE) can occur on Mekinist monotherapy and when Mekinist is used in combination with dabrafenib. Patients should be advised to immediately seek medical care if they develop symptoms of VTE (see ADVERSE DRUG REACTIONS).

Pyrexia

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

A cross-study comparison in 1,810 patients treated with combination therapy demonstrated a reduction in the incidence of high-grade pyrexia and other pyrexia-related adverse outcomes when both Mekinist and Dabrafenib were interrupted, compared to when only Dabrafenib was interrupted. Therefore, interruption of both Mekinist and Dabrafenib is recommended if patient's temperature is ≥38ºC (100.4°F), and in case of recurrence, therapy can also be interrupted at the first symptom of pyrexia (see DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL STUDIES).

Colitis and gastrointestinal perforation

Colitis and gastrointestinal perforation, including fatal outcome, have been reported in patients taking Mekinist as monotherapy and in combination with dabrafenib (see ADVERSE DRUG REACTIONS). Treatment with Mekinist 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 recognized risk of gastrointestinal perforation.

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

Hemophagocytic lymphohistiocytosis (HLH)

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

Tumour Lysis Syndrome (TLS)

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

ADVERSE DRUG REACTIONS

Summary of the safety profile

Unresectable or metastatic melanoma

Mekinist monotherapy

The safety of Mekinist monotherapy was evaluated in an integrated population of 329 patients with BRAF V600 mutant unresectable or metastatic melanoma treated with Mekinist 2 mg orally once daily in studies MEK114267, MEK113583, and MEK111054. Of these patients, 211 patients were treated with Mekinist for BRAF V600 mutant melanoma in the randomized open-label study MEK114267 (see CLINICAL STUDIES). The most common adverse events (≥20%) for Mekinist were rash, diarrhoea, fatigue, oedema peripheral, nausea, and dermatitis acneiform. In clinical trials with Mekinist, adverse events of diarrhoea and rash were managed with appropriate supportive care (see DOSAGE REGIMEN AND ADMINISTRATION).

Mekinist and Dabrafenib combination therapy

The safety of Mekinist and Dabrafenib combination therapy was evaluated in two randomized Phase III studies of patients with BRAF V600 mutant unresectable or metastatic melanoma treated with Mekinist 2 mg orally once daily and Dabrafenib 150 mg orally twice daily (see CLINICAL STUDIES). The most common adverse events (≥20%) for Mekinist and Dabrafenib combination therapy were pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, vomiting, peripheral edema and cough.

Tabulated summary of adverse events from clinical trials in unresectable or metastatic melanoma:

Adverse events from clinical trials in patients with unresectable or metastatic melanoma are listed by MedDRA system organ class in Table 5 and Table 6 for Mekinist monotherapy and Mekinist in combination with Dabrafenib, respectively. Within each system organ class, the adverse events are ranked by frequency, with the most frequent adverse events first. In addition, the corresponding frequency category for each adverse event 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 5: Unresectable or metastatic melanoma-Adverse events for Mekinist monotherapy

Adverse events	**Frequency category** Integrated Safety Data N=329
Infections and Infestations	
Folliculitis	Common
Paronychia	Common
Cellulitis	Common
Rash pustular	Common

Adverse events	**Frequency category** Integrated Safety Data N=329
Blood and lymphatic system disorders	
Anaemia	Common
Immune system disorders	
Hypersensitivity[1)]	Common
Metabolism and nutrition disorders	
Dehydration	Common
Eye disorders	
Vision blurred	Common
Periorbital oedema	Common
Visual impairment	Common
Chorioretinopathy	Uncommon
Retinal vein occlusion	Uncommon
Papilloedema	Uncommon
Retinal detachment	Uncommon
Cardiac disorders	
Left ventricular dysfunction	Common
Ejection fraction decreased	Common
Bradycardia	Common
Cardiac failure	Uncommon
Vascular disorders	
Hypertension	Very common
Haemorrhage[2)]	Very common
Lymphoedema	Common
Respiratory, thoracic and mediastinal disorders	
Cough	Very common
Dyspnoea	Very common
Epistaxis	Common
Pneumonitis	Common
Interstitial lung disease	Uncommon
Gastrointestinal disorders	
Diarrhoea	Very common
Nausea	Very common
Vomiting	Very common
Constipation	Very common
Abdominal pain	Very common
Dry mouth	Very common
Stomatitis	Common
Gastrointestinal perforation	Uncommon
Colitis	Uncommon
Skin and Subcutaneous Tissue Disorders	
Rash	Very common
Dermatitis acneiform	Very common
Dry skin	Very common
Pruritus	Very common
Alopecia	Very common
Skin chapped	Common

Adverse events	**Frequency category** Integrated Safety Data N=329
Erythema	Common
Palmar-plantar erythrodysaesthesia syndrome	Common
Skin fissures	Common
Musculoskeletal and connective tissue disorder	
Rhabdomyolysis	Uncommon
Blood creatine phosphokinase increased	Common
General disorders	
Fatigue	Very common
Oedema peripheral	Very common
Pyrexia	Very common
Face oedema	Common
Mucosal inflammation	Common
Asthenia	Common
Investigations	
Aspartate aminotransferase increased	Common
Alanine aminotransferase increased	Common
Blood alkaline phosphatase increased	Common
1) May present with symptoms such as fever, rash, increased liver function tests, and visual disturbances. 2) *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.*	

Table 6 lists adverse events when Mekinist was used in combination with Dabrafenib from the randomized double-blind Phase III study MEK115306 (N=209), and integrated safety data from MEK115306 (N=209) and from the randomized open-label Phase III study MEK116513 (N=350).

Table 6: Unresectable or metastatic melanoma-Adverse events for Mekinist in combination with Dabrafenib

Adverse events	**Frequency category**	
	MEK115306 (COMBI-d) N=209	**MEK115306 (COMBI-d) + MEK116513 (COMBI-v) Integrated Safety Data 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

Adverse events	Frequency category	
	MEK115306 (COMBI-d) N=209	**MEK115306 (COMBI-d) + MEK116513 (COMBI-v) Integrated Safety Data N=559**
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
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	Not reported	Uncommon
Cardiac failure	Not reported	Uncommon
Vascular disorders		
Hypertension	Very common	Very common
Haemorrhage[1)]	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	Not reported	Uncommon
Gastrointestinal disorders		
Abdominal pain	Very common	Very common
Constipation	Very common	Very common

Adverse events	Frequency category	
	MEK115306 (COMBI-d) N=209	**MEK115306 (COMBI-d) + MEK116513 (COMBI-v) Integrated Safety Data N=559**
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	Not reported	Uncommon
Colitis	Uncommon	Uncommon
Skin and subcutaneous tissue disorders		
Dry skin	Very common	Very common
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 [2)]	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	Not reported	Uncommon
Renal disorders		
Renal failure	Uncommon	Common
Nephritis	Uncommon	Uncommon
Renal failure acute	Not reported	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

Adverse events	Frequency category	
	MEK115306 (COMBI-d) N=209	**MEK115306 (COMBI-d) + MEK116513 (COMBI-v) Integrated Safety Data N=559**
Influenza-like illness	Common	Common
Face oedema	Common	Common
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
[1)] *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.* *2) 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.*		

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 Mekinist in combination with Dabrafenib in unresectable or metastatic melanoma (see CLINICAL STUDIES).

Adjuvant treatment of melanoma

Mekinist in combination with Dabrafenib

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

In the Mekinist 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, arthralgia, and myalgia.

Table 7 lists the adverse drug reactions in study BRF115532 (COMBI-AD) occurring at an incidence ≥10% for all grade adverse reactions or at an incidence ≥2% for Grade 3 and Grade 4 adverse drugs reactions or adverse events that are medically significant in the Mekinist in combination with 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

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

Adverse drug reactions	Mekinist 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

Adverse drug reactions	Mekinist 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 %	
Fatigue[18)]	59	5	37	<1	Very common
Chills	37	1	4	NR	Very common
Oedema peripheral[19)]	16	<1	6	NR	Very common
Influenza-like illness	15	<1	7	NR	Very common
Investigations					
Alanine aminotransferase increased[20)]	17	4	2	<1	Very common
Aspartate aminotransferase increased[21)]	16	4	2	<1	Very common
Alkaline phosphatase increased	7	<1	<1	<1	Common
Ejection fraction decreased	5	NR	2	<1	Common

1) Nasopharyngitis also includes pharyngitis.

2) Neutropenia also includes febrile neutropenia and cases of neutrophil count decreased that met the criteria for neutropenia.

3) Headache also includes tension headache.

4) Dizziness also includes vertigo.

5) Chorioretinopathy also includes chorioretinal disorder.

6) Retinal detachment also includes detachment of macular retinal pigment epithelium and detachment of retinal pigment epithelium.

7) Haemorrhage includes a comprehensive list of hundreds of event terms that capture bleeding events.

8) Hypertension also includes hypertensive crisis.

9) Cough also includes productive cough.

10) Abdominal pain also includes abdominal pain upper and abdominal pain lower.

11) Rash also includes rash maculo-papular, rash macular, rash generalized, rash erythematous, rash papular, rash pruritic, nodular rash, rash vesicular, and rash pustular.

12) Dry skin also includes xerosis and xeroderma.

13) Erythema also includes generalized erythema.

14) Pruritus also includes puritus generalized and pruritus genital.

15) Myalgia also includes musculoskeletal pain and musculoskeletal chest pain.

16) Muscle spasms also includes musculoskeletal stiffness.

17) Pyrexia also includes hyperpyrexia.

18) Fatigue also includes asthenia and malaise.

19) Oedema peripheral also includes peripheral swelling.

20) Alanine aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia.

21) Aspartate aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia.

NR: not reported

Advanced non-small cell lung cancer

Mekinist in combination with Dabrafenib:

The safety of Mekinist in combination with Dabrafenib was evaluated in a Phase II, multicenter, multi-cohort, non-randomized, open label study of patients with BRAF V600E mutation positive metastatic NSCLC (see CLINICAL STUDIES).

In the Mekinist 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 Mekinist and Dabrafenib combination therapy were pyrexia, nausea, vomiting, peripheral oedema, diarrhoea, decreased appetite, asthenia, dry skin, chills, cough, fatigue, rash, and dyspnoea.

Table 8 lists the adverse drug reactions for Mekinist 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 8: Advanced NSCLC - Adverse drug reactions for Mekinist in combination with Dabrafenib

Adverse drug reactions	**Mekinist in combination with Dabrafenib N=93**		
	All grades %	**Grades 3/4 %**	**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

Adverse drug reactions	Mekinist in combination with Dabrafenib N=93		
	All grades %	Grades 3/4 %	Frequency category
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
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, pulmonary and retroperitoneal haemorrhage.

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

4) Pruritus includes pruritus, pruritus generalized, and eye pruritus.

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

6) Asthenia also includes fatigue and malaise.

7) Oedema includes generalized oedema and peripheral oedema.

NR: Not Reported

Unresectable or metastatic solid tumors

Mekinist in combination with Dabrafenib

Further safety of Mekinist in combination with Dabrafenib was evaluated, as part of Study BRF117019, a multi-cohort, multi-center, non-randomized, open-label study in adult patients with cancers with the BRAF V600E mutation. A total of 206 patients were enrolled in the trial, 36 of whom were enrolled in the ATC cohort, 105 in solid tumor cohorts, and 65 in hematological malignancy cohorts (see CLINICAL STUDIES). Patients received Mekinist

2 mg orally once daily and Dabrafenib 150 mg orally twice daily until disease progression or unacceptable toxicity.

Among these 206 patients, 101 (49%) were exposed to Mekinist for ≥1 year and 103 (50%) were exposed to dabrafenib for ≥1 year. The median age was 60 years (range: 18 to 89); 56% were male; 79% were white; and 34% had baseline ECOG performance status 0 and 60% had ECOG performance status 1. The adverse reaction profile among all patients was similar to that observed in other approved indications.

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

The following ADRs have been derived from post-marketing experience including spontaneous case reports with Mekinist in combination with Dabrafenib. Because post-marketing ADRs are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency. Where applicable, these ADR frequencies have been calculated from the pooled clinical trials across indications. ADRs are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness (Table 9).

Table 9: ADRs from post-marketing experience and pooled clinical trials across indications

Adverse drug reaction	Mekinist in Combination with Dabrafenib Frequency category	Mekinist Monotherapy Frequency category
Immune system disorders		
Sarcoidosis	Uncommon	-
Haemophagocytic lymphohistiocytosis	Not known	-
Metabolism and nutrition disorders		
Tumour lysis syndrome	Not known	-
Nervous system disorders		
Peripheral neuropathy	Common	Common
Guillain-Barré syndrome	Uncommon	-
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	-

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

Pediatric patients

Mekinist in combination with Dabrafenib

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

years of age, 54 (31.6%) patients were 6 to <12 years of age, and 74 (43.3%) patients were 12 to <18 years of age.

The overall safety profile in the pediatric 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 pediatric safety pool with a frequency of 15.2% (very common). Fifty-one out of 171 patients (29.8%) had an increase from baseline of ≥2 BMI-for-age- percentile categories.

Adverse drug reactions occurring at a higher frequency category in pediatric patients compared to adult patients were neutropenia, dermatitis acneiform, paronychia, anaemia, leukopenia, skin papilloma (very common); bradycardia, dermatitis exfoliative generalised, hypersensitivity and pancreatitis (common) (Table 10).

Table 10 Most frequent Grade 3/4 Adverse drug reactions (≥2%) for Mekinist in combination with Dabrafenib in pediatric patients

Adverse drug reactions	Mekinist 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.*

INTERACTIONS

Monotherapy

As trametinib is metabolized 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, Mekinist is unlikely to significantly affect the pharmacokinetics of other medicinal products via interactions with CYP enzymes or transporters (see CLINICAL PHARMACOLOGY, PHARMACOKINETICS). Repeat-dose administration of Mekinist 2 mg once daily had no clinically relevant effect on the single dose C_{max} and AUC of dabrafenib, a CYP2C8/CYP3A4 substrate.

Combination therapy and non-fixed dose combination therapy

Combination with Dabrafenib

Co-administration of repeat dosing of Mekinist 2 mg once daily and Dabrafenib 150 mg twice daily resulted in a 16% increase in dabrafenib C_{max} and a 23% increase in dabrafenib AUC. A small decrease in trametinib bioavailability, corresponding to a decrease in AUC of 12%, was estimated when Mekinist is administered in combination with Dabrafenib using a population pharmacokinetic analysis. These changes in dabrafenib or trametinib C_{max} and AUC are considered not clinically relevant. See the full prescribing information for dabrafenib for guidelines on drug interactions associated with Dabrafenib monotherapy.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

Mekinist can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Mekinist in pregnant women. Reproductive studies in animals (rats and rabbits) have demonstrated that trametinib induces maternal and developmental toxicity. In rats decreased fetal weight and increased incidences of post implantation loss were observed following maternal exposure to trametinib at concentrations 0.3 and 1.8 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. Pregnant women should be advised of the potential risk to the fetus.

Animal data

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

Risk summary

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

Females and males of reproductive potential

Contraception

Females

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

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

Males

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

Infertility

There is no information on the effect of Mekinist on human fertility. In animals, no fertility studies have been performed, but adverse effects were seen on female reproductive organs (see NON-CLINICAL SAFETY DATA). Mekinist may impair fertility in humans

OVERDOSAGE

No cases of overdose have been reported. There were no cases of Mekinist dose above 4 mg once daily reported from the clinical trials. Doses up to 4 mg orally once daily and loading doses of 10 mg orally once daily, administered on two consecutive days, have been evaluated in clinical trials.

Further management should be as clinically indicated or as recommended by the national poisons center, where available. There is no specific treatment for an overdose of trametinib. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Hemodialysis is not expected to enhance the elimination as trametinib is highly bound to plasma proteins.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Mekinist Monotherapy

Trametinib (Mekinist) is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinases 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 activate MEK and stimulate tumor cell growth. Trametinib inhibits MEK kinase activity, suppresses growth of BRAF V600 mutant melanoma and non-small cell lung cancer (NSCLC) cell lines *in vitro,* and demonstrates anti-tumor effects in BRAF V600 mutant melanoma xenograft models.

Mekinist in combination with dabrafenib

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

Pharmacodynamics (PD)

Trametinib suppressed levels of phosphorylated ERK in BRAF V600 mutant melanoma and NSCLC tumor cell lines and melanoma xenografts models.

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

Cardiac electrophysiology

The heart rate-corrected QT (QTc) prolongation potential of trametinib was assessed in a dedicated study in 32 patients who received placebo on Day 1 and Mekinist tablets 2 mg once daily on Days 2-14 followed by Mekinist tablets 3 mg on Day 15. No clinically relevant QTc prolongation was detected in the study.

In clinical trials in patients who received Mekinist with dabrafenib, QTc prolongation > 500 ms occurred in 0.8% of patients and QTc increased by> 60 ms from baseline in 3.8% of patients.

Pharmacokinetics (PK)

Absorption

Trametinib is absorbed orally with median time to achieve peak concentrations of 1.5 hours post-dose. The mean absolute bioavailability of a single 2 mg tablet dose is 72% relative to an intravenous (IV) micro-dose. The increase in exposure (C_{max} and AUC) was dose-proportional following repeat dosing. Following administration of 2 mg once daily, geometric mean C_{max}, AUC(0-τ) and pre-dose 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%). Administration of a single dose of trametinib with a high-fat, high-calorie meal resulted in a 70% and 10% decrease in C_{max} and AUC, respectively compared to fasted conditions (see DOSAGE REGIMEN AND 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 micro-dose.

Biotransformation/Metabolism

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

Elimination

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

Total dose recovery is low after a 10-day collection period (<50%) following administration of a single oral dose of radiolabeled trametinib as a solution, due to the long half-life. Drug-related material was excreted predominantly in the feces (≥81% of recovered radioactivity) and to a small extent in urine (≤19%). Less than 0.1% of the excreted dose was recovered as parent in urine.

***In Vitro* evaluation of drug interaction potential**

Effects of other drugs on trametinib:

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

Special Populations

Pediatric population (below 18 years)

The pharmacokinetics of trametinib in glioma and other solid tumors were evaluated in 244 pediatric patients (1 to <18 years old) following single or repeat weight-adjusted dosing. Pharmacokinetic characteristics (drug absorption rate and drug clearance) of trametinib in pediatric 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 pediatric patients were within range of those observed in adults.

Geriatric patients (65 years or above)

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

Gender/Weight

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

Race/Ethnicity

There are insufficient data to evaluate the potential effect of race on trametinib pharmacokinetics.

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 characterized 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 DOSAGE REGIMEN AND ADMINISTRATION).

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.

CLINICAL STUDIES

Unresectable or metastatic melanoma

Mekinist monotherapy

Study MEK114267

The efficacy and safety of Mekinist in patients with BRAF mutant unresectable or metastatic melanoma (V600E and V600K) were evaluated in a randomized 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 tumor sample available.

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

The primary endpoint of the study was to evaluate the efficacy of trametinib compared to chemotherapy with respect to progression-free survival (PFS) in patients with advanced (unresectable or metastatic) BRAF V600E mutation-positive melanoma without a prior history of brain metastases (N=273), which is considered the primary efficacy population. The secondary endpoints were progression-free survival in the ITT population and overall survival (OS), overall response rate (ORR), and duration of response (DoR) in the primary efficacy population and ITT population. Patients in the chemotherapy arm were allowed to cross over to the trametinib arm after independent confirmation of progression. Fifty-one (47%) 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 Caucasians (100%). The median age was 54 years (22% were ≥65 years), most patients (64%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, and 11 patients (3%) had a history of brain metastases. Most patients (87%) in the ITT population had a BRAF V600E mutation and 12% of patients had a BRAF V600K mutation. Most patients (66%) had received no prior chemotherapy for advanced or metastatic disease.

The efficacy results in the primary efficacy population were consistent with those in the ITT population; therefore, only the efficacy data for the ITT population are presented in Table 11 and Figure 1.

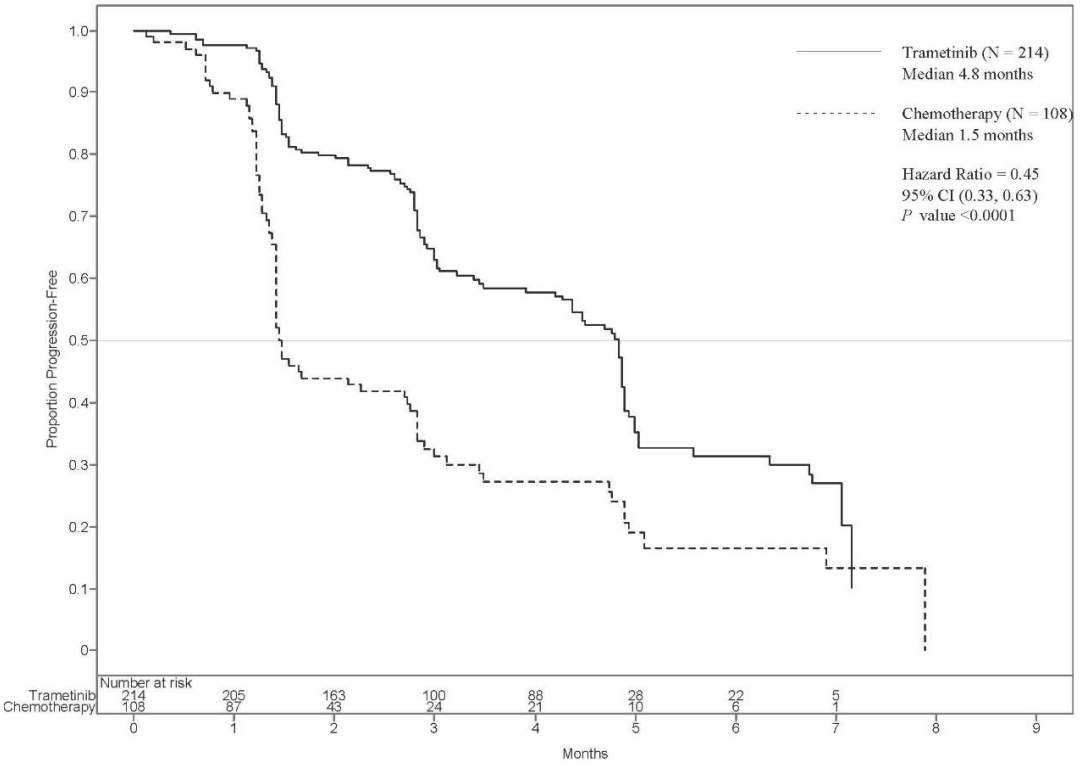
Table 11: MEK114267 - Investigator assessed efficacy results (ITT population).

	Intention-to-Treat Population	
Endpoints/ Assessments	**Trametinib (N=214)**	**Chemotherapy[a] (N=108)**
Progression-Free Survival		
Median (months)	4.8	1.5
(95% CI)	(4.3, 4.9)	(1.4, 2.7)
Hazard Ratio	0.45	
(95% CI)	(0.33, 0.63)	
P value	<0.0001	
Overall Survival		
Died, n (%)	35 (16)	29 (27)
Hazard Ratio	0.54	
(95% CI)	(0.32, 0.92)	
P value	0.0136	
Survival at 6 months (%)	81	67
(95% CI)	(73, 86)	(55, 77)
Overall Response Rate (%)	22	8

ITT = Intention 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 - Kaplan-Meier investigator-assessed progression-free survival curves (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).

In a single arm Phase II study, Mekinist did not demonstrate clinical activity in patients who progressed on a prior BRAF inhibitor therapy in one of the cohorts (see INDICATIONS).

Mekinist in combination with Dabrafenib

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

MEK115306 (COMBI-d)

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

A total of 423 patients were randomized 1:1 to either the combination therapy arm (Mekinist 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. The majority of patients had an ECOG performance score of 0 (72%) and had Stage IVM1c disease (66%). Most patients (85%) had the BRAF V600E mutation; the remaining 15% of patients had the BRAF V600K mutation.

Median OS and estimated 1-year, 2-year, 3-year, 4 year and 5-year survival rates are presented

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

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

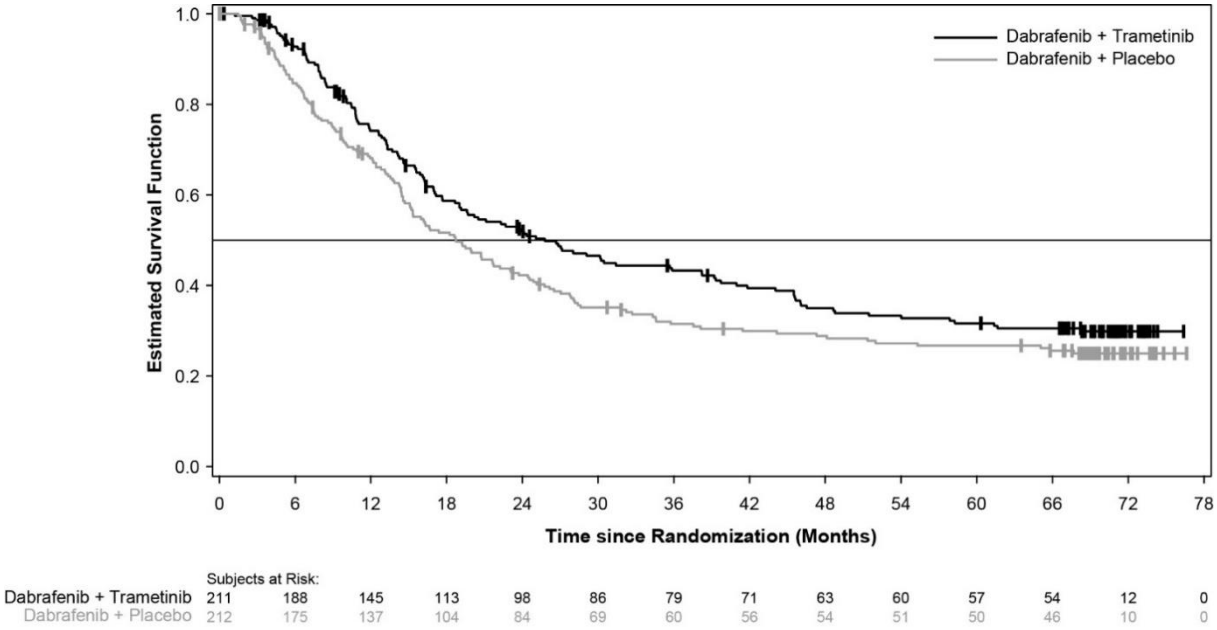
Table 12: COMBI-d - Overall Survival results (ITT population)

	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: 12Jan2015; 3-year OS analysis data cut-off: 15Feb2016; 5-year OS analysis data cut-off: 10Dec2018*
NR = Not reached, NA = Not applicable

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



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

Table 13: Investigator-assessed efficacy results for MEK115306 (COMBI-d) study

Endpoints	Primary Analysis*		Updated Analysis*		3 Year Analysis*		5 Year Analysis*	
	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)	Dabrafenib + Trametinib (N=211)	Dabrafenib + Placebo (N=212)
Investigator Assessed PFS								
Progressive disease or death, n (%)	102 (48)	109 (51)	139 (66)	162 (76)	153 (73)	168[f] (79)	160 (76)	166 (78)
Median, months (95% CI[a])	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)	10.2 (8.0, 12.8)	7.6 (5.8, 9.3)	10.2 (8.1, 12.8)	8.8 (5.9, 9.3)
Hazard Ratio (95% CI)	0.75 (0.57, 0.99)		0.67 (0.53, 0.84)		0.71 (0.57, 0.88)		0.73 (0.59, 0.91)	
P value (log-rank test)	0.035		<0.001[g]		NA		NA	
Overall Response Rate[b] (%) (95% CI)	67 (59.9, 73.0)	51 (44.5,58.4)	69 (61.8, 74.8)	53 (46.3, 60.2)	68 (61.5, 74.5)	55 (47.8, 61.5)	69 (62.5, 75.4)	54 (46.8, 60.6)
Difference in response rate (CR[c] +PR[c]), % 95% CI for difference P value	15[d] 5.9, 24.5 0.0015		15[d] 6.0, 24.5 0.0014[g]		NA		NA	
Duration of Response (months)								
Median (95% CI)	9.2[e] (7.4, NR)	10.2[e] (7.5, NR)	12.9 (9.4,19.5)	10.6 (9.1,13.8)	12.0 (9.3, 17.1)	10.6 (8.3, 12.9)	12.9 (9.3, 18.4)	10.2 (8.3, 13.8)

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

a- Confidence interval

b- Overall Response Rate = Complete Response + Partial Response

c- CR: Complete Response, PR: Partial Response

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

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

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

g- Updated analysis was not pre-planned and the p-value was not adjusted for multiple testing.

NR = Not reached

NA = Not applicable

MEK116513 (COMBI-v)

Study MEK116513 was a two-arm, randomized, open-label, Phase III study comparing Mekinist 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. Patients were stratified by lactate dehydrogenase (LDH) level (>the upper limit of normal (ULN) versus ≤ULN) and BRAF mutation (V600E versus V600K).

A total of 704 patients were randomized 1:1 to either the combination therapy arm (Mekinist 2 mg once daily and Dabrafenib 150 mg twice daily) or the vemurafenib monotherapy arm (960 mg twice daily). Most patients were Caucasians (>96%) and male (55%), with a median age of 55 years (24% were ≥65 years). The majority of patients had Stage IV M1c disease (61%). Most patients had LDH ≤ULN (67%), ECOG performance status of 0 (70%), and visceral disease (78%) at baseline. Overall, 54% of patients 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 14, Figure 3). The Kaplan-Meier OS curve appears to stabilize from 3 years to 5 years (see Figure 3). The 5-year overall survival rate was 46% (95% CI: 38.8, 52.0) in the combination arm versus 28% (95% CI: 22.5, 34.6) in the vemurafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 9.3, 23.3) in the combination arm versus 10% (95% CI: 5.1, 17.4) in the vemurafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline.

Table 14: Overall Survival results for Study MEK116513 (COMBIv)

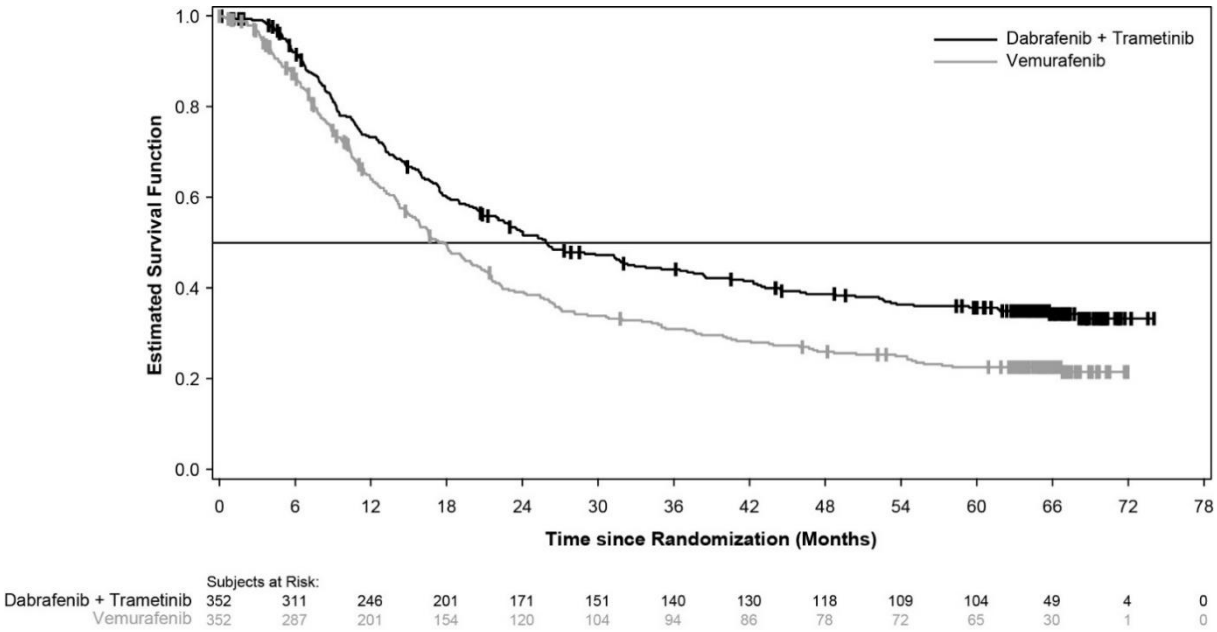
	OS analysis*		**3-year OS analysis***		**5-year OS analysis***	
	Dabrafenib + Trametinib (N=352)	**Vemurafenib (N=352)**	**Dabrafenib + Trametinib (N=352)**	**Vemurafenib (N=352)**	**Dabrafenib + Trametinib (N=352)**	**Vemurafenib (N=352)**
Number of patients						
Died (event), n (%)	100 (28)	122 (35)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

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

NR = Not reached, NA = Not applicable

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

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



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

Table 15: 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-Jul-2016, 5-year analysis data cut-off: 8-Oct-2018
PFS = Progression Free Survival; NR = Not reached; NA = Not applicable

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

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

A total of 125 patients were enrolled into four cohorts:

- Cohort A: patients with 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 16. Secondary endpoints were duration of intracranial response, ORR, PFS and OS. Efficacy results are summarized in Table 16.

Table 16: 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

Study BRF115532 / DRB436F2301 (COMBI-AD)

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

Patients were randomized 1:1 to receive either dabrafenib and trametinib combination therapy (Mekinist 2 mg once daily and Dabrafenib 150 mg twice daily) or two placebos for a period of 12 months. Enrollment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomization. Any prior systemic anticancer treatment, including radiotherapy, was not allowed. Patients with a history of prior malignancy, if disease free for at least 5 years, were eligible. Patients presenting with malignancies with confirmed activating RAS mutations were not eligible. Patients were stratified by BRAF mutation status (V600E or V600K) and stage of disease prior to surgery (by Stage III sub-stage, indicating different levels of lymph node involvement and primary tumor size and ulceration). The primary endpoint was investigator-assessed relapse-free survival (RFS), defined as the time from randomization to disease recurrence or death from any cause. Radiological tumor assessment was conducted every 3 months for the first two years and every 6 months thereafter, until first relapse was observed. Secondary endpoints include overall survival (OS; key secondary endpoint) and distant metastasis-free survival (DMFS).

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

Results for the primary analysis of RFS are presented in in Table 17. The study showed a statistically significant difference for the primary outcome of RFS between treatment arms, with an estimated 53% risk reduction in the dabrafenib and trametinib combination arm as compared to the placebo arm (HR=0.47; 95% CI: 0.39, 0.58; $p=1.53\times10^{-14}$). Results were consistent across subgroups, including stratification factors for disease stage and BRAF V600 mutation type. Median RFS was 16.6 months for the placebo arm, and was not reached for the combination arm at the time of the primary analysis.

Table 17: COMBI-AD – primary analysis Relapse-free survival results

	Dabrafenib + Trametinib	**Placebo**
RFS parameter	**N=438**	**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)	

RFS parameter	Dabrafenib + Trametinib N=438	Placebo N=432
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)

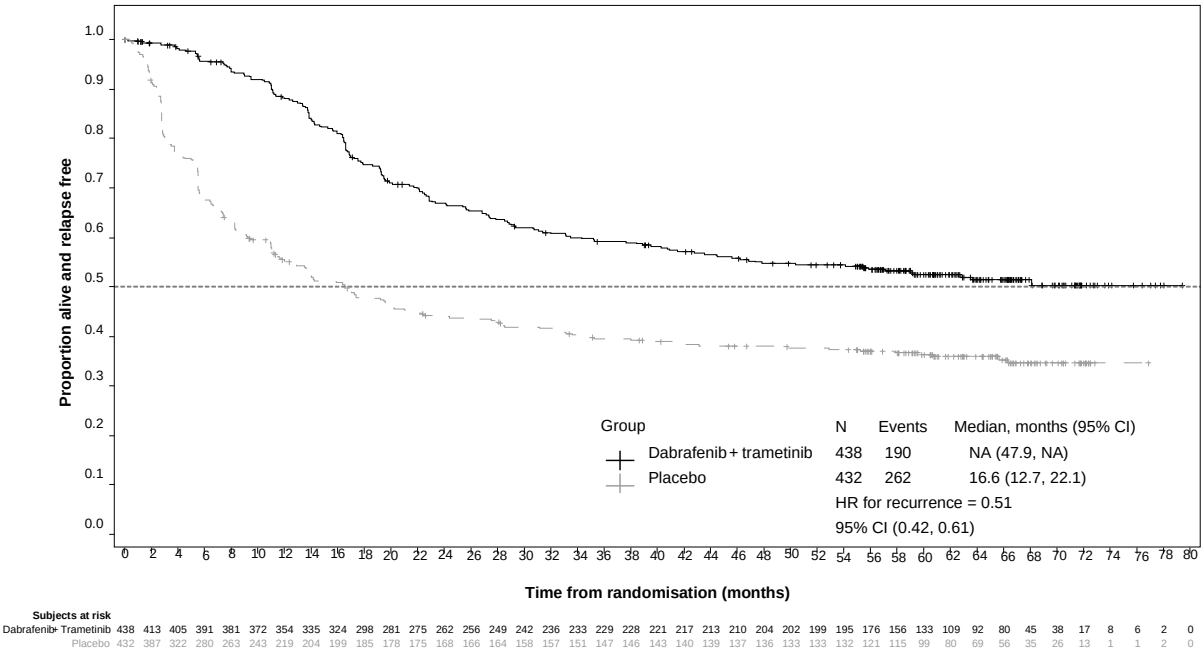
[1] Hazard ratio is obtained from the stratified Pike model.

[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

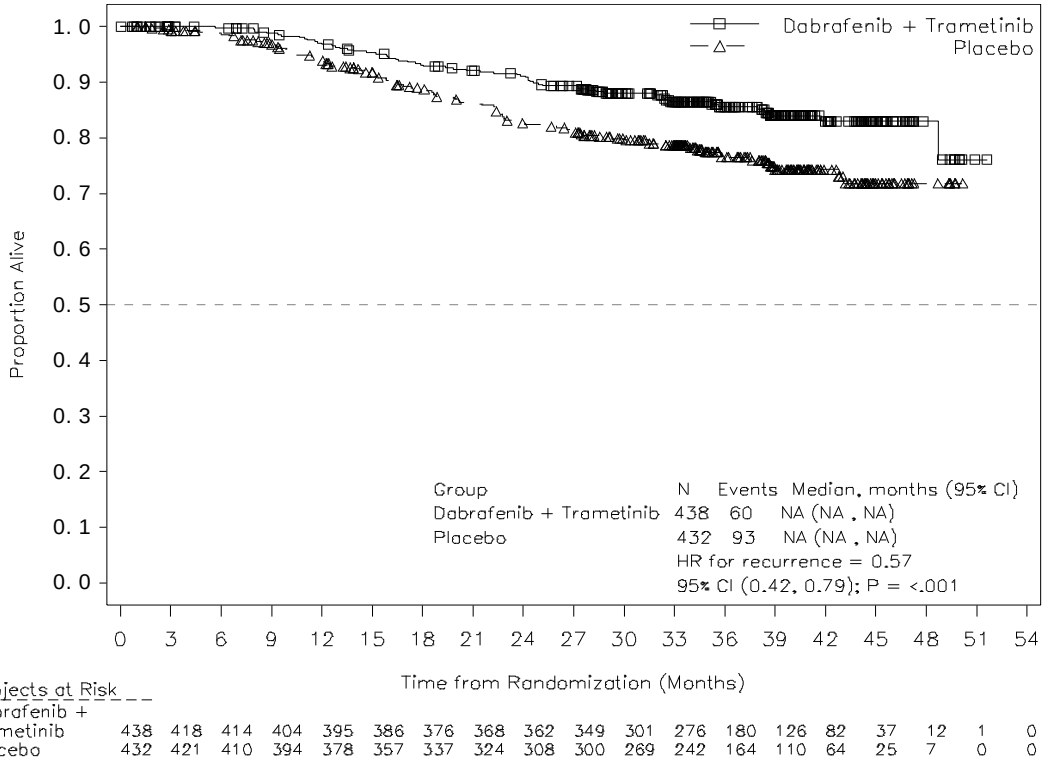
Based on updated data with an additional 29 months of follow-up compared to the primary analysis (minimum follow-up of 59 months), the RFS benefit was maintained with an estimated HR of 0.51 (95% CI: 0.42, 0.61) (Figure 4). The 5-year RFS rate was 52% (95% CI: 48, 58) in the combination arm compared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

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



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

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



Advanced NSCLC

Study E2201 (BRF113928)

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

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

Cohorts were enrolled sequentially:

- Cohort A: Monotherapy (dabrafenib 150 mg twice daily): 84 patients enrolled. 78 patients had previous systemic treatment for their metastatic disease (see prescribing information for dabrafenib on results from Cohort A).
- Cohort B (N=57): Combination therapy (Mekinist 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 (Mekinist 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.

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 Mekinist 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 18

Table 18: Efficacy Results in Patients with BRAF V600E NSCLC

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

Unresectable or metastatic solid tumors

The safety and efficacy of Mekinist in combination with Dabrafenib for the treatment of BRAF V600E mutation-positive unresectable or metastatic solid tumors were evaluated in Trials BRF117019, NCI-MATCH, and CTMT212X2101, and supported by results in COMBI-d, COMBI-v, and BRF113928.

In adult studies, patients received MEKINIST 2 mg once daily and dabrafenib 150 mg twice daily. The major efficacy outcome measures were ORR per RECIST v1.1, RANO [HGG] or modified RANO [LGG] criteria and duration of response (DoR).

BRF117019 Study and NCI-MATCH Study

Study BRF117019 is a multi-cohort, multi-center, non-randomized, open-label trial in adult patients with selected tumors with the BRAF V600E mutation, including high grade glioma (HGG) (n = 45), biliary tract cancer (BTC) (n = 43), low grade glioma (LGG) (n = 13),

adenocarcinoma of small intestine (ASI) (n = 3), gastrointestinal stromal tumor (GIST) (n = 1), and anaplastic thyroid cancer. Patients were enrolled based on local assessments of BRAF V600E mutation status; a central laboratory confirmed the BRAF mutation in 93 of 105 patients.

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

Among the 131 patients enrolled in BRF117019 and NCI-MATCH with the tumor types shown in Table 19, the baseline characteristics were: median age of 51 years with 20% age 65 or older; 56% female; 85% white, 9% Asian, 3% black, 3% Other; and 37% ECOG 0, 56% ECOG 1, and 6% ECOG 2. Of the 131 patients, 90% received prior systemic therapy.

Efficacy results in patients with solid tumors are summarized in Table 19.

Table 19 Efficacy Results Based on Independent Review in Study BRF117019 and NCI-MATCH Arm H

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

Mixed ductal / adenoneuroendocrine carcinoma	2	0	NA	NA
Neuroendocrine carcinoma of colon	2	0	NA	NA
Ameloblastoma of mandible	1	PR	(2.5, 100)	30
Combined small cell-squamous carcinoma of lung	1	PR	(2.5, 100)	5
Mucinous-papillary serous adenocarcinoma of peritoneum	1	PR	(2.5, 100)	8
Adenocarcinoma of anus	1	0	NA	NA
Gastrointestinal stromal tumor	1	0	NA	NA

Abbreviations: PR, partial response.

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

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

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

[d] *Denotes a right-censored DoR.*

CTMT212X2101 (X2101) Study

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

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

For patients with BRAF V600E mutant LGG and HGG in Parts C and D, the median age was 10 years (range: 1-17); 50% were male, 75% white, 8% Asian, 3% black; and 58% had Karnofsky/Lansky performance status of 100. Prior anti-cancer treatments included surgery (83%), external beam radiotherapy (2.8%), and systemic therapy (92%). The ORR was 25% (95% CI: 12%, 42%). For the 9 patients who responded, DoR was ≥6 months for 78% of patients, ≥12 months for 56% of patients, and ≥24 months for 44% of patients.

Low-grade glioma (LGG)

Study DRB436G2201

The clinical efficacy and safety of Mekinist plus Dabrafenib combination therapy in pediatric patients aged 1 to <18 years of age with BRAF V600E mutation-positive glioma was evaluated in the multi-center, open-label, Phase II clinical trial CDRB436G2201. Patients with low-grade glioma (WHO grades 1 and 2) who required first systemic therapy were randomized 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 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 tumor samples by the central laboratory was performed to confirm the BRAF V600E mutation status.

Dabrafenib and Mekinist dosing was age and weight dependent, with Dabrafenib dosed orally at 2.625 mg/kg twice daily for ages <12 years and 2.25 mg/kg twice daily for ages 12 years and older; Mekinist was dosed orally at 0.032 mg/kg once daily for ages <6 years and 0.025 mg/kg once daily for ages 6 years and older. Dabrafenib doses were capped at 150 mg twice daily and Mekinist doses at 2 mg once daily. Carboplatin and vincristine were dosed based on age and body surface area at doses 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 (2017) criteria for the LGG cohort, and RANO (2010) criteria for the HGG cohort. The primary analysis was performed when all patients in both cohorts had completed at least 32 weeks of therapy.

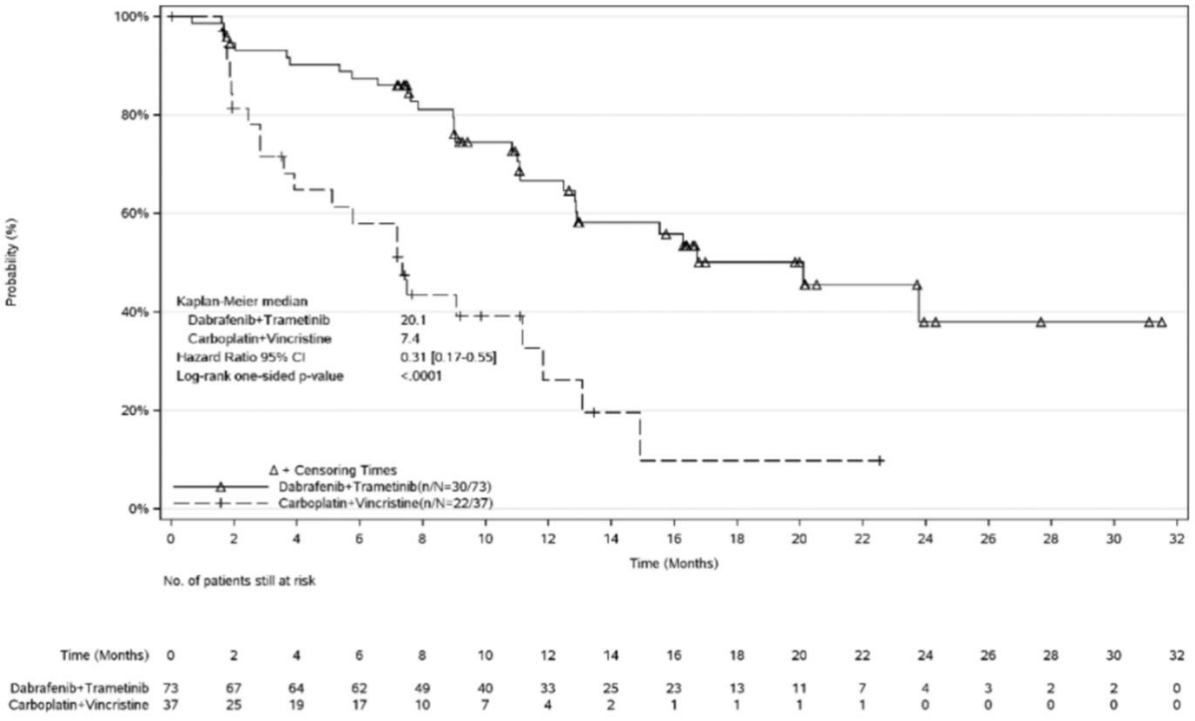
BRAF mutation-positive low-grade glioma (WHO grades 1 and 2)

In the low-grade glioma (LGG) cohort of study G2201, 110 patients were randomized 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. 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 20). 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) (Figure 6).

Table 20 Response and progression-free survival in Study G2201 (LGG cohort)

	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)
Overall Response Rate		
ORR (CR+PR), 95% CI, p-value	46.6% (34.8 - 58.6%), p<0.001	10.8% (3.0 - 25.4%)
Odds ratio	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	7.41 (2.9 – 18.8)	
Progression-free survival		
Median (months)	20.1 (12.8, NE)	7.4 (3.6, 11.8)
Hazard ratio (95% CI), p-value	0.31 (0.17-0.55), p<0.001	

Figure 6 Kaplan-Meier progression-free survival curves for Study G2201 (LGG cohort)



BRAF mutation-positive 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 Dabrafenib plus Mekinist for a median duration of 72.7 weeks. 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.

The ORR in this cohort was 56.1% (23/41). The Kaplan-Meier percent progression free estimate at 6 months was 66.8% (95% CI: 49.6 - 79.2%), the median progression-free survival

was 9.0 months (95% CI: 5.3 to 24.0), and the median overall survival was 32.8 months (95% CI: 19.2, NE), with 27 subjects censored at the time of the primary analysis.

Other studies

Pyrexia Management Analysis

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

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

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

NON-CLINICAL SAFETY DATA

Safety pharmacology and repeat dose toxicity

In mice, lower heart rate, heart weight and left ventricular function were observed without cardiac histopathology after 3 weeks at ≥0.25 mg/kg/day trametinib (approximately three times human clinical exposure based on AUC) for up to three weeks. In adult rats, myocardial mineralization and necrosis associated with increased serum phosphorus were seen at doses ≥1 mg/kg/day (approximately 12 times human clinical exposure based on AUC). In juvenile rats, increased heart weight with no histopathology was observed at 0.35 mg/kg/day (approximately twice the adult human clinical exposure based on AUC).

Trametinib was phototoxic in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay at significantly higher concentrations than clinical exposures (IC50 at 2.92 microgram/mL, ≥130 times the clinical exposure based on C_{max}), indicating that there is low risk for phototoxicity to patients taking trametinib.

In repeat-dose studies in rats, hepatocellular necrosis and transaminase elevations were seen after 8 weeks at ≥0.062 mg/kg/day (approximately 0.8 times human clinical exposure based on AUC).

Carcinogenicity and mutagenicity

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

Reproductive Toxicity

Embryofetal development and fertility

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

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

Juvenile animal studies

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

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

With the exception of corneal mineralization/dystrophy and increased heart weight, similar effects have been observed in adult animals given trametinib. At the lowest combined dose level evaluated, the systemic exposure is approximately 0.3 times the human exposure at clinical dose of 2 mg/day based on AUC.

Non-fixed dose combination therapy

Trametinib in combination with dabrafenib

Dogs given trametinib and dabrafenib in combination for 4 weeks demonstrated similar toxicities to those observed in comparable monotherapy studies.

Refer to the full prescribing information for Dabrafenib.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Store in a refrigerator 2 to 8°C. Store in the original package to protect from light and moisture. Keep the bottle tightly closed. Contains desiccant, do not remove or eat. Mekinist should not be used after the date marked “EXP” on the pack.

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

INSTRUCTIONS FOR USE AND HANDLING

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

Manufacturer:

See folding box.

National Package Leaflet

Information issued: September 2024

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