NOVARTIS

Dabrafenib

(as mesylate)

Tafinlar

50 mg, and 75 mg Capsules

Protein kinase inhibitor

DESCRIPTION AND COMPOSITION

Pharmaceutical form

50 mg and 75 mg hard capsules.

50 mg hard capsules

Opaque, size 2 capsules composed of a dark red body and dark red cap containing a white to slightly coloured solid. Capsule shells imprinted with GS TEW and 50 mg.

75 mg hard capsules

Opaque, size 1 capsules composed of a dark pink body and dark pink cap containing a white to slightly coloured solid. Capsule shells imprinted with GS LHF and 75 mg.

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

Active substance(s)

50 mg hard capsules

Each hard capsule contains dabrafenib mesilate equivalent to 50 mg of dabrafenib.

75 mg hard capsules

Each hard capsule contains dabrafenib mesilate equivalent to 75 mg of dabrafenib.

Excipients

Hard capsule: microcrystalline cellulose (cellulose, microcrystalline), magnesium stearate, vegetable source, colloidal silicon dioxide (silica, colloidal anhydrous).

Shell composition: red iron oxide, titanium dioxide, hypromellose.

Monogramming: black iron oxide, shellac, n-butyl alcohol, isopropyl alcohol, propylene glycol, ammonium hydroxide.

Pharmaceutical formulations may vary between countries.

INDICATIONS

Unresectable or metastatic melanoma

Dabrafenib (as mesylate) [Tafinlar] in combination with trametinib is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see section CLINICAL STUDIES).

Dabrafenib (as mesylate) [Tafinlar] as a monotherapy is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see section CLINICAL STUDIES).

Advanced non-small cell lung cancer

Dabrafenib (as mesylate) [Tafinlar] in combination with trametinib is indicated for the treatment of patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation.

DOSAGE REGIMEN AND ADMINISTRATION

Treatment with Dabrafenib (as mesylate) [Tafinlar] should be initiated by a physician experienced in the use of anticancer therapies.

Dosage regimen

General target population

Adults

The efficacy and safety of Dabrafenib (as mesylate) [Tafinlar] have not been established in patients with wild-type BRAF melanoma or wild-type BRAF NSCLC (see section CLINICAL STUDIES). Dabrafenib (as mesylate) [Tafinlar] should not be used in patients with wild-type BRAF melanoma or wild-type BRAF NSCLC.

Confirmation of BRAF V600 mutation using an approved/validated test is required for selection of patients appropriate for treatment with Dabrafenib (as mesylate) [Tafinlar] as monotherapy and in combination with trametinib (see section CLINICAL STUDIES).

When Dabrafenib (as mesylate) [Tafinlar] is used in combination with trametinib, please refer to the full trametinib prescribing information.

The recommended dose of Dabrafenib (as mesylate) [Tafinlar] either as monotherapy or in combination with trametinib is 150 mg twice daily (corresponding to a total daily dose of 300 mg).

Dabrafenib (as mesylate) [Tafinlar] should be taken either at least one hour before, or at least two hours after a meal (see section CLINICAL PHARMACOLOGY), leaving an interval of approximately 12 hours between doses. Dabrafenib (as mesylate) [Tafinlar] should be taken at similar times every day.

When Dabrafenib (as mesylate) [Tafinlar] and trametinib are taken in combination, the once-daily dose of trametinib should be taken at the same time each day with either the morning dose or the evening dose of Dabrafenib (as mesylate) [Tafinlar].

If a dose of Dabrafenib (as mesylate) [Tafinlar] is missed, it should not be taken if it is less than six hours until the next scheduled dose.

Dose adjustments

Dabrafenib (as mesylate) [Tafinlar] as monotherapy and in combination with Trametinib (as dimethyl sulfoxide) [Mekinist]

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

Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (see section WARNINGS AND PRECAUTIONS).

For pyrexia management guidance see section below.

Recommended dose level reductions and recommendations for dose modifications are provided in Table 1. Doses below 50 mg twice daily are not recommended.

Table 1 Recommended Dabrafenib (as mesylate) [Tafinlar] dose level reductions

Dose Level	Dabrafenib (as mesylate) [Tafinlar] Dose
Full dose	150 mg twice daily
First reduction	100 mg twice daily
Second reduction	75 mg twice daily
Third reduction	50 mg twice daily

The recommended dose modification schedule is provided in Table 2. When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The Dabrafenib (as mesylate) [Tafinlar] dose should not exceed 150 mg twice daily.

Table 2 Dabrafenib (as mesylate) [Tafinlar] 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 (Dabrafenib (as mesylate) [Tafinlar] when used as monotherapy, and both Dabrafenib (as mesylate) [Tafinlar] and Trametinib (as dimethyl sulfoxide) [Mekinist] when used in combination) if a patient's temperature is ≥38ºC (100.4°F). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. Patients should be evaluated for signs and symptoms of infection (see section

WARNINGS AND PRECAUTIONS). Dabrafenib (as mesylate) [Tafinlar], or both Dabrafenib (as mesylate) [Tafinlar] and Trametinib (as dimethyl sulfoxide) [Mekinist] 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 Dabrafenib (as mesylate) [Tafinlar] is used in combination with Trametinib (as dimethyl sulfoxide) [Mekinist] then both treatments should be simultaneously dose reduced, interrupted or discontinued with the exception of uveitis shown below.

Exceptions where dose modifications are necessary for Dabrafenib (as mesylate) [Tafinlar] only:

Uveitis management: No dose modifications are required as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, withhold Dabrafenib (as mesylate) [Tafinlar] until resolution of ocular inflammation and then restart Dabrafenib (as mesylate) [Tafinlar] reduced by one dose level. No dose modification of trametinib is required when taken in combination with Dabrafenib (as mesylate) [Tafinlar].

Special populations

Renal impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Based on the population pharmacokinetic analysis, mild and moderate renal impairment had no significant effect on the oral clearance of dabrafenib or on the concentrations of its metabolites (see section CLINICAL PHARMACOLOGY, PHARMACOKINETICS). There are no clinical data in patients with severe renal impairment and the potential need for dose adjustment cannot be determined. Dabrafenib (as mesylate) [Tafinlar] should be used with caution in patients with severe renal impairment.

Hepatic impairment

No dose adjustment is required for patients with mild hepatic impairment. Based on the population pharmacokinetic analysis, mild hepatic impairment had no significant effect on the oral clearance of dabrafenib or on the concentrations of its metabolites (see section CLINICAL PHARMACOLOGY, PHARMACOKINETICS). There are no clinical data in patients with moderate to severe hepatic impairment and the potential need for dose adjustment cannot be determined. Hepatic metabolism and biliary secretion are the primary routes of elimination of Dabrafenib (as mesylate) [Tafinlar] and its metabolites and patients with moderate to severe hepatic impairment may have increased exposure. Dabrafenib (as mesylate) [Tafinlar] should be used with caution in patients with moderate or severe hepatic impairment.

Pediatric patients (below 18 years)

The safety and efficacy of Dabrafenib (as mesylate) [Tafinlar] in pediatric patients have not been established. Dabrafenib (as mesylate) [Tafinlar] 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 section CLINICAL PHARMACOLOGY, PHARMACOKINETICS).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

When Dabrafenib (as mesylate) [Tafinlar] is used together with Trametinib (as dimethyl sulfoxide) [Mekinist], read the full prescribing information for Trametinib (as dimethyl sulfoxide) [Mekinist] section WARNINGS AND PRECAUTIONS

Pyrexia

Pyrexia was reported in clinical trials with Dabrafenib (as mesylate) [Tafinlar] monotherapy and in combination with trametinib (see section ADVERSE DRUG REACTIONS). In a Phase III clinical trial in patients with melanoma, the incidence and severity of pyrexia were increased when Dabrafenib (as mesylate) [Tafinlar] was used in combination with trametinib (57% [119/209], 7% Grade 3) as compared to dabrafenib monotherapy (33% [69/211], 2% Grade 3). In a Phase II trial in patients with NSCLC the incidence and severity of pyrexia were increased slightly when Dabrafenib (as mesylate) [Tafinlar] was used in combination with trametinib (55% [51/93], 5% Grade 3) as compared to Dabrafenib (as mesylate) [Tafinlar] monotherapy (37% [31/84], 2% Grade 3). In patients with melanoma who received the combination dose of Dabrafenib (as mesylate) [Tafinlar] 150 mg twice daily and trametinib 2 mg once daily and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy. About one-third of the patients receiving combination therapy who experienced pyrexia had 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 Dabrafenib (as mesylate) [Tafinlar] and Trametinib (as dimethyl sulfoxide) [Mekinist] were interrupted, compared to when only Dabrafenib (as mesylate) [Tafinlar] was interrupted. Therefore, interruption of both Dabrafenib (as mesylate) [Tafinlar] and Trametinib (as dimethyl sulfoxide) [Mekinist] is recommended if patient's temperature is ≥38ºC (100.4°F), and in case of recurrence, therapy can also be interrupted at the first symptom of pyrexia (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL STUDIES).

Cutaneous malignancies

Cutaneous Squamous Cell Carcinoma (cuSCC)

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with Dabrafenib (as mesylate) [Tafinlar] as monotherapy and in combination with trametinib (see section

ADVERSE DRUG REACTIONS). In a Phase III study in patients with melanoma, 10% (22/211) of patients receiving Dabrafenib (as mesylate) [Tafinlar] monotherapy developed cuSCC, with a median time to onset of the first occurrence of approximately 8 weeks. In patients who received Dabrafenib (as mesylate) [Tafinlar] in combination with trametinib, 3% (6/209) of patients developed cuSCC and events occurred later, with the median time to onset of the first occurrence of 20 to 32 weeks. More than 90 % of patients on Dabrafenib (as mesylate) [Tafinlar] who developed cuSCC continued on treatment without dose modification. In a Phase II trial in patients with NSCLC, 18% (15/84) of patients receiving Dabrafenib (as mesylate) [Tafinlar] monotherapy developed cuSCC, with a median time to onset of the first occurrence of approximately 11 weeks. In patients who received Dabrafenib (as mesylate) [Tafinlar] in combination with trametinib, only 2% (2/93) of patients developed cuSCC.

Skin examination should be performed prior to initiation of Dabrafenib (as mesylate) [Tafinlar] and during treatment with Dabrafenib (as mesylate) [Tafinlar], every 2 months throughout therapy. Monitoring should continue every 2 to 3 months for 6 months following discontinuation of Dabrafenib (as mesylate) [Tafinlar] or until initiation of another anti-neoplastic therapy.

Cases of cuSCC should be managed by dermatological excision and Dabrafenib (as mesylate) [Tafinlar] treatment should be continued without any dose adjustment. Patients should be instructed to immediately inform their physician if new lesions develop.

New primary melanoma

New primary melanomas have been reported in patients treated with Dabrafenib (as mesylate) [Tafinlar]. In clinical trials in unresectable or metastatic melanoma these were identified within the first 5 months of therapy and did not require treatment modification other than excision. Monitoring for skin lesions should occur as described for cuSCC.

Non-cutaneous malignancies

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signalling in BRAF wild-type cells with RAS mutations when exposed to BRAF inhibitors, which may lead to increased risk of non-cutaneous malignancies in patients treated with Dabrafenib (as mesylate) [Tafinlar]. Cases of RAS-driven malignancies have been seen with BRAF inhibitors.

Patients should be monitored as clinically appropriate. In patients with a non-cutaneous malignancy that has a RAS mutation the benefits and risks should be considered before continuing treatment with Dabrafenib (as mesylate) [Tafinlar]. No dose modification of trametinib is required when taken in combination with Dabrafenib (as mesylate) [Tafinlar].

Following discontinuation of Dabrafenib (as mesylate) [Tafinlar], monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy.

Pancreatitis

Pancreatitis has been reported in < 1 % of Dabrafenib (as mesylate) [Tafinlar] -treated patients in metastatic melanoma clinical trials, and acute pancreatitis has been reported in 1% of Dabrafenib (as mesylate) [Tafinlar]-treated patients in the NSCLC trial. One of the events occurred on the first day of dosing of a melanoma patient and recurred following re-challenge

at a reduced dose. Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when re-starting Dabrafenib (as mesylate) [Tafinlar] after an episode of pancreatitis.

Uveitis

Treatment with Dabrafenib (as mesylate) [Tafinlar] has been associated with the development of uveitis (including iritis). Patients should be monitored during therapy for visual signs and symptoms (such as, change in vision, photophobia and eye pain) (see section Dosage regimen and administration).

Hemorrhage

Hemorrhagic events, including major hemorrhagic events have occurred in patients taking Dabrafenib (as mesylate) [Tafinlar] in combination with trametinib (see section ADVERSE DRUG REACTIONS). Out of the 559 unresectable or metastatic patients treated with Dabrafenib (as mesylate) [Tafinlar] in combination with trametinib, 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). Two out of 93 patients (2%) receiving Dabrafenib (as mesylate) [Tafinlar] in combination with trametinib in a Phase II trial in patients with metastatic NSCLC had fatal intracranial hemorrhagic events. If patients develop symptoms of hemorrhage they should immediately seek medical care.

Venous thromboembolism (VTE)

VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE) can occur when Dabrafenib (as mesylate) [Tafinlar] is used in combination with Trametinib (as dimethyl sulfoxide) [Mekinist]. Patients should be advised to immediately seek medical care if they develop symptoms of VTE.

Skin toxicity

Severe cutaneous adverse reactions

Cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with Dabrafenib (as mesylate) [Tafinlar] in combination with Trametinib (as dimethyl sulfoxide) [Mekinist]. Before initiating treatment, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of SCARs appear, Dabrafenib (as mesylate) [Tafinlar] and Trametinib (as dimethyl sulfoxide) [Mekinist] should be withdrawn.

ADVERSE DRUG REACTIONS

Summary of the safety profile

Unresectable or metastatic melanoma

Dabrafenib (as mesylate) [Tafinlar] monotherapy:

Safety data for Dabrafenib (as mesylate) [Tafinlar] monotherapy was integrated from five clinical monotherapy studies BRF113683 (BREAK-3), BRF113929 (BREAK-MB), BRF113710 (BREAK-2), BRF113220, and BRF112680 and included 578 patients with

BRAF V600 mutant unresectable or metastatic melanoma. Approximately 30% of patients received treatment with Dabrafenib (as mesylate) [Tafinlar] for more than six months. In the integrated Dabrafenib (as mesylate) [Tafinlar] safety population, the most common (≥15%) adverse events were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, skin papilloma, alopecia, rash and vomiting.

Dabrafenib (as mesylate) [Tafinlar] and Trametinib (as dimethyl sulfoxide) [Mekinist] combination therapy:

The safety of Dabrafenib (as mesylate) [Tafinlar] and trametinib combination therapy was evaluated in two randomized Phase III studies of patients with BRAF V600 mutant unresectable or metastatic melanoma treated with Dabrafenib (as mesylate) [Tafinlar] 150 mg orally twice daily and trametinib 2 mg orally once daily (see section Clinical studies). The most common adverse events (≥20%) for Dabrafenib (as mesylate) [Tafinlar] and trametinib 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 metastatic melanoma are listed by MedDRA system organ class in Table 3 and Table 4 for Dabrafenib (as mesylate) [Tafinlar] monotherapy and Dabrafenib (as mesylate) [Tafinlar] in combination with trametinib, 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 3 Unresectable or metastatic melanoma – Adverse events for Dabrafenib (as mesylate) [Tafinlar] monotherapy

Adverse events	**Frequency category** Integrated Safety Data N=578
Infections and infestations	
Nasopharyngitis	Common
Neoplasms benign and malignant (including cysts and polyps)	
Papilloma	Very common
Acrochordon (skin tags), cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma, seborrhoeic keratosis	Common
New primary melanoma	Uncommon
Immune System Disorders	
Hypersensitivity	Uncommon
Metabolism and nutrition disorders	
Decreased appetite	Very common
Hypophosphataemia Hyperglycaemia	Common

Adverse events	Frequency category Integrated Safety Data N=578
Nervous system disorders	
Headache	Very common
Eye disorders	
Uveitis	Uncommon
Respiratory, thoracic and mediastinal disorders	
Cough	Very common
Gastrointestinal disorders	
Nausea, vomiting, diarrhoea	Very common
Constipation	Common
Pancreatitis	Uncommon
Skin and subcutaneous tissue disorders	
Skin effects (rash, hyperkeratosis), alopecia, palmar-plantar erythrodysaesthesia syndrome	Very common
Skin effects (actinic keratosis, skin lesion, dry skin, erythema, pruritus	Common
Panniculitis	Uncommon
Photosensitivity[1)]	Common
Musculoskeletal and connective tissue disorders	
Arthralgia, myalgia, pain in extremity	Very common
Renal disorders	
Renal failure, acute renal failure	Uncommon
Tubulointerstitial nephritis	Uncommon
General disorders and administration site conditions	
Asthenia, chills, fatigue, pyrexia	Very common
Influenza-like illness	Common
1) Photosensitivity cases were also observed in post-marketing experience. All cases reported in clinical trials (BRF113683 (BREAK-3), BRF113929 (BREAK-MB), BRF113710 (BREAK-2), BRF113220, and BRF112680 were Grade 1 and no dose modification was required.	

Table 4 lists adverse events when Dabrafenib (as mesylate) [Tafinlar] was used in combination with trametinib 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 4 Unresectable or metastatic melanoma - Adverse events for Dabrafenib (as mesylate) [Tafinlar] in combination with Trametinib (as dimethyl sulfoxide) [Mekinist]

Adverse events	Frequency category

	MEK115306 (COMBI-d) N=209	MEK115306 (COMBI-d) plus 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
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 edema	Uncommon	Uncommon
Cardiac disorders		
Ejection fraction decreased	Common	Common
Left ventricular dysfunction	Not reported	Uncommon
Cardiac failure	Not reported	Uncommon

Adverse events	Frequency category	
	MEK115306 (COMBI-d) N=209	MEK115306 (COMBI-d) plus MEK116513 (COMBI-v) Integrated Safety Data N=559
Bradycardia	Common	Common
Vascular disorders		
Hypertension	Very common	Very common
Hemorrhage[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		
Gastrointestinal perforation	Not reported	Uncommon
Colitis	Uncommon	Uncommon
Abdominal pain	Very common	Very common
Constipation	Very common	Very common
Diarrhoea	Very common	Very common
Nausea	Very common	Very common
Vomiting	Very common	Very common
Dry mouth	Common	Common
Stomatitis	Common	Common
Pancreatitis	Uncommon	Uncommon
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

Adverse events	Frequency category	
	MEK115306 (COMBI-d) N=209	MEK115306 (COMBI-d) plus MEK116513 (COMBI-v) Integrated Safety Data N=559
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
Edema peripheral	Very common	Very common
Pyrexia	Very common	Very common
Chills	Very common	Very common
Asthenia	Very common	Very common
Mucosal inflammation	Common	Common
Influenza-like illness	Common	Common
Face edema	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 hemorrhages have been reported*

[2] *Photosensitivity cases were also observed in post-marketing experience. All cases reported in 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 Dabrafenib (as mesylate) [Tafinlar] in combination with Trametinib (as dimethyl sulfoxide) [Mekinist] in unresectable or metastatic melanoma (see also section CLINICAL STUDIES).

Advanced non-small cell lung cancer

Dabrafenib (as mesylate) [Tafinlar] monotherapy:

The safety of Dabrafenib (as mesylate) [Tafinlar] monotherapy was evaluated in a Phase II, multicenter, multi-cohort, non-randomised, open-label study of patients with BRAF V600E mutation positive metastatic NSCLC (see section CLINICAL STUDIES).

In the Dabrafenib (as mesylate) [Tafinlar] 150 mg twice daily (N=84) monotherapy arm (Cohort A) the most common adverse drug reactions (≥20%) were pyrexia, asthenia, fatigue, hyperkeratosis, cough, skin papilloma, dry skin, palmar-plantar erythrodysaesthesia syndrome, alopecia, nausea, and dyspnoea.

Dabrafenib (as mesylate) [Tafinlar] in combination with trametinib:

The safety of Dabrafenib (as mesylate) [Tafinlar] in combination with trametinib was evaluated in a Phase II, multicenter, multi-cohort, non-randomised, open-label study of patients with BRAF V600E mutation positive metastatic NSCLC (see section CLINICAL STUDIES).

In the Dabrafenib (as mesylate) [Tafinlar] 150 mg orally twice daily and Trametinib (as dimethyl sulfoxide) [Mekinist] 2 mg orally once daily arms (Cohorts B and C), the most common adverse events (≥20%) reported for Dabrafenib (as mesylate) [Tafinlar] and Trametinib (as dimethyl sulfoxide) [Mekinist] combination therapy were pyrexia, nausea, vomiting, peripheral edema, diarrhea, decreased appetite, asthenia, dry skin, chills, cough, fatigue, rash, and dyspnea.

Table 5 lists the adverse drug reactions for Dabrafenib (as mesylate) [Tafinlar] in combination with trametinib occurring at an incidence ≥10% for all grade adverse drug reactions or at an incidence ≥2% for Grade 3 and Grade 4 adverse drug reactions or events which are medically significant in 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 5 Advanced NSCLC - Adverse drug reactions for Dabrafenib (as mesylate) [Tafinlar] in combination with trametinib

Adverse drug reactions[1]	**Dabrafenib (as mesylate) [Tafinlar] in combination with Trametinib (as dimethyl sulfoxide) [Mekinist] N=93**		**Frequency category**
	All grades %	Grades 3/4 %	
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			
Hyponatremia	14	9	Very common
Dehydration	8	3	Common
Eye disorders			
Detachment of retina/retinal pigment epithelium[1]	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			
Hemorrhage[2]	26	3	Very common

Adverse drug reactions[1]	Dabrafenib (as mesylate) [Tafinlar] in combination with Trametinib (as dimethyl sulfoxide) [Mekinist] N=93		Frequency category
	All grades %	Grades 3/4 %	
Hypotension	15	2	Very common
Hypertension	8	6	Common
Pulmonary embolism	4	2	Common
Gastrointestinal disorders			
Nausea	46	NR	Very common
Vomiting	37	3	Very common
Diarrhoea	33	2	Very common
Decreased appetite	28	NR	Very common
Constipation	16	NR	Very common
Pancreatitis acute	1	NR	Common
Skin and subcutaneous tissue disorders			
Erythema	10	NR	Very common
Dry skin	32	1	Very common
Rash[3)]	31	3	Very common
Pruritus[4)]	15	2	Very common
Hyperkeratosis[5)]	13	1	Very common
Musculoskeletal and connective tissue disorders			
Muscle spasms	10	NR	Very common
Arthralgia	16	NR	Very common
Myalgia	13	NR	Very common
Renal and urinary disorders			
Renal failure	3	1	Common
Tubulointerstitial nephritis	2	2	Common
General disorders and administration site disorders			
Pyrexia	55	5	Very common
Asthenia[6)]	47	6	Very common
Edema[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

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 Dabrafenib (as mesylate) [Tafinlar] in combination with Trametinib (as dimethyl sulfoxide) [Mekinist]. 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 6 ADRs from post-marketing experience and pooled clinical trials across indications

Adverse drug reaction	Frequency category
Immune system disorders	
Sarcoidosis	Uncommon
Vascular disorders	
Venous thrombo-embolism[1]	Common
[1)] VTE includes pulmonary embolism, deep vein thrombosis, embolism and venous thrombosis.	

INTERACTIONS

Effect of other drugs on Dabrafenib (as mesylate) [Tafinlar]:

Based on in vitro studies, dabrafenib was shown to be primarily metabolized by cytochrome P450 (CYP) 2C8 and CYP3A4 (see section CLINICAL PHARMACOLOGY, PHARMACOKINETICS). Pharmacokinetic data showed an increase in repeat dose dabrafenib Cmax (33%) and AUC (71%) upon co-administration with ketoconazole (CYP3A4 inhibitor), and increases of 82% and 68% of hydroxy- and desmethyl-dabrafenib AUC, respectively. A decrease in AUC was noted for carboxy-dabrafenib (decrease of 16%). Co-administration of dabrafenib and gemfibrozil (CYP2C8 inhibitor) resulted in an increase in repeat-dose dabrafenib AUC (47%) and no meaningful change in the concentrations of the metabolites. Pharmacokinetic data showed a decrease in repeat dose dabrafenib C_{max} (27%) and AUC (34%) upon co-administration with rifampin (CYP3A4/CYP2C8 inducer). No relevant change in AUC was noted for hydroxy-dabrafenib, there was an increase in AUC of 73% for carboxy-dabrafenib and a decrease in AUC of 30% for desmethyl-dabrafenib. Medicinal products that are strong inhibitors or inducers of CYP2C8 or CYP3A4 are likely to increase or decrease, respectively, dabrafenib concentrations. Alternative agents should be considered during administration with Dabrafenib (as mesylate) [Tafinlar] when possible. Use caution if strong inhibitors (e.g., ketoconazole, nefazodone, clarithromycin, ritonavir, gemfibrozil) or inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St John's wort) of CYP2C8 or CYP3A4 are coadministered with Dabrafenib (as mesylate) [Tafinlar].

Drugs that affect gastric pH:

Co-administration of repeat dosing of dabrafenib 150 mg twice daily and a pH elevating agent, rabeprazole 40 mg once daily, resulted in a 3% increase in dabrafenib AUC and a 12% decrease in dabrafenib C_{max}. These changes in dabrafenib AUC and Cmax are considered not clinically meaningful. Medicinal products that alter the pH of the upper gastrointestinal (GI)

tract (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) are not expected to reduce the bioavailability of dabrafenib.

Effect of Dabrafenib (as mesylate) [Tafinlar] on other drugs:

Dabrafenib induces CYP3A4- and CYP2C9-mediated metabolism (see section CLINICAL PHARMACOLOGY, PHARMACOKINETICS) and may induce other enzymes including CYP2B6, CYP2C8, CYP2C19 and UDP glucuronosyltransferases (UGT). Dabrafenib may also induce transporters (e.g., Pglycoprotein (Pgp)). In a clinical study in 16 patients using a single-dose of midazolam, a CYP3A4 substrate, C_{max} and AUC were decreased by 47% and 65%, respectively with co-administration of repeat-dose Dabrafenib (as mesylate) [Tafinlar] 150 mg twice daily. In a separate trial in 14 patients, repeat-dose Dabrafenib (as mesylate) [Tafinlar] decreased the single-dose AUC of S-warfarin (a substrate of CYP2C9) and of R-warfarin (a substrate of CYP3A4/CYP1A2) by 37% and 33%, respectively, with a small increase in C_{max} (18 and 19% respectively). Co-administration of Dabrafenib (as mesylate) [Tafinlar] and medicinal products which are affected by the induction of CYP3A4 or CYP2C9 such as hormonal contraceptives (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL), warfarin or dexamethasone may result in decreased concentrations and loss of efficacy. If co-administration of these medications is necessary, monitor patients for loss of efficacy or consider substitutions of these medicinal products. Dabrafenib inhibits OATP1B1 and OATP1B3 (see section CLINICAL PHARMACOLOGY, PHARMACOKINETICS). Following co-administration of a single dose of rosuvastatin (OATP1B1 and OATP1B3 substrate) with repeat dose Dabrafenib (as mesylate) [Tafinlar] 150 mg twice daily in 16 patients, AUC was minimally changed (7% increase) and Cmax was increased by 156%. Monitoring is recommended for adverse reactions if Dabrafenib (as mesylate) [Tafinlar] is coadministered with drugs that are OATP1B1 or OATP1B3 substrates with a narrow therapeutic index with regards to high peak concentrations.

Combination therapy and non-fixed dose combination therapy

Combination with Trametinib (as dimethyl sulfoxide) [Mekinist]:

Co-administration of repeat dosing of Dabrafenib (as mesylate) [Tafinlar] 150 mg twice daily and trametinib 2 mg once 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 Dabrafenib (as mesylate) [Tafinlar] is administered in combination with trametinib 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 trametinib for guidelines on drug interactions associated with trametinib monotherapy.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

Dabrafenib (as mesylate) [Tafinlar] can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Dabrafenib (as mesylate) [Tafinlar] in pregnant women. Reproductive studies in animals (rats) have demonstrated dabrafenib induced embryotoxicity and teratogenicity. Increased incidences of delays in skeletal development and reduced fetal body weight were observed following prenatal exposure to dabrafenib at concentrations 0.5 times the exposure in humans at the highest recommended dose of 150 mg twice daily. Embryo-lethality, ventricular septal defects, and variation in thymic shape were observed following prenatal exposure to dabrafenib at concentrations three times the exposure in humans at the highest recommended dose of 150 mg twice daily. Pregnant women should be advised of the potential risk to the fetus.

Animal data

In a combined embryo-fetal development study in rats, animals received oral doses of dabrafenib up to 300 mg/kg/day during the period of organogenesis. At ≥20 mg/kg/day, maternal systemic exposure (AUC) was 4.1 microgram*h/mL corresponding to approximately 0.5 times the human exposure at the highest recommended dose of 150 mg twice daily. Developmental toxicity consisted of delays in skeletal development and reduced fetal body weight. At a dose of 300 mg/kg/day maternal systemic exposure (AUC) was 22.6 microgram*h/mL corresponding to approximately three times the human exposure at the highest recommended dose of 150 mg twice daily. Developmental toxicity consisted of embryo-lethality, ventricular septal defects, and variation in thymic shape.

Lactation

Risk summary

There are no data on the effect of Dabrafenib (as mesylate) [Tafinlar] on the breast-fed child, or the effect of Dabrafenib (as mesylate) [Tafinlar] on milk production. Because many drugs are transferred into human milk and because of the potential for adverse reactions in nursing infants from Dabrafenib (as mesylate) [Tafinlar], 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 Dabrafenib (as mesylate) [Tafinlar] and any potential adverse effects on the breast-fed child from Dabrafenib (as mesylate) [Tafinlar] 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 Dabrafenib (as mesylate) [Tafinlar] 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 Dabrafenib (as mesylate) [Tafinlar] and for at least two weeks after stopping treatment with Dabrafenib (as mesylate) [Tafinlar]. If taking Dabrafenib (as mesylate) [Tafinlar] in combination with Trametinib (as dimethyl sulfoxide) [Mekinist], sexually-active females of reproductive potential are recommended to use effective contraception and for at least 16 weeks after stopping treatment.

Dabrafenib (as mesylate) [Tafinlar] may decrease the efficacy of oral or any other systemic hormonal contraceptives and an effective alternate method of contraception should be used (see section INTERACTIONS).

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 Dabrafenib (as mesylate) [Tafinlar] monotherapy and for at least 2 weeks after stopping treatment with Dabrafenib (as mesylate) [Tafinlar]. If taking Dabrafenib (as mesylate) [Tafinlar] in combination with Trametinib (as dimethyl sulfoxide) [Mekinist], male patients should use condoms during sexual intercourse, and for at least 16 weeks after stopping treatment.

Infertility

There are no data in humans. Adverse effects on male reproductive organs have been seen in animals (see section NON-CLINICAL SAFETY DATA). Male patients should be informed of the potential risk for impaired spermatogenesis, which may be irreversible.

OVERDOSAGE

There is currently very limited experience of overdosage with Dabrafenib (as mesylate) [Tafinlar]. The maximum dose of Dabrafenib (as mesylate) [Tafinlar] administered during clinical trials was 600 mg (300 mg twice daily). There is no specific antidote for overdosage of Dabrafenib (as mesylate) [Tafinlar]. Patients who develop adverse reactions should receive appropriate symptomatic treatment. In case of suspected overdose, Dabrafenib (as mesylate) [Tafinlar] should be withheld and supportive care instituted. Further management should be as clinically indicated or as recommended by the national poisons center, where available.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Dabrafenib (as mesylate) [Tafinlar] Monotherapy

Dabrafenib (as mesylate) [Tafinlar] (dabrafenib) is a potent, selective, ATP-competitive inhibitor of RAF kinases with IC50 values of 0.65, 0.5 and 1.84 nM for $BRAF^{V600E}$, $BRAF^{V600K}$ and $BRAF^{V600D}$ enzymes, respectively. Oncogenic amino acid variants in BRAF at valine 600 (V600) lead to constitutive activation of the RAS/RAF/MEK/ERK pathway and stimulation of tumour cell growth. BRAF mutations have been identified in specific cancers, including approximately 50% of melanoma and 1 to 3% of NSCLC. The most commonly observed BRAF mutation (V600E) and the next most common (V600K) account for 95 % of the BRAF mutations found in all patients with cancer. A number of rare substitutions also occur including V600D, V600G and V600R.Dabrafenib also inhibits wildtype BRAF and CRAF enzymes with IC50 values of 3.2 and 5.0 nM, respectively in biochemical assays. Dabrafenib inhibits BRAF V600 mutant melanoma and NSCLC cell line growth *in vitro* and melanoma xenograft models *in vivo*.

Dabrafenib (as mesylate) [Tafinlar] in combination with Trametinib (as dimethyl sulfoxide) [Mekinist]

Trametinib (as dimethyl sulfoxide) [Mekinist] (trametinib) is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and

MEK2 activation and kinase activity. MEK proteins are components of the extracellular signal- related kinase (ERK) pathway. Dabrafenib and trametinib inhibit two kinases in this pathway, BRAF and MEK, and the combination provides concomitant inhibition of the pathway. The combination of dabrafenib with trametinib is synergistic 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)

Dabrafenib demonstrated suppression of a downstream pharmacodynamic biomarker (phosphorylated ERK) in BRAF V600 mutant melanoma cell lines, in vitro and in animal models.

In patients with BRAF V600 mutant melanoma, administration of dabrafenib resulted in inhibition of tumour phosphorylated ERK relative to baseline.

Cardiac electrophysiology

The potential effect of dabrafenib on QT prolongation was assessed in a dedicated multiple dose QT study. A supratherapeutic dose of 300 mg Dabrafenib (as mesylate) [Tafinlar] twice daily was administered in 32 patients with BRAF V600 mutation-positive tumours. No clinically relevant effect of dabrafenib or its metabolites on the QTc interval was observed.

Pharmacokinetics (PK)

Absorption

Dabrafenib is absorbed orally with median time to achieve peak plasma concentration of 2 hours post-dose. Mean absolute bioavailability of oral dabrafenib is 95 % (90 % CI: 81, 110). Dabrafenib exposure (C_{max} and AUC) increased in a dose proportional manner between 12 and 300 mg following single-dose administration, but the increase was less than dose-proportional after repeat twice daily dosing. There was a decrease in exposure observed with repeat dosing, likely due to induction of its own metabolism. Mean accumulation AUC Day 18/Day 1 ratios was 0.73. Following administration of 150 mg twice daily, geometric mean C_{max}, AUC0-τ and pre-dose concentration (Cτ) were 1,478 ng/mL, 4,341 ng*hr/mL and 26 ng/mL, respectively. Administration of dabrafenib with food reduced the bioavailability (C_{max} and AUC decreased by 51% and 31% respectively) and delayed absorption of dabrafenib when compared to the fasted state.

Distribution

Dabrafenib binds to human plasma protein and is 99.7% bound. The steady-state volume of distribution following intravenous micro-dose administration is 46 L.

Biotransformation/metabolism

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidized via CYP3A4 to form carboxy-dabrafenib. Carboxy-dabrafenib can be decarboxylated via a non-enzymatic process to form desmethyl-dabrafenib. Carboxy-dabrafenib is excreted in bile and urine. Desmethyl- dabrafenib may also be formed in the gut and reabsorbed. Desmethyl-dabrafenib is metabolized by CYP3A4 to

oxidative metabolites. Hydroxy-dabrafenib terminal half-life parallels that of parent with a half-life of 10 hours while the carboxy- and desmethyl- metabolites exhibited longer half-lives (21 to 22 hours). Mean metabolite to parent AUC ratios following repeat-dose administration were 0.9, 11 and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib; while the activity of carboxy-dabrafenib is not likely to be significant.

Elimination

Terminal half-life following IV microdose is 2.6 hours. Dabrafenib terminal half-life is 8 hours due to a prolonged terminal phase after oral administration. IV plasma clearance is 12 L/hour. Fecal excretion is the major route of elimination after oral dosing, accounting for 71% of a radioactive dose while urinary excretion accounted for 23% of radioactivity.

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

Effect of other drugs on dabrafenib:

In vitro results indicate that CYP2C8 and CYP3A4 are the primary CYP enzymes involved in the oxidative metabolism of dabrafenib while hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates. Therefore, inhibitors or inducers of these enzymes have the potential to affect the PK of dabrafenib or its metabolites (see section INTERACTIONS). Dabrafenib is a substrate of human Pgp and breast cancer resistance protein (BCRP) *in vitro*. However, these transporters have minimal impact on dabrafenib oral bioavailability and elimination, and the risk of a drug-drug interaction is minimal.

Effect of dabrafenib on other drugs:

In human hepatocytes, dabrafenib produced concentration-dependent increases in CYP2B6 and CYP3A4 mRNA levels up to 32 times the control levels. Although Dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, were inhibitors of human organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1 and OAT3, and dabrafenib and its desmethyl metabolite were found to be inhibitors of organic cation transporter 2 (OCT2) *in vitro.* The risk of a drug-drug interaction is minimal based on clinical exposure for OAT1, OAT3 and OCT2. For OATP1B1 and OATP1B3 the drug-drug interaction risk was assessed in a clinical study (see section INTERACTIONS). Dabrafenib and desmethyl-dabrafenib were shown to be moderate inhibitors of human BCRP; however, based on clinical exposure, the risk of a drug-drug interaction is minimal. Neither dabrafenib nor its three metabolites were demonstrated to be inhibitors of Pgp *in vitro*.

Special populations

Pediatric population (below 18 years)

No studies have been conducted to investigate the pharmacokinetics of Dabrafenib (as mesylate) [Tafinlar] in pediatric patients.

Geriatric patients (65 years or above)

Based on the population pharmacokinetic analysis, age had no significant effect on dabrafenib pharmacokinetics. Age greater than 75 years was a significant predictor of carboxy- and

desmethyl-dabrafenib plasma concentrations with a 40% greater exposure in patients ≥75 years of age, relative to patients <75 years old.

Gender/Weight

Based on the population pharmacokinetic analysis, gender and weight were found to influence dabrafenib oral clearance; weight also impacted oral volume of distribution and distributional clearance. These pharmacokinetic differences were not considered clinically relevant.

Race/Ethnicity

The population pharmacokinetic analysis showed no significant differences in the pharmacokinetics of dabrafenib between Asian and Caucasian patients. No dabrafenib dose adjustment is needed in Asian patients.

There are insufficient data to evaluate the potential effect of other races/ethnicities on dabrafenib pharmacokinetics.

Renal impairment:

The pharmacokinetics of dabrafenib were characterized in 233 patients with mild renal impairment (GFR 60 to 89 mL/min/1.73m^2) and 30 patients with moderate renal impairment (GFR 30 to 59 mL/min/1.73m^2) enrolled in clinical trials using a population analysis. The effect of mild or moderate renal impairment on dabrafenib oral clearance was small (<6% for both categories) and not clinically relevant. In addition, mild and moderate renal impairment did not have a significant effect on hydroxy-, carboxy-, and desmethyl-dabrafenib plasma concentrations. No data are available in patients with severe renal impairment (see section DOSAGE REGIMEN AND ADMINISTRATION).

Hepatic impairment

The pharmacokinetics of dabrafenib were characterized in 65 patients with mild hepatic impairment (based on National Cancer Institute [NCI] classification) enrolled in clinical trials using a population analysis. Dabrafenib oral clearance was not significantly different between these patients and patients with normal hepatic function (4% difference). In addition, mild hepatic impairment did not have a significant effect on dabrafenib metabolite plasma concentrations. No data are available in patients with moderate to severe hepatic impairment (see section Dosage regimen and administration).

CLINICAL STUDIES

Unresectable or metastatic melanoma

Dabrafenib (as mesylate) [Tafinlar] monotherapy

The efficacy and safety of Dabrafenib (as mesylate) [Tafinlar] in the treatment of adult patients with BRAF V600 mutation positive unresectable or metastatic melanoma have been evaluated in 3 studies (BRF113683 [BREAK-3], BRF113929 [BREAK-MB], and BRF113710 [BREAK-2]) including patients with BRAF V600E and/or V600K mutations.

Previously untreated patients

The efficacy and safety of Dabrafenib (as mesylate) [Tafinlar] were evaluated in a Phase III randomized, open- label study [BREAK-3] comparing Dabrafenib (as mesylate) [Tafinlar] to dacarbazine (DTIC) in previously untreated patients with BRAF V600E mutation positive,

advanced (unresectable Stage III) or metastatic (Stage IV) melanoma. Screening included central testing of BRAF mutation V600E using a BRAF mutation assay conducted on the most recent tumor sample available.

The trial enrolled 250 patients randomized 3:1 to receive either Dabrafenib (as mesylate) [Tafinlar] 150 mg twice daily or intravenous DTIC 1,000 mg/m2 every 3 weeks. The primary objective for this study was to evaluate the efficacy of Dabrafenib (as mesylate) [Tafinlar] compared to DTIC with respect to progression-free survival (PFS) for patients with BRAF V600E mutation positive metastatic melanoma. Patients on the DTIC arm were allowed to receive Dabrafenib (as mesylate) [Tafinlar] after independent radiographic confirmation of initial progression. Baseline characteristics were balanced between treatment groups. Sixty percent of patients were male and 99.6% were Caucasians; the median age was 52 years with 21 % of patients being ≥ 65 years, 98.4% had an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1, and 97% of patients had metastatic disease.

The primary analysis was based on 118 events at the time of the data cut off. Efficacy results are summarized in Table 7 and Figure 1.

Table 7: Intention-to-Treat Population

Endpoints/Assessments	**Dabrafenib N=187**	**DTIC N=63**
PFS		
Median, months (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
Hazard Ration (95% CI) *P value*	0.30 (0.18, 0.51) P <0.0001	
OS[a]		
% at 6 months (95% CI)	87 (79.2, 91.9)	79 (59.7, 89.5)
Hazard Ratio (95% CI)	0.61 (0.25, 1.48)	
OR[b]		
% (95% CI)[c]	53 (45.5, 60.3)	19 (10.2, 30.9)
DoR		
	N=99	N=12
Median, months (95 % CI)	5.6 (4.8, NR)	NR (5.0, NR)

CI: confidence interval; DTIC: dacarbazine; NR-Not reached; PFS: Progression-free survival; OS: Overall survival; OR: Overall response; DoR: Duration of response.

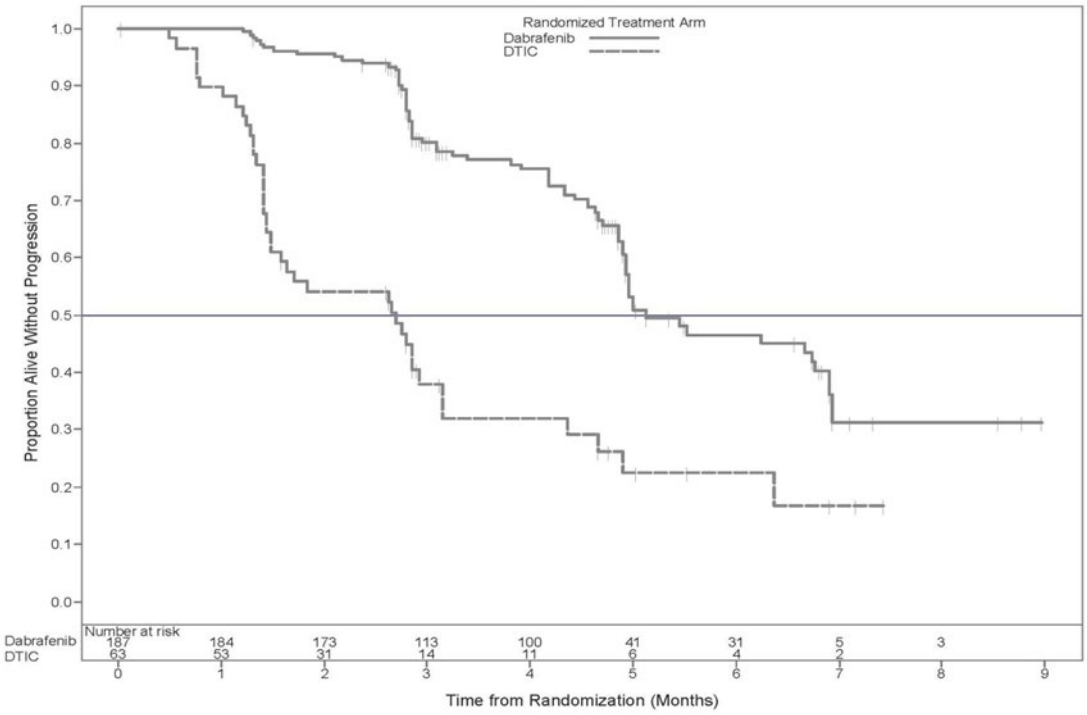
a. *Estimated from Kaplan-Meier estimates at 6 months; with a median follow-up time of 4.9 months (range = 0 to 9,9 months) and 30 deaths, overall survival data are not yet mature and median overall survival has not been reached for either arm. Patients are summarized by randomized treatment; the estimates include data from the crossover phase for patients randomized to DTIC and thus reflects any benefit of second-line Dabrafenib (as mesylate) [Tafinlar].*

b. *Defined as complete response + partial response.*

c. *Confirmed response.*

Twenty-eight patients (44 %) randomized to DTIC crossed over to Dabrafenib (as mesylate) [Tafinlar] following independently verified disease progression. Median time on Dabrafenib (as mesylate) [Tafinlar] after cross-over was 2.8 months and unconfirmed ORR was 46 %.

Figure 1 BREAK-3 Kaplan-Meier investigator-assessed PFS curves (ITT population)



Patients with brain metastases

BREAK-MB was a multi-center, open-label, two-cohort, Phase II study designed to evaluate the intracranial response of Dabrafenib (as mesylate) [Tafinlar] in patients with histologically confirmed (Stage IV) BRAF-mutation positive (V600E or V600K) melanoma metastatic to the brain. Patients were enrolled into Cohort A (patients with no prior local therapy for brain metastasis) or Cohort B (patients who received prior local therapy for brain metastasis).

The results are summarized in Table 8.

Table 8 Efficacy data by investigator assessment from the BREAK-MB study

	All Treated Patients Population			
	BRAF V600E (Primary)		**BRAF V600K**	
Endpoints/ Assessment	**Cohort A N=74**	**Cohort B N=65**	**Cohort A N=15**	**Cohort B N=18**
Overall intracranial response rate, % (95% CI)[a]				
	39% (28.0, 51.2) P < 0.001[b]	31% (19.9, 43.4) P < 0.001[b]	7% (0.2, 31.9)	22% (6.4, 47.6)
Duration of intracranial response, median, months (95% CI)				
	N=29 4.6 (2.8, NR)	N=20 6.5 (4.6, 6.5)	N=1 2.9 (NR, NR)	N=4 3.8 (NR, NR)
OR, % (95% CI)[a]				
	38% (26.8, 49.9)	31% (19.9, 43.4)	0 (0, 21.8)	28% (9.7, 53.5)
DoR, median, months (95% CI)				
	N=28 5.1 (3.7, NR)	N=20 4.6 (4.6, 6.5)	NA	N=5 3.1 (2.8, NR)
PFS, median, months (95% CI)				
	3.7 (3.6, 5.0)	3.8 (3.6, 5.5)	1.9 (0.7, 3.7)	3.6 (1.8, 5.2)

OS, median, months (95% CI)				
Median, months	7.6 (5.9, NR)	7.2 (5.9, NR)	3.7 (1.6, 5.2)	5.0 (3.5, NR)

Abbreviations: CI: confidence interval; INV: investigator-assessed; NR: not reached; NA: not applicable; OS: Overall survival; OR: Overall response; DoR: Duration of response; PFS: Progression –free survival.

a - Confirmed response.

b - This study was designed to support or reject the null hypothesis of OIRR ≤10% (based on historical results) in favour of the alternative hypothesis of OIRR ≥ 30% in BRAF V600E positive patients.

Patients who were previously untreated or failed at least one prior systemic therapy

BRF113710 (BREAK-2) was a multi-center, global, open-label, single-arm, Phase II study that enrolled 92 patients with histologically confirmed metastatic melanoma (Stage IV) with confirmed BRAF V600E or V600K mutation-positive melanoma. Patients were treatment-naïve (N = 15) or received prior treatment (N= 77) in the metastatic setting (i.e., chemotherapy, immunotherapy, prior targeted therapy.

The investigator assessed confirmed response rate in the primary efficacy population of patients with BRAF V600E metastatic melanoma (N=76) was 59% (95% CI: 48.2, 70.3) including 7% complete response. Median PFS was 6.3 months (95% CI: 4.6, 7.7) and the median duration of response was 5.2 months (95% CI: 3.9, not calculable). Prior systemic therapy did not appear to significantly impact response. The investigator assessed confirmed response rate in a secondary efficacy population of patients with BRAF V600K mutation positive metastatic melanoma (N=16) was 13 % (95% CI: 0.0, 28.7) with a median duration of response of 5.3 months (95% CI: 3.7, 6.8). There were no complete responses in the V600K patient population.

Dabrafenib (as mesylate) [Tafinlar] in combination with Trametinib (as dimethyl sulfoxide) [Mekinist] :

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

MEK115306 (COMBI-d)

MEK115306 (COMBI-d) was a Phase III, randomized, double-blind study comparing the combination of Dabrafenib (as mesylate) [Tafinlar] and trametinib to Dabrafenib (as mesylate) [Tafinlar] 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 (Dabrafenib (as mesylate) [Tafinlar] 150 mg twice daily and trametinib 2 mg once daily) (N=211) or Dabrafenib (as mesylate) [Tafinlar] 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 zero (72%) and had Stage IVM1c disease (66%). Most patients had the BRAF V600E mutation (85 %); the remaining 15% of patients had the BRAF V600K mutation.

Median OS and estimated 1-year, 2-year, 3-year, 4 year and 5-year survival rates are presented in Table 9. 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 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 10, 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 9 Overall Survival results for Study MEK115306 (COMBI d)

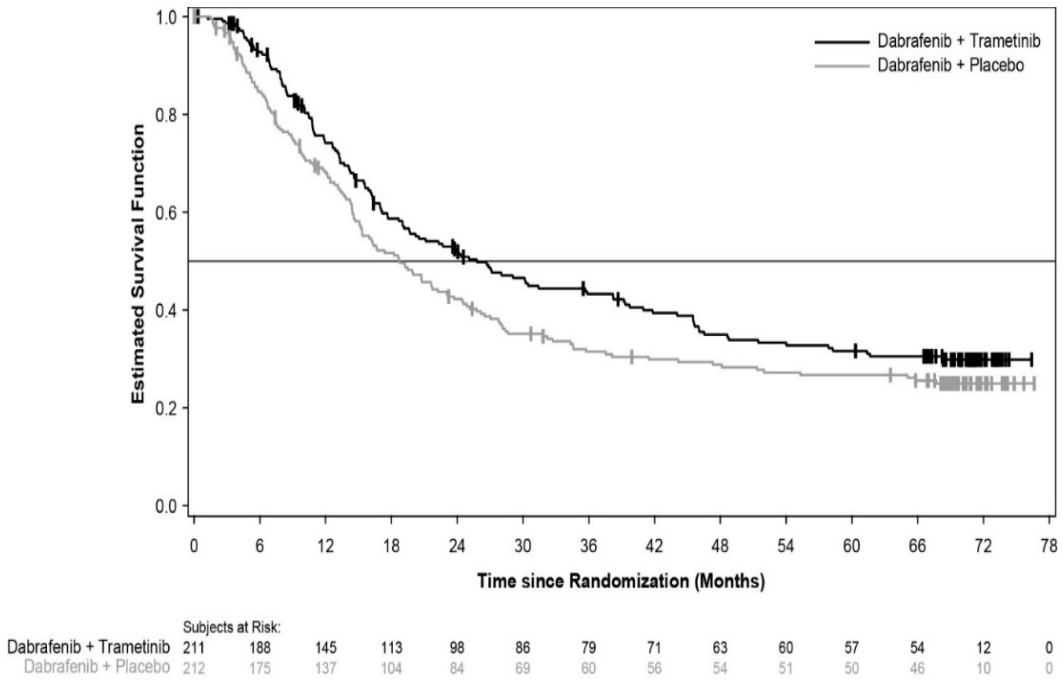
	OS analysis*		**3-year OS analysis***		**5-year OS analysis***	
	Dabrafenib + Trametinib (n=211)	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**
Number of Patients						
Died (event), n (%)	99 (47)	123 (58)	114 (54)	139 (66)	135 (64)	151 (71)
Estimates of OS (months)						
Median (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.7)	26.7 (19.0, 38.2)	18.7 (15.2, 23.1)	25.8 (19.2, 38.2)	18.7 (15.2, 23.1)
Hazard ratio (95% CI)	0.71 (0.55, 0.92)		0.75 (0.58, 0.96)		0.80 (0.63, 1.01)	
p-value	0.011		NA		NA	

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

*OS analysis data cut-off: 12-Jan-2015, 3-year OS analysis data cut-off: 15-Feb-2016, 5-year OS analysis data cut-off: 10-Dec-2018

NR = Not reached, NA = Not applicable

Figure 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 in Table 10.

Table 10: 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[f] (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-	0.035		<0.001		NA		NA	

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

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

a- Confidence interval

b- Overall Response Rate = Complete Response + Partial Response

c- CR: Complete Response, PR: Partial Response

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

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

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

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

NR = Not reached

NA=Not applicable

MEK116513 (COMBI-v)

Study MEK116513 was a two-arm, randomized, open-label, Phase III study comparing Dabrafenib (as mesylate) [Tafinlar] and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive 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 (Dabrafenib (as mesylate) [Tafinlar] 150 mg twice daily and trametinib 2 mg once 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 11, 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 11 Overall Survival results for Study MEK116513 (COMBI-v)

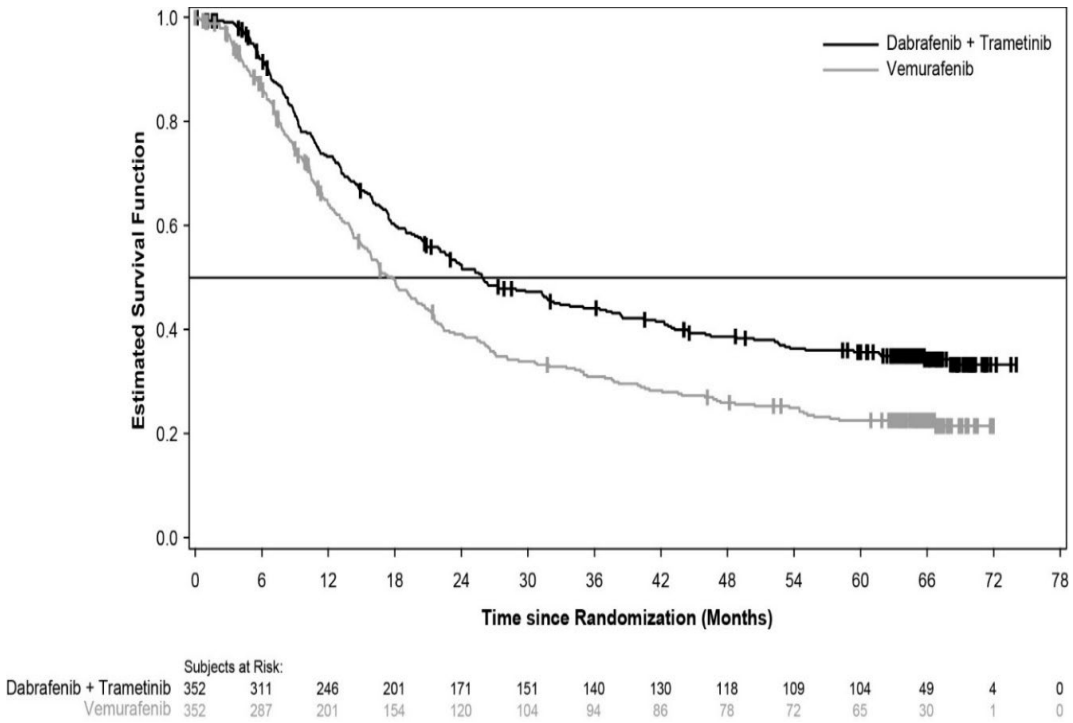
	OS analysis*		**3-year OS analysis***		**5-year OS analysis***	
	Dabrafenib + Trametinib (n=352)	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
Number of patients						
Died (event), n (%)	100 (28)	122 (35)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

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

NR = Not reached, NA = Not applicable

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

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



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

Table 12 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			NA		NA	

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)
response rate (CR+PR), % 95% CI for difference	13 (5.7, 20.2)					
P value	0.0005		NA		NA	
Duration of Response (months)						
Median (95% CI)	13.8 (11.0, NR)	7.5 (7.3, 9.3)	13.8 (11.3, 17.7)	7.9 (7.4, 9.3)	13.8 (11.3, 18.6)	8.5 (7.4, 9.3)

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

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

The efficacy and safety of Dabrafenib (as mesylate) [Tafinlar] in combination with Trametinib (as dimethyl sulfoxide) [Mekinist] 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 or1.
- 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 13 Secondary endpoints were duration of intracranial response, ORR, PFS and OS. Efficacy results are summarized in Table 13.

Table 13 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*				

Advanced NSCLC

Study E2201 (BRF113928)

The efficacy and safety of Dabrafenib (as mesylate) [Tafinlar] in combination with Trametinib (as dimethyl sulfoxide) [Mekinist] 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 (as mesylate) [Tafinlar] 150 mg twice daily): 84 patients enrolled. 78 patients had previous systemic treatment for their metastatic disease.
- Cohort B (n=57): Combination therapy (Dabrafenib (as mesylate) [Tafinlar] 150 mg twice daily and trametinib 2 mg once 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 (Dabrafenib (as mesylate) [Tafinlar] 150 mg twice daily and Trametinib (as dimethyl sulfoxide) [Mekinist] 2 mg once 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 a for 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 primary endpoint, the investigator-assessed ORR was 61.1% (95% CI, 43.5, 76.9) in the first-line population and 66.7% (95% CI, 52.9%, 78.6%) in the previously treated population. These results met the statistical significance to reject the null hypothesis that the ORR of Trametinib (as dimethyl sulfoxide) [Mekinist] in combination with Dabrafenib (as mesylate) [Tafinlar] for both NSCLC population was less than or equal to 30%.

The ORR results assessed by IRC were consistent to the investigator assessment (Table 14).

The efficacy of the combination with trametinib was superior when indirectly compared to Dabrafenib (as mesylate) [Tafinlar] monotherapy in Cohort A. The final analysis of efficacy performed 5 years after last subject first dose is presented in Table 14.

Table 14 Efficacy Results in Patients with BRAF V600E NSCLC

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

Dabrafenib (as mesylate) [Tafinlar] Monotherapy:

At the time of the primary objective analysis for Cohort A, ORR as per investigator assessment was observed in 32.1% of second line plus all treated patients (95% CI: 21.9, 43.6). Partial response was the best response among all these patients. At a subsequent data cut for mature DoR, the estimated median DoR was 9.6 months (95% CI: 5.4, 15.2). The estimated median PFS was 5.5 months (95% CI: 3.4, 7.3). With an additional 18 months of

follow-up from the primary objective analysis for Cohort A to determine a mature OS, the estimated median OS was 12.7 months (95% CI: 7.3, 16.3).

Other Studies

Pyrexia Management Analysis

Pyrexia is observed in patients treated with Dabrafenib (as mesylate) [Tafinlar] and Trametinib (as dimethyl sulfoxide) [Mekinist] 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 (as mesylate) [Tafinlar] in case of pyrexia. In two subsequent studies in unresectable or metastatic melanoma (COMBI-i control arm, N=264) and in the adjuvant melanoma setting (COMBI-Aplus, N=552), interruption of both Dabrafenib (as mesylate) [Tafinlar] and Trametinib (as dimethyl sulfoxide) [Mekinist] 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% vs 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

Cardiovascular effects, including coronary arterial degeneration/necrosis and/or hemorrhage, cardiac atrioventricular valve hypertrophy/hemorrhage and atrial fibrovascular proliferation were seen in dogs (≥2 times clinical exposure based on AUC). Focal arterial/perivascular inflammation in various tissues was observed in mice and an increased incidence of hepatic arterial degeneration and spontaneous cardiomyocyte degeneration with inflammation (spontaneous cardiomyopathy) was observed in rats (≥0.5 and 0.6 times clinical exposure for rats and mice, respectively). Hepatic effects, including hepatocellular necrosis and inflammation were observed in mice (≥0.6 times clinical exposure). Bronchoalveolar inflammation of the lungs was observed in several dogs at ≥ 20 mg/kg/day (≥9 times human clinical exposure based on AUC) and was associated with shallow and/or laboured breathing.

Reversible hematological effects have been observed in dogs and rats given dabrafenib. In studies of up to 13 weeks, decreases in reticulocyte counts and/or red cell mass were observed in dogs and rats (≥10 and 1.4 times clinical exposure, respectively).

Dabrafenib was phototoxic in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay and *in vivo* at doses ≥ 100 mg/kg (>44 times clinical exposure based on C_{max}) in an oral phototoxicity study in hairless mice. Although dabrafenib was phototoxic in nonclinical studies, based on clinical safety data, there is low risk for phototoxicity to patients taking Dabrafenib (as mesylate) [Tafinlar].

Carcinogenicity and mutagenicity

Carcinogenicity studies with dabrafenib have not been conducted. Dabrafenib was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay.

Reproductive toxicity

Embryofetal development and fertility

In combined female fertility, early embryonic and embryofetal development studies in rats numbers of ovarian corpora lutea were reduced in pregnant females at 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC), but there were no effects on estrous cycle, mating or fertility. Developmental toxicity including embryo-lethality and ventricular septal defects and variation in thymic shape were seen at 300 mg/kg/day, and delayed skeletal development and reduced foetal body weight at ≥20 mg/kg/day (≥0.5 times human clinical exposure based on AUC) (see also section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL - ANIMAL DATA).

Male fertility studies with dabrafenib have not been conducted. However, in repeat dose studies, testicular degeneration/depletion was seen in rats and dogs (≥0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period.

Juvenile animal studies

In juvenile toxicity studies in rats, effects on growth (shorter long bone length), renal toxicity (tubular deposits, increased incidence of cortical cysts and tubular basophilia and reversible increases in urea and/or creatinine concentrations) and testicular toxicity (degeneration and tubular dilation) were observed (≥0.2 times adult human clinical exposure based on AUC).

Non-fixed dose combination therapy

Dabrafenib (as mesylate) [Tafinlar] in combination with Trametinib (as dimethyl sulfoxide) [Mekinist]

Dogs given Dabrafenib (as mesylate) [Tafinlar] and trametinib in combination for 4 weeks demonstrated similar toxicities to those observed in comparable monotherapy studies. Refer to the full prescribing information for Trametinib (as dimethyl sulfoxide) [Mekinist].

Pharmaceutical information

Incompatibilities

Not applicable.

AVAILABILITY

50 mg, and 75 mg Capsules: Opaque white HDPE bottle with polypropylene child resistant closure (Bottle x 28's, and 120's)

STORAGE

Do not store above 30ºC.

The drug should not be used after the date marked "EXP" on the pack.

Drugs should 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.

Special precautions for disposal

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

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**

The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

Manufactured by:

Glaxo Operations UK Limited (trading as Glaxo Wellcome Operations)
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Packed by:

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Imported by:

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Registration Number/Date of First Authorization:
50 mg Capsule: DR-XY44999/ 2 February 2016
75 mg Capsule: DR-XY44998/ 2 February 2016

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