# Tafinlar® 50 mg

# Tafinlar®75 mg

## 1. NAME OF THE MEDICINAL PRODUCT

Tafinlar® 50 mg
Tafinlar® 75 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule

Tafinlar 50 mg hard capsules
Opaque dark red capsules, approximately 18 mm long, with capsule shell imprinted with 'GS TEW' and '50 mg'.

Tafinlar 75 mg hard capsules
Opaque dark pink capsules, approximately 19 mm long, with capsule shell imprinted with 'GS LHF' and '75 mg'.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1).

### 4.2 Posology and method of administration

Treatment with dabrafenib should be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products.

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

The efficacy and safety of dabrafenib have not been established in patients with wild-type

BRAF melanoma therefore dabrafenib should not be used in patients with BRAF wild-type melanoma (see sections 4.4 and 5.1).

Posology

The recommended dose of dabrafenib, either used as monotherapy or in combination with trametinib, is 150 mg (two 75 mg capsules) twice daily (corresponding to a total daily dose of 300 mg). The recommended dose of trametinib, when used in combination with dabrafenib, is 2 mg once daily.

*Duration of treatment*

Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity (see Table 2).

*Missed doses*

If a dose of dabrafenib is missed, it should not be taken if it is less than 6 hours until the next dose.

If a dose of trametinib is missed, when dabrafenib is given in combination with trametinib, only take the dose of trametinib if it is more than 12 hours until the next scheduled dose.

*Dose modification*

Two dabrafenib capsule strengths, 50 mg and 75 mg, are available to effectively manage dose modification requirements.

The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation (see Tables 1 and 2).

Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (see section 4.4).

Therapy should be interrupted if the patient's temperature is ≥38.5ºC. Patients should be evaluated for signs and symptoms of infection (see section 4.4).

No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, withhold dabrafenib until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level (see section 4.4).

Recommended dose level reductions and recommendations for dose modifications are provided in Tables 1 and 2, respectively.

Table 1 Recommended dose level reductions

| **Dose level** | **Dabrafenib dose**<br>Used as monotherapy or in combination with trametinib | **Trametinib dose***<br>Only when used in combination with dabrafenib |
|---|---|---|
| Starting dose | 150 mg twice daily | 2 mg once daily |
| 1st dose reduction | 100 mg twice daily | 1.5 mg once daily |
| 2nd dose reduction | 75 mg twice daily | 1 mg once daily |

| | | |
|---|---|---|
| 3rd dose reduction | 50 mg twice daily | 1 mg once daily |
| Dose adjustment for dabrafenib below 50 mg twice daily is not recommended, whether used as monotherapy or in combination with trametinib. Dose adjustment for trametinib below 1 mg once daily is not recommended, when used in combination with dabrafenib. | | |
| *Please refer to the trametinib SmPC, Posology and method of administration, for dosing instructions for treatment with trametinib monotherapy. | | |

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

| **Grade (CTC-AE)*** | **Recommended dabrafenib dose modifications**<br>Used as monotherapy or in combination with trametinib |
|---|---|
| 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 (CTC-AE) v4.0 | |

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 dose should not exceed 150 mg twice daily.

If treatment-related toxicities occur when dabrafenib is used in combination with trametinib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for only one of the two treatments are detailed below for pyrexia, uveitis, RAS mutation positive non-cutaneous malignancies, left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and interstitial lung disease (ILD)/pneumonitis (primarily related to trametinib).

*Dose modification exceptions (where only one of the two therapies is dose reduced) for selected adverse reactions*

*Pyrexia*
When dabrafenib is used alone and in combination with trametinib, therapy with dabrafenib should be interrupted if the patient's temperature is ≥38.5$^{o}$C (please refer to Table 2 for dose modification guidance). Trametinib should be continued at the same dose. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection and if necessary treated in line with local practice (see section 4.4).

Upon resolution of pyrexia dabrafenib should be restarted with appropriate anti-pyretic prophylaxis, either 1) at the same dose level, or 2) reduced by one dose level if the pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure.

*Uveitis*
No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, dabrafenib should be withheld until resolution of ocular inflammation and then dabrafenib should be restarted

reduced by one dose level. No dose modification of trametinib is required when taken in combination with dabrafenib (see section 4.4).

*RAS-mutation-positive non-cutaneous malignancies*
The benefits and risks should be considered before continuing treatment with dabrafenib in patients with a non-cutaneous malignancy that has a RAS mutation. No dose modification of trametinib is required when taken in combination with dabrafenib.

*Left ventricular ejection fraction (LVEF) reduction/Left ventricular dysfunction*
If dabrafenib is being used in combination with trametinib and absolute decrease of >10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN), please refer to the trametinib SmPC (see section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib.

*Retinal vein occlusion (RVO) and Retinal pigment epithelial detachment (RPED)*
If patients report new visual disturbances such as diminished central vision, blurred vision, or loss of vision at any time while on combination therapy with dabrafenib and trametinib, please refer to the trametinib SmPC (see section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib for confirmed cases of RVO or RPED.

*Interstitial lung disease (ILD)/Pneumonitis*
In patients treated with dabrafenib in combination with trametinib with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations, please refer to the trametinib SmPC (see section 4.2) for dose modification instructions for trametinib. No dose modification of dabrafenib is required when taken in combination with trametinib for cases of ILD or pneumonitis.

*Non-Caucasian patients*

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

*Elderly*

No adjustment of the initial dose is required in patients >65 years of age.

*Renal impairment*

No dose adjustment is required for patients with mild or moderate renal impairment. There are no clinical data in subjects with severe renal impairment and the potential need for dose adjustment cannot be determined (see section 5.2). Dabrafenib should be used with caution in patients with severe renal impairment when administered as monotherapy or in combination with trametinib.

*Hepatic impairment*

No dose adjustment is required for patients with mild hepatic impairment. There are no clinical data in subjects with moderate to severe hepatic impairment and the potential need for dose adjustment cannot be determined (see section 5.2). Hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites and patients with moderate to severe hepatic impairment may have increased exposure. Dabrafenib should be used with caution in patients with moderate or severe hepatic impairment when

administered as monotherapy or in combination with trametinib.

*Paediatric population*

The safety and efficacy of dabrafenib have not yet been established in children and adolescents (<18 years). No clinical data are available. Studies in juvenile animals have shown adverse effects of dabrafenib which had not been observed in adult animals (see section 5.3).

Method of administration

The dabrafenib capsules are to be swallowed whole with water. The capsules should not be chewed or opened and should not be mixed with food or liquids due to chemical instability of dabrafenib.

It is recommended that the doses of dabrafenib be taken at similar times every day, leaving an interval of approximately 12 hours between doses. When dabrafenib 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.

Dabrafenib should be taken at least one hour before, or at least 2 hours after a meal.

If a patient vomits after taking dabrafenib, the patient should not retake the dose and should take the next scheduled dose.

Please refer to trametinib SmPC for information on method of administration when given in combination with dabrafenib.

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

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

BRAF V600 testing

The efficacy and safety of dabrafenib have not been established in patients with wild-type BRAF melanoma therefore dabrafenib should not be used in patients with wild-type BRAF melanoma (see sections 4.2 and 5.1).

Dabrafenib in combination with trametinib in patients who have progressed on a BRAF inhibitor

There are limited data in patients taking the combination of dabrafenib with trametinib who have progressed on a prior BRAF inhibitor. These data show that the efficacy of the combination will be lower in these patients (see section 5.1). Therefore, other treatment options should be considered before treatment with the combination in this prior BRAF inhibitor treated population. The sequencing of treatments following progression on a BRAF inhibitor therapy has not been established.

Trametinib in combination with dabrafenib in patients with brain metastases

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

New malignancies

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

*Cutaneous squamous cell carcinoma (cuSCC)*

Cases of cuSCC (including keratoacanthoma) have been reported in patients treated with dabrafenib alone and in combination with trametinib (see section 4.8). In the Phase III study MEK115306, cuSCC occurred in 3% (6/209) of patients receiving trametinib in combination with dabrafenib and 10% (22/211) of patients receiving dabrafenib as a single agent. In the Phase III study MEK116513, cuSCC occurred in 1% (5/350) of patients receiving trametinib in combination with dabrafenib and 18% (63/349) of patients receiving vemurafenib as a single agent. The median time to diagnosis of the first occurrence of cuSCC in study MEK115306 was 223 days (range 56 to 510 days) in the combination therapy arm and 60 days (range 9 to 653 days) in the dabrafenib monotherapy arm.

It is recommended that skin examination be performed prior to initiation of therapy with dabrafenib and monthly throughout treatment and for up to six months after treatment for cuSCC. Monitoring should continue for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy.

Cases of cuSCC should be managed by dermatological excision and dabrafenib treatment or, if taken in combination, dabrafenib and trametinib 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 clinical trials in patients treated with dabrafenib. These cases were identified within the first 5 months of dabrafenib as monotherapy. Cases of new primary melanoma can be managed with excision and do not require treatment modification. Monitoring for skin lesions should occur as described for cuSCC.

*Non-cutaneous secondary/recurrent malignancy*

*In vitro* experiments have demonstrated paradoxical activation of mitogen-activated protein kinase (MAP kinase) signalling in BRAF wild-type cells with RAS mutations when exposed to BRAF inhibitors. This may lead to increased risk of non-cutaneous malignancies with dabrafenib exposure (see section 4.8) when RAS mutations are present. RAS-associated malignancies have been reported in clinical trials, both with another BRAF inhibitor (chronic myelomonocytic leukaemia and non-cutaneous SCC of the head and neck) as well as with dabrafenib monotherapy (pancreatic adenocarcinoma, bile duct adenocarcinoma) and with dabrafenib in combination with the MEK inhibitor, trametinib (colorectal cancer, pancreatic cancer).

Prior to initiation of treatment patients should undergo a head and neck examination with minimally visual inspection of oral mucosa and lymph node palpation, as well as

chest/abdomen computerised tomography (CT) scan. During treatment patients should be monitored as clinically appropriate which may include a head and neck examination every 3 months and a chest/abdomen CT scan every 6 months. Anal examinations and pelvic examinations (for women) are recommended before and at the end of treatment or when considered clinically indicated. Complete blood cell counts should be performed as clinically indicated.

Carefully consider benefits and risks before administering dabrafenib to patients with a prior or concurrent cancer associated with RAS mutations. No dose modification of trametinib is required when taken in combination with dabrafenib.

Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.

Haemorrhage

Haemorrhagic events, including major haemorrhagic and fatal haemorrhages, have occurred in patients taking the combination of dabrafenib with trametinib (see section 4.8). Please refer to the trametinib SmPC for additional information (see section 4.4).

Visual impairment

In clincial trials ophthalmologic reactions, including uveitis, iridocyclitis and iritis, have been reported in patients treated with dabrafenib as monotherapy and in combination with trametinib. Patients should be routinely monitored for visual signs and symptoms (such as change in vision, photophobia and eye pain) while on therapy.

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 until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level. No dose modification of trametinib is required when taken in combination with dabrafenib following diagnosis of uveitis.

RPED and RVO may occur with dabrafenib in combination with trametinib. Please refer to the trametinib SmPC (see section 4.4). No dose modification of dabrafenib is required when taken in combination with trametinib following diagnosis of RVO or RPED.

Pyrexia

Fever has been reported in clinical trials with dabrafenib as monotherapy and in combination with trametinib (see section 4.8). In 1% of patients in clinical trials with dabrafenib monotherapy, serious non-infectious febrile events were identified defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency of pre-renal origin in subjects with normal baseline renal function (see section 4.8). The onset of these serious non-infectious febrile events was typically within the first month of dabrafenib as monotherapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care.

The incidence and severity of pyrexia are increased with combination therapy. In the combination therapy arm of study MEK115306 pyrexia was reported in 57% (119/209) of patients with 7% Grade 3, as compared to the dabrafenib monotherapy arm with 33% (69/211) of patients reporting pyrexia, 2% Grade 3.

For patients who received dabrafenib in combination with trametinib and developed pyrexia,

approximately half of the first occurrences of pyrexia happened within the first month of therapy and approximately one-third of the patients had 3 or more events.

Therapy with dabrafenib should be interrupted if the patient's temperature is ≥38.5ºC (please refer to Table 2 for dose modification guidance). Patients should be evaluated for signs and symptoms of infection. Dabrafenib can be restarted once the fever resolves with appropriate prophylaxis using non-steroidal anti-inflammatory medicinal products or paracetamol. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. If fever is associated with other severe signs or symptoms, dabrafenib should be restarted at a reduced dose once fever resolves and as clinically appropriate (see section 4.2). No dose modification of trametinib is required when taken in combination with dabrafenib.

LVEF reduction/Left ventricular dysfunction

Dabrafenib in combination with trametinib has been reported to decrease LVEF (see section 4.8). Please refer to the trametinib SmPC for additional information (see section 4.4). No dose modification of dabrafenib is required when taken in combination with trametinib.

Renal failure

Renal failure has been identified in <1% of patients treated with dabrafenib alone and in ≤1% of patients treated with dabrafenib in combination with trametinib. Observed cases were generally associated with pyrexia and dehydration and responded well to dose interruption and general supportive measures. Granulomatous nephritis has been reported (see section 4.8). Patients should be routinely monitored for serum creatinine while on therapy. If creatinine increases, dabrafenib may need to be interrupted as clinically appropriate. Dabrafenib has not been studied in patients with renal insufficiency (defined as creatinine >1.5 x ULN) therefore caution should be used in this setting (see section 5.2).

Hepatic events

Hepatic adverse events have been reported in clinical trials with dabrafenib in combination with trametinib (see section 4.8). It is recommended that patients receiving treatment with dabrafenib in combination with trametinib have liver function monitored every four weeks for 6 months after treatment initiation with trametinib. Liver monitoring may be continued thereafter as clinically indicated. Please refer to the trametinib SmPC for additional information.

Hypertension

Elevations in blood pressure have been reported in association with dabrafenib in combination with trametinib, in patients with or without pre-existing hypertension (see section 4.8). Please refer to the trametinib SmPC for additional information.

Interstitial lung disease (ILD)/Pneumonitis

Cases of pneumonitis or ILD have been reported in clinical trials with dabrafenib in combination with trametinib. Please refer to the trametinib SmPC section 4.4 for additional information. If dabrafenib is being used in combination with trametinib then therapy with dabrafenib may be continued at the same dose.

Rash

Rash has been observed in about 25% of patients in clincial studies when dabrafenib is used in combination with trametinib. Please refer to the trametinib SmPC section 4.4 for additional

information.

Rhabdomyolysis

Rhabdomyolysis has been reported in patients taking dabrafenib in combination with trametinib (see section 4.8). Please refer to the trametinib SmPC section 4.4 for additional information.

Pancreatitis

Pancreatitis has been reported in <1% of dabrafenib-treated subjects as monotherapy and in combination with trametinib. One of the events occurred on the first day of dabrafenib dosing 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 after an episode of pancreatitis.

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

Pulmonary embolism or deep vein thrombosis can occur when dabrafenib is used in combination with trametinib. If patients develop symptoms of pulmonary embolism or deep vein thrombosis such as shortness of breath, chest pain, or arm or leg swelling, they should immediately seek medical care. Permanently discontinue trametinib and dabrafenib for life-threatening pulmonary embolism.

Effects of other substances on dabrafenib

Dabrafenib is a substrate of CYP2C8 and CYP3A4. Potent inducers of these enzymes should be avoided when possible as these agents may decrease the efficacy of dabrafenib (see section 4.5).

Agents that increase gastric pH might decrease the bioavailability of dabrafenib and should be avoided when possible (see section 4.5).

Effects of dabrafenib on other substances

Dabrafenib is an inducer of metabolising enzymes which may lead to loss of efficacy of many commonly used medicinal products (see examples in section 4.5). A drug utilisation review (DUR) is therefore essential when initiating dabrafenib treatment. Concomitant use of dabrafenib with medicinal products that are sensitive substrates of certain metabolising enzymes or transporters (see section 4.5) should generally be avoided if monitoring for efficacy and dose adjustment is not possible.

Concomitant administration of dabrafenib with warfarin results in decreased warfarin exposure. Caution should be exercised and additional International Normalized Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin and at discontinuation of dabrafenib (see section 4.5).

Concomitant administration of dabrafenib with digoxin may result in decreased digoxin exposure. Caution should be exercised and additional monitoring of digoxin is recommended when digoxin (a transporter substrate) is used concomitantly with dabrafenib and at discontinuation of dabrafenib (see section 4.5).

## 4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on dabrafenib

Dabrafenib is a substrate for the metabolising enzymes CYP2C8 and CYP3A4, while the active metabolites hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates. Medicinal products that are strong inhibitors or inducers of CYP2C8 or CYP3A4 are therefore likely to increase or decrease, respectively, dabrafenib concentrations. Alternative agents should be considered during administration with dabrafenib when possible. Use caution if strong inhibitors (e.g. ketoconazole, gemfibrozil, nefazodone, clarithromycin, ritonavir, saquinavir, telithromycin, itraconazole, voriconazole, posaconazole, atazanavir) are co-administered with dabrafenib. Avoid co-administration of dabrafenib with potent inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, or St John's wort (*Hypericum perforatum*)) of CYP2C8 or CYP3A4.

Administration of ketoconazole (a CYP3A4 inhibitor) 400 mg once daily, with dabrafenib 75 mg twice daily, resulted in a 71% increase in dabrafenib AUC and a 33% increase in dabrafenib $C_{max}$ relative to administration of dabrafenib 75 mg twice daily alone. Co-administration resulted in increases in hydroxy- and desmethyl-dabrafenib AUC (increases of 82% and 68%, respectively). A decrease of 16% in AUC was noted for carboxy-dabrafenib.

Administration of gemfibrozil (a CYP2C8 inhibitor) 600 mg twice daily, with dabrafenib 75 mg twice daily, resulted in a 47% increase in dabrafenib AUC but did not alter dabrafenib $C_{max}$ relative to administration of dabrafenib 75 mg twice daily alone. Gemfibrozil had no clinically relevant effect on the systemic exposure to dabrafenib metabolites (≤13%).

Dabrafenib solubility is pH-dependent with decreased solubility at higher pH. Medicinal products such as proton pump inhibitors that inhibit gastric acid secretion to elevate gastric pH may decrease the solubility of dabrafenib and reduce its bioavailability. No clinical study has been conducted to evaluate the effect of pH on dabrafenib pharmacokinetics. Due to the theoretical risk that pH-elevating agents may decrease oral bioavailability and exposure to dabrafenib, these medicinal products that increase gastric pH should, if possible, be avoided during treatment with dabrafenib.

Effect of dabrafenib on other medicinal products

Dabrafenib is an enzyme inducer and increases the synthesis of drug-metabolising enzymes including CYP3A4, CYP2Cs and CYP2B6 and may increase the synthesis of transporters. This results in reduced plasma levels of medicinal products metabolised by these enzymes, and may affect some transported medicinal products. The reduction in plasma concentrations can lead to lost or reduced clinical effect of these medicinal products. There is also a risk of increased formation of active metabolites of these medicinal products. Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and UGTs (glucuronide conjugating enzymes). The transport protein Pgp may also be induced as well as other transporters, e.g. MRP-2, BCRP and OATP1B1/1B3.

*In vitro*, dabrafenib produced dose-dependent increases in CYP2B6 and CYP3A4. In a clinical drug interaction study, $C_{max}$ and AUC of oral midazolam (a CYP3A4 substrate) decreased by 61% and 74%, respectively with co-administration of repeat-dose dabrafenib using a formulation with lower bioavailability than dabrafenib formulation.

Administration of dabrafenib 150 mg twice daily and warfarin resulted in a decrease in AUC of S- and R- warfarin and of 37% and 33% compared to administration of warfarin alone. $C_{max}$ of S- and R-warfarin increased 18% and 19%.

Interactions with many medicinal products eliminated through metabolism or active transport is expected. If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations, these medicinal products are to be avoided or used with caution. The risk for liver injury after paracetamol administration is suspected to be higher in patients concomitantly treated with enzyme inducers.

The number of affected medicinal products is expected to be large; although the magnitude of the interaction will vary. Groups of medicinal products that can be affected include, but are not limited to:

- Analgesics (e.g. fentanyl, methadone)
- Antibiotics (e.g. clarithromycin, doxycycline)
- Anticancer agents (e.g. cabazitaxel)
- Anticoagulants (e.g. acenocoumarol, warfarin, see section 4.4)
- Antiepileptic (e.g. carbamazepine, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin, see section 4.4)
- Corticosteroids (e.g. dexamethasone, methylprednisolone)
- HIV antivirals (e.g. amprenavir, atazanavir, darunavir, delavirdine, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, tipranavir)
- Hormonal contraceptives (see section 4.6)
- Hypnotics (e.g. diazepam, midazolam, zolpidem)
- Immunosuppressants (e.g. cyclosporin, tacrolimus, sirolimus)
- Statins metabolised by CYP3A4 (e.g. atorvastatin, simvastatin)

Onset of induction is likely to occur after 3 days of repeat dosing with dabrafenib. Upon discontinuation of dabrafenib offset of induction is gradual, concentrations of sensitive CYP3A4, CYP2B6, CYP2C8, CYP2C9 and CYP2C19, UDP glucuronosyl transferase (UGT) and transporter substrates may increase and patients should be monitored for toxicity and dosage of these agents may need to be adjusted.

*In vitro*, dabrafenib is a mechanism based inhibitor of CYP3A4. Therefore, transient inhibition of CYP3A4 may be observed during the first few days of treatment.

Effects of dabrafenib on substance transport systems

Dabrafenib is an *in vitro* inhibitor of of human organic anion transporting polypeptide (OATP) 1B1 (OATP1B1) and OATP1B3 and clinical relevance can not be excluded. Therefore caution is recommended at co-administration of dabrafenib and OATP1B1 or OATP1B3 substrates such as statins.

Although dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, were inhibitors of human organic anion transporter (OAT) 1 and OAT3 *in vitro*, the risk of a drug-drug interaction is minimal based on clinical exposure. Dabrafenib and desmethyl-dabrafenib were also shown to be moderate inhibitors of human breast cancer resistance protein (BCRP); however, based on clinical exposure, the risk of a drug-drug interaction is minimal.

Combination with trametinib

Co-administration of repeat dosing of trametinib 2 mg once daily and dabrafenib 150 mg twice daily resulted in no clinically meaningful changes in trametinib or dabrafenib $C_{max}$ and

AUC with increases of 16 and 23%, respectively, in dabrafenib $C_{max}$ and AUC. A small decrease in trametinib bioavailability, corresponding to a decrease in AUC of 12%, was estimated when trametinib is administered in combination with dabrafenib, a CYP3A4 inducer, using a population PK analysis.

When dabrafenib is used in combination with trametinib refer to the guidance for medicinal product interactions found in sections 4.4 and 4.5 of dabrafenib and trametinib SmPC.

Effect of food on dabrafenib

Patients should take dabrafenib as monotherapy or in combination with trametinib at least one hour prior to or two hours after a meal due to the effect of food on dabrafenib absorption (see section 5.2).

Paediatric population

Interaction studies have only been performed in adults.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential must use effective methods of contraception during therapy and for 4 weeks following discontinuation of dabrafenib and 4 months following the last dose of trametinib when given in combination with dabrafenib. Dabrafenib may decrease the efficacy of hormonal contraceptives and an alternate method of contraception, such as a barrier method, should be used (see section 4.5).

Pregnancy

There are no data from the use of dabrafenib in pregnant women. Animal studies have shown reproductive toxicity and embryofoetal developmental toxicities, including teratogenic effects (see section 5.3). Dabrafenib should not be administered to pregnant women unless the potential benefit to the mother outweighs the possible risk to the foetus. If the patient becomes pregnant while taking dabrafenib, the patient should be informed of the potential hazard to the foetus. Please see trametinib SmPC (see section 4.6) when used in combination with trametinib.

Breast-feeding

It is not known whether dabrafenib is excreted in human milk. Because many medicinal products are excreted in human milk, a risk to the breast-feeding child cannot be excluded. A decision should be made whether to discontinue breast-feeding or discontinue dabrafenib, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data in humans for dabrafenib as monotherapy or in combination with trametinib. Dabrafenib may impair male and female fertility as adverse effects on male and female reproductive organs have been seen in animals (see section 5.3). Male patients taking dabrafenib as monotherapy or in combination with trametinib should be informed of the potential risk for impaired spermatogenesis, which may be irreversible.

## 4.7 Effects on ability to drive and use machines

Dabrafenib has minor influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of dabrafenib should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills. Patients should be made aware of the potential for fatigue and eye problems to affect these activities.

## 4.8 Undesirable effects

Summary of the safety profile

The dabrafenib monotherapy safety profile is based on data from five clinical studies and included 578 patients with melanoma. The most frequently occurring adverse drug reactions (ADRs) (≥15%) reported with dabrafenib were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, papilloma, alopecia, rash and vomiting.

The safety of dabrafenib in combination with trametinib has been evaluated in 2 Phase III studies, MEK115306 and MEK116513, where an analysis of the safety of dabrafenib in combination with trametinib has been conducted in 209 and 350 patients, respectively, with BRAF V600 mutation positive unresectable or metastatic melanoma receiving dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) combination therapy (see information on combination therapy in section 5.1). The most common adverse reactions (≥20%) for dabrafenib and trametinib combination therapy include pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, vomiting and cough.

Tabulated summary of adverse reactions

ADRs which were reported are listed below by MedDRA body system organ class and by frequency. The following convention has been utilised for the classification of frequency:

| | |
|---|---|
| Very common | ≥1/10 |
| Common | ≥1/100 to <1/10 |
| Uncommon | ≥1/1,000 to <1/100 |
| Rare | ≥1/10,000 to <1/1,000 |
| Not known | (cannot be estimated from the available data) |

*Dabrafenib monotherapy*

Table 3 Adverse reactions reported in melanoma trials

| System Organ Class | Frequency (all grades) | Adverse Reactions |
|---|---|---|
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | Very common | Papilloma |
| | Common | Cutaneous squamous cell carcinoma |
| | | Seborrhoeic keratosis |
| | | Acrochordon (skin tags) |
| | | Basal cell carcinoma |
| | Uncommon | New primary melanoma |
| **Immune system disorders** | Uncommon | Hypersensitivity |
| **Metabolism and nutrition disorders** | Very common | Decreased appetite |
| | Common | Hypophosphataemia |
| | | Hyperglycaemia |
| **Nervous system disorders** | Very common | Headache |

| | | |
|---|---|---|
| **Eye disorders** | Uncommon | Uveitis |
| **Respiratory, thoracic and mediastinal disorders** | Very common | Cough |
| **Gastrointestinal disorders** | Very common | Nausea |
| | | Vomiting |
| | | Diarrhoea |
| | Common | Constipation |
| | Uncommon | Pancreatitis |
| **Skin and subcutaneous tissue disorders** | Very common | Hyperkeratosis |
| | | Alopecia |
| | | Rash |
| | | Palmar –plantar erythrodysaesthesia syndrome |
| | Common | Dry skin |
| | | Pruritus |
| | | Actinic keratosis |
| | | Skin lesion |
| | | Erythema |
| | Uncommon | Panniculitis |
| **Musculoskeletal and connective tissue disorders** | Very common | Arthralgia |
| | | Myalgia |
| | | Pain in extremity |
| **Renal and urinary disorders** | Uncommon | Renal failure, acute renal failure |
| | | Nephritis |
| **General disorders and administration site conditions** | Very common | Pyrexia |
| | | Fatigue |
| | | Chills |
| | | Asthenia |
| | Common | Influenza-like illness |
| **Investigations** | Common | LVEF decrease |
| | Uncommon | QT prolongation |

*Dabrafenib and trametinib combination therapy*

Table 4 Adverse reactions occurring in the two randomised Phase III combination studies MEK115306 (n=209) and MEK116513[a] (n=350)

| System Organ Class | Frequency (all grades) | Adverse Reactions |
|---|---|---|
| **Infections and infestations** | Very common | Urinary tract infection |
| | | Nasopharyngitis |
| | Common | Cellulitis |
| | | Folliculitis |
| | | Paronychia |
| | | Rash pustular |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | Common | Cutaneous squamous cell carcinoma[b] |
| | | Papilloma[c] |
| | | Seborrhoeic keratosis |
| | | Acrochordon (skin tags) |
| | Uncommon | New primary melanoma |
| **Blood and lymphatic system disorders** | Very common | Neutropenia |
| | Common | Anaemia |
| | | Thrombocytopenia |

| | | |
|---|---|---|
| | | Leukopenia |
| **Immune system disorders** | Uncommon | Drug Hypersensitivity |
| **Metabolism and nutrition disorders** | Very common | Decreased appetite |
| | Common | Dehydration |
| | | Hyponatraemia |
| | | Hypophosphataemia |
| | | Hyperglycaemia |
| **Nervous system disorders** | Very common | Headache |
| | | Dizziness |
| **Eye disorders** | Common | Vision blurred |
| | | Visual impairment |
| | Uncommon | Chorioretinopathy |
| | | Uveitis |
| | | Retinal detachment |
| | | Periorbital oedema |
| **Cardiac disorder** | Common | Ejection fraction decreased |
| | | Bradycardia |
| **Vascular disorders** | Very common | Hypertension |
| | | Haemorrhage[d] |
| | Common | Hypotension |
| | Uncommon | Lymphoedema[a] |
| **Respiratory, thoracic and mediastinal disorders** | Very common | Cough |
| | Common | Dyspnoea |
| | Uncommon | Pneumonitis |
| **Gastrointestinal disorders** | Very common | Abdominal pain |
| | | Constipation |
| | | Diarrhoea |
| | | Nausea |
| | | Vomiting |
| | Common | Dry mouth |
| | | Stomatitis |
| | Uncommon | Pancreatitis |
| **Hepatobiliary disorder** | Very common | Alanine aminotransferase increased |
| | | Aspartate aminotransferase increased |
| | Common | Blood alkaline phosphatase increased |
| | | Gamma-glutamyltransferase increased |
| **Skin and subcutaneous disorders** | Very common | Dry skin |
| | | Pruritus |
| | | Rash |
| | | Dermatitis acneiform |
| | Common | Erythema |
| | | Actinic keratosis |
| | | Night sweats |
| | | Hyperkeratosis |
| | | Alopecia |
| | | Palmar-plantar erythrodysaesthesia syndrome |
| | | Skin lesion |
| | | Hyperhidrosis |
| | | Panniculitis |

| | | |
|---|---|---|
| | | Skin fissures |
| **Musculoskeletal and connective tissue disorders** | Very common | Arthralgia |
| | | Myalgia |
| | | Pain in extremity |
| | Common | Muscle spasms[a] |
| | | Blood creatine phosphokinase increased |
| **Renal and urinary disorders** | Uncommon | Renal failure[a] |
| | | Nephritis |
| **General disorders and administration site conditions** | Very common | Fatigue |
| | | Chills |
| | | Asthenia |
| | | Oedema peripheral |
| | | Pyrexia |
| | Common | Mucosal inflammation |
| | | Influenza-like illness |
| | | Face oedema |
| **Investigations** | Common | Heart rate decreased |

[a] The safety profile from MEK116513 is generally similar to that of MEK115306 with the following exceptions: 1) The following adverse reactions have a higher frequency category as compared to MEK115306: muscle spasm (very common); renal failure and lymphoedema (common); acute renal failure (uncommon); 2) The following adverse reactions have occurred in MEK116513 but not in MEK115306: cardiac failure, left ventricular dysfunction, interstitial lung disease, rhabdomyolysis (uncommon).
[b] cu SCC: SCC of the skin, SCC *in situ* (Bowen's disease) and keratoacanthoma
[c] Papilloma, skin papilloma
[d] Bleeding from various sites, including intracranial bleeding and fatal bleeding

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il ).

Description of selected adverse reactions

*Cutaneous squamous cell carcinoma*

Cutaneous squamous cell carcinomas (including those classified as keratoacanthoma or mixed keratoacanthoma subtype) occurred in 9% of patients treated with dabrafenib monotherapy in the integrated safety population and 3% of patients treated with dabrafenib in combination with trametinib in MEK115306. With dabrafenib monotherapy, approximately 70% of events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. In patients who received the combination dose of dabrafenib in combination with trametinib, events occurred later with the median time to onset of 22 weeks. Ninety-six percent of patients on dabrafenib monotherapy in the integrated safety population and all patients on combination therapy in the Phase III studies who developed cuSCC continued on treatment without dose modification.

*New primary melanoma*

New primary melanomas have been reported in clinical trials with dabrafenib as monotherapy

and in combination with trametinib. Cases were managed with excision and did not require treatment modification (see section 4.4).

*Non-cutaneous malignancy*

Activation of MAP-kinase signalling in BRAF wild type cells which are exposed to BRAF inhibitors may lead to increased risk of non-cutaneous malignancies, including those with RAS mutations (see section 4.4). In clinical trials non-cutaneous malignancies were reported in 1% (6/586) of patients with dabrafenib monotherapy, and 1% (3/209) of patients in study MEK115306 and <1% (3/350) of patients in study MEK116513 with dabrafenib in combination with trametinib. Cases of RAS-driven malignancies have been seen with dabrafenib as monotherapy and in combination with trametinib. Patients should be monitored as clinically appropriate.

*Haemorrhage*

Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages, have occurred in patients taking dabrafenib in combination with trametinib. Please refer to the trametinib SmPC.

*LVEF reduction/Left ventricular dysfunction*

In the integrated safety population decreased LVEF has been reported in 1% of patients treated with dabrafenib as monotherapy, and 6 to 8% of patients treated with dabrafenib in combination with trametinib in two Phase III clinical trials, with most cases being asymptomatic and reversible. Patients with LVEF lower than the institutional lower limit of normal were not included in clinical trials with dabrafenib. Dabrafenib in combination with trametinib should be used with caution in patients with conditions that could impair left ventricular function.

*Pyrexia*

Fever has been reported in clinical trials with dabrafenib as monotherapy and in combination with trametinib; the incidence and severity of pyrexia are increased with the combination therapy (see section 4.4). For patients who received dabrafenib in combination with trametinib and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy and approximately one-third of the patients had 3 or more events. In 1% of patients receiving dabrafenib as monotherapy in the integrated safety population in clinical trials, serious non-infectious febrile events were identified as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency or pre-renal origin in subjects with normal baseline renal function. The onset of these serious non-infectious febrile events was typically within the first month of therapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care (see sections 4.2 and 4.4).

*Hepatic events*

Hepatic adverse events have been reported in clinical trials with dabrafenib in combination with trametinib. Please refer to the trametinib SmPC.

*Hypertension*

Elevations in blood pressure have been reported in association with dabrafenib in combination with trametinib, in patients with or without pre-existing hypertension. Blood pressure should be measured at baseline and monitored during treatment, with control of

hypertension by standard therapy as appropriate.

*Arthralgia*

Arthralgia was reported very commonly in clinical trials with dabrafenib as monotherapy and in combination with trametinib (approximately 25%) although these were mainly Grade 1 and 2 in severity with Grade 3 occurring uncommonly (<1%) and no Grade 4 occurrences being reported.

*Hypophosphataemia*

Hypophosphataemia has been reported commonly in the integrated safety population in clinical trials with dabrafenib monotherapy (7%) and in combination with trametinib in Phase III trials (3 to 4%). It should be noted that approximately half of these occurrences with dabrafenib monotherapy (4%) and ≤1% with dabrafenib in combination with trametinib were Grade 3 in severity.

*Pancreatitis*

Pancreatitis has been reported in dabrafenib monotherapy and in combination with trametinib. Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis (see section 4.4).

*Renal failure*

Renal failure due to pyrexia-associated pre-renal azotaemia or granulomatous nephritis was uncommon; however dabrafenib has not been studied in patients with renal insufficiency (defined as creatinine >1.5 x ULN). Caution should be used in this setting (see section 4.4).

Special populations

*Elderly*

Of the total number of patients in clinical studies of dabrafenib (N=578), 22% were 65 years of age and older, and 6% were 75 years of age and older. Compared with younger subjects (<65), more subjects ≥65 years old had adverse reactions that led to study drug dose reductions (22% versus 12%) or interruptions (39% versus 27%). In addition, older patients experienced more serious adverse reactions compared to younger patients (41% versus 22%). No overall differences in efficacy were observed between these subjects and younger subjects.

In the Phase III studies MEK115306 (n=209) and MEK116513 (n=350) with dabrafenib in combination with trametinib in patients with unresectable or metastatic melanoma, 56 patients (27%) and 77 patients (22%) respectively were ≥65 years of age, 11 patients (5%) and 21 patients (6%) respectively were ≥75 years of age. The proportion of patients experiencing AEs was similar in those aged <65 years and those aged ≥65 years in both studies. Patients ≥65 years were more likely to experience SAEs and AEs leading to permanent discontinuation of medicinal product, dose reduction and dose interruption than those <65 years.

## 4.9 Overdose

There is no specific treatment for an overdose of dabrafenib. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitor, ATC code: L01XE23

Mechanism of action

Dabrafenib is an inhibitor of RAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50% of melanoma. The most commonly observed BRAF mutation is V600E which accounts for approximately 90% of the BRAF mutations that are seen in melanoma.

Preclinical data generated in biochemical assays demonstrated that dabrafenib inhibits BRAF kinases with activating codon 600 mutations (Table 5).

Table 5 Kinase inhibitory activity of dabrafenib against RAF kinases

| Kinase | Inhibitory concentration 50 (nM) |
|---|---|
| BRAF V600E | 0.65 |
| BRAF V600K | 0.50 |
| BRAF V600D | 1.8 |
| BRAF WT | 3.2 |
| CRAF WT | 5.0 |

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

In subjects with BRAF V600 mutation positive melanoma, administration of dabrafenib resulted in inhibition of tumour phosphorylated ERK relative to baseline.

*Combination with trametinib*

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. Thus, trametinib and dabrafenib inhibit two kinases in this pathway, MEK and RAF, and therefore the combination provides concomitant inhibition of the pathway. The combination of dabrafenib with trametinib has shown anti-tumour activity in BRAF V600 mutation positive melanoma cell lines *in vitro* and delays the emergence of resistance *in vivo* in BRAF V600 mutation positive melanoma xenografts.

*Determination of BRAF mutation status*

Before taking dabrafenib or combination with trametinib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. In the Phase II and III clinical trials, screening for eligibility required central testing for BRAF V600 mutation using a BRAF mutation assay conducted on the most recent tumour sample available. Primary tumour or tumour from a metastatic site was tested with an investigational use only assay (IUO). The IUO is an allele-specific polymerase chain reaction (PCR) assay performed on DNA extracted

from formalin-fixed paraffin-embedded (FFPE) tumour tissue. The assay was specifically designed to differentiate between the V600E and V600K mutations. Only subjects with BRAF V600E or V600K mutation positive tumours were eligible for study participation.

Subsequently, all patient samples were re-tested using the bioMerieux (bMx) THxID BRAF validated assay, which has CE marking. The bMx THxID BRAF assay is an allele-specific PCR performed on DNA extracted from FFPE tumour tissue. The assay was designed to detect the BRAF V600E and V600K mutations with high sensitivity (down to 5% V600E and V600K sequence in a background of wild-type sequence using DNA extracted from FFPE tissue). Non-clinical and clinical studies with retrospective bi-directional Sanger sequencing analyses have shown that the test also detects the less common BRAF V600D mutation and V600E/K601E mutation with lower sensitivity. Of the specimens from the non-clinical and clinical studies (n=876) that were mutation positive by the THxID BRAF assay and subsequently were sequenced using the reference method, the specificity of the assay was 94%.

Clinical efficacy and safety

*Dabrafenib in combination with trametinib*

*Treatment-naïve patients*
The safety and efficacy of the recommended dose of trametinib (2 mg once daily) in combination with dabrafenib (150 mg twice daily) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation was studied in two Phase III studies and one supportive Phase I/II study.

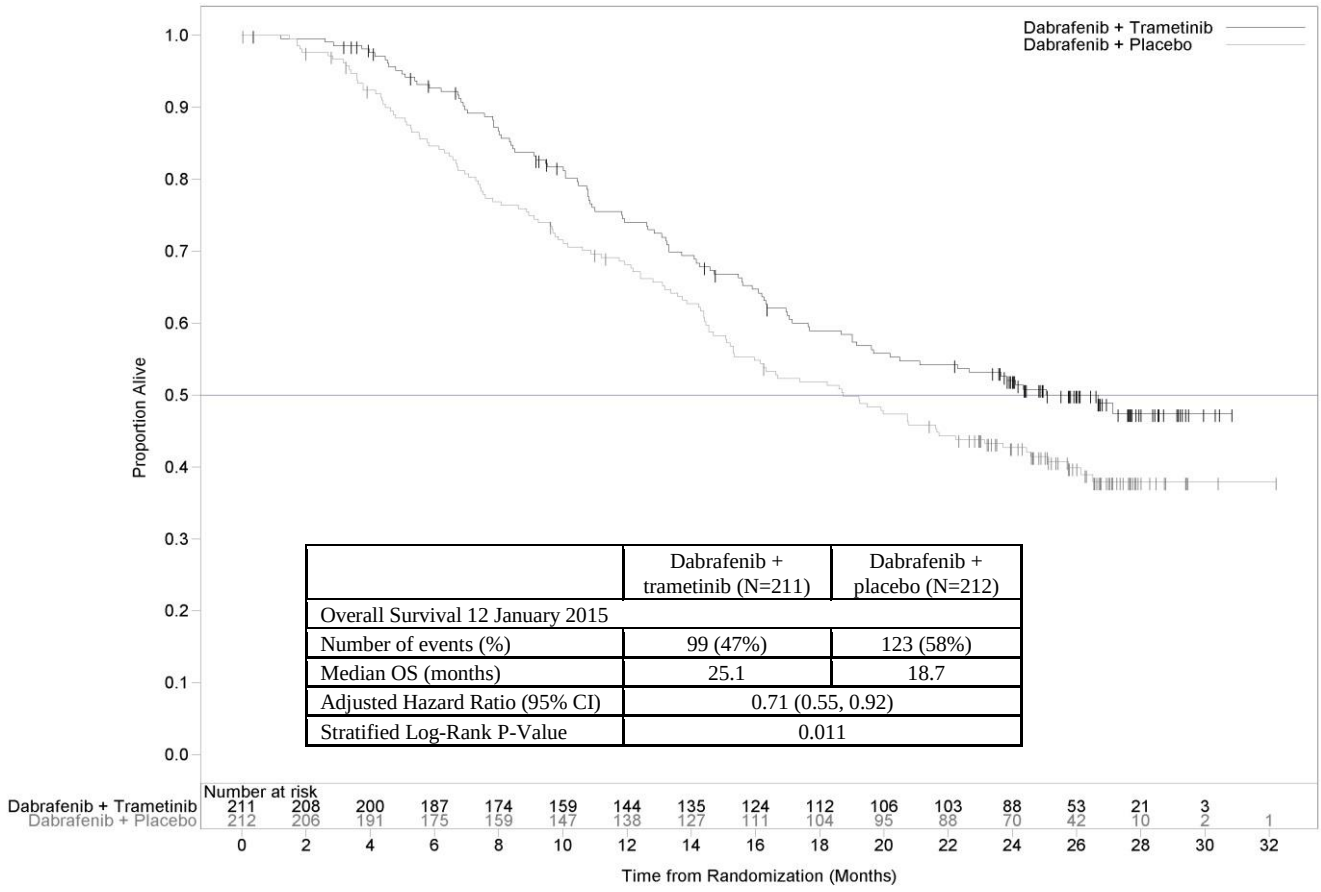
MEK115306 (COMBI-d):
MEK115306 was a Phase III, randomised, double-blinded study comparing the combination of dabrafenib and trametinib to dabrafenib and placebo in first-line therapy for subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma.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

A total of 423 subjects were randomised 1:1 to either combination (N=211) or dabrafenib (N=212). Most subjects were Caucasian (>99%) and male (53%), with a median age of 56 years (28% were ≥65 years). The majority of subjects had Stage IVM1c disease (67%). Most subjects had LDH ≤ULN (65%), ECOG performance status of 0 (72%), and visceral disease (73%) at baseline. The majority of subjects had a BRAF V600E mutation (85%). Subjects with brain metastases were not included in the trial.

The final OS analysis (12 January 2015) demonstrated a statistically significant improvement in OS for the combination compared with dabrafenib monotherapy (Figure 1). The 1-year (74%) and 2-year (51%) OS estimates for the combination arm were greater than those for dabrafenib monotherapy (68% and 42% respectively).

Figure 1 Kaplan-Meier overall survival curves for Study MEK115306 (ITT population)






| | Dabrafenib + trametinib (N=211) | Dabrafenib + placebo (N=212) |
|---|---|---|
| Overall Survival 12 January 2015 | | |
| Number of events (%) | 99 (47%) | 123 (58%) |
| Median OS (months) | 25.1 | 18.7 |
| Adjusted Hazard Ratio (95% CI) | 0.71 (0.55, 0.92) | |
| Stratified Log-Rank P-Value | 0.011 | |

Statistically significant improvements were observed for the primary endpoint of PFS and secondary endpoint of ORR. A longer duration of response is also observed (Table 6).

Table 6 Efficacy results for Study MEK115306 (COMBI-d)

| **Endpoint** | **Dabrafenib + Trametinib (N=211)** | **Dabrafenib + Placebo (N=212)** | **Dabrafenib + Trametinib (N=211)** | **Dabrafenib + Placebo (N=212)** |
|---|---|---|---|---|
| **Data cut-off date** | **26 August 2013** | | **12 January 2015** | |
| **PFS**[a] | | | | |
| Progressive disease or death, n (%) | 102 (48) | 109 (51) | 139 (66) | 162 (76) |
| Median PFS (months) (95% CI) | 9.3 (7.7, 11.1) | 8.8 (5.9, 10.9) | 11.0 (8.0, 13.9) | 8.8 (5.9, 9.3) |
| Hazard Ratio (95% CI) | 0.75 (0.57, 0.99) | | 0.67 (0.53, 0.84) | |
| P value | 0.035 | | <0.001 | |
| **ORR**[b] (95% CI) | 67 (59.9, 73.0) | 51 (44.5, 58.4) | 69 (61.8,74.8) | 53 (46.3, 60.2) |
| ORR difference (95% CI) | 15[e] (5.9, 24.5) | | 15[e] (6.0, 24.5) | |
| P value | 0.0015 | | 0.0014 | |
| **DoR**[c] **(months)** Median (95% CI) | 9.2[d] (7.4, NR) | 10.2[d] (7.5, NR) | 12.9 (9.4,19.5) | 10.6 (9.1, 13.8) |

a – Progression-free survival (investigator assessed)
b – Overall Response Rate = Complete Response + Partial Response
c – Duration of response
d - At the time of the reporting the majority (≥59%) of investigator-assessed responses were still ongoing
e – ORR difference calculated based on the ORR result not rounded
NR = Not reached

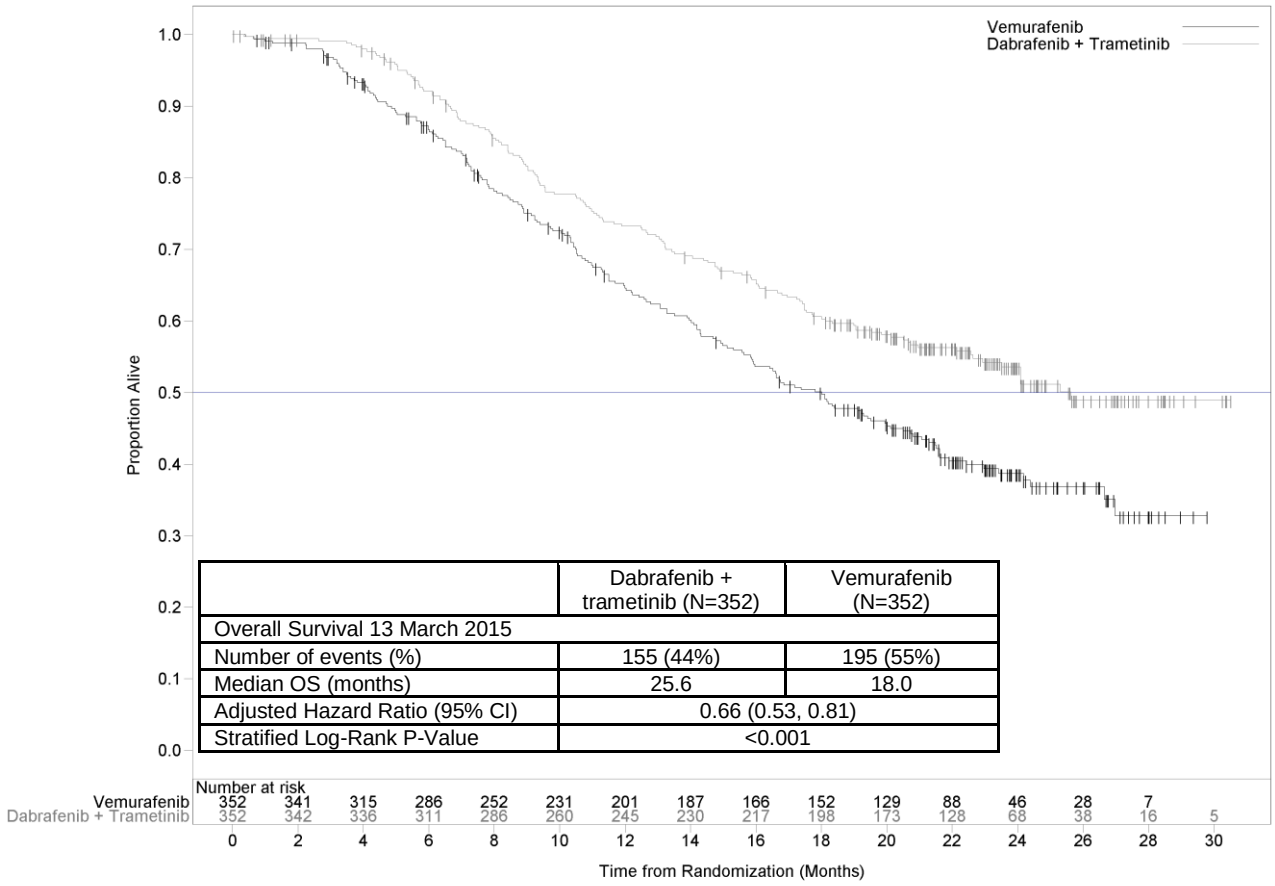
MEK116513 (COMBI-v):
Study MEK116513 was a 2-arm, randomised, open-label, Phase III study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive metastatic melanoma. The primary endpoint of the study was overall survival with a key secondary endpoint of PFS. Subjects were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ULN) and BRAF mutation (V600E versus V600K).

A total of 704 subjects were randomised 1:1 to either combination or vemurafenib. Most subjects were Caucasian (>96%) and male (55%), with a median age of 55 years (24% were ≥65 years). The majority of subjects had Stage IV M1c disease (61% overall). Most subjects had LDH ≤ULN (67%), ECOG performance status of 0 (70%), and visceral disease (78%) at Baseline. Overall, 54% of subjects had <3 disease sites at baseline. The majority of subjects had BRAF V600E mutation-positive melanoma (89%). Subjects with brain metastases were not included in the trial.

The updated OS analysis (13 March 2015) demonstrated a statistically significant improvement in OS for the combination compared with vemurafenib monotherapy (Figure 2). The 12-month OS estimate was 72% for combination therapy and 65% for vemurafenib.

Figure 2: Kaplan-Meier curves Updated OS analysis for Study MEK116513






| | Dabrafenib + trametinib (N=352) | Vemurafenib (N=352) |
|---|---|---|
| Overall Survival 13 March 2015 | | |
| Number of events (%) | 155 (44%) | 195 (55%) |
| Median OS (months) | 25.6 | 18.0 |
| Adjusted Hazard Ratio (95% CI) | 0.66 (0.53, 0.81) | |
| Stratified Log-Rank P-Value | <0.001 | |

Statistically significant improvements are observed for the secondary endpoints of PFS and ORR. A longer duration of response is also observed (Table 7).

Table 7 Efficacy results for Study MEK116513 (COMBI-v)

| **Endpoint** | **Dabrafenib + Trametinib (N=352)** | **Vemurafenib (N=352)** |
|---|---|---|
| **PFS**[a] | | |
| Progressive disease or death, n (%) | 166 (47) | 217 (62) |
| Median PFS (months) (95% CI) | 11.4 (9.9, 14.9) | 7.3 (5.8, 7.8) |
| Hazard Ratio (95% CI) | 0.56 (0.46, 0.69) | |
| *P* value | <0.001 | |
| **ORR**[b] (95% CI) | 226 (64) (59.1, 69.4) | 180 (51) (46.1, 56.8) |
| ORR difference (95% CI) | 13 (5.7, 20.2) | |
| P value | 0.0005 | |
| **DoR (months)** Median (95% CI) | 13.8 (11.0, NR) | 7.5 (7.3, 9.3) |

*Prior BRAF inhibitor therapy*
There are limited data in patients taking the combination of dabrafenib with trametinib who have progressed on a prior BRAF inhibitor.

Part B of study BRF113220 included a cohort of 26 patients that had progressed on a BRAF inhibitor. The trametinib 2 mg once daily and dabrafenib 150 mg twice daily combination demonstrated limited clinical activity in patients who had progressed on a BRAF inhibitor. The investigator-assessed confirmed response rate was 15% (95% CI: 4.4, 34.9) and the median PFS was 3.6 months (95% CI: 1.9, 5.2). Similar results were seen in the 45 patients who crossed over from dabrafenib monotherapy to the trametinib 2 mg once daily and dabrafenib 150 mg twice daily combination in Part C of this study. In these patients a 13% (95 CI: 5.0, 27.0) confirmed response rate was observed with a median PFS of 3.6 months (95% CI: 2, 4).

*Dabrafenib monotherapy*

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

Included in these studies were in total 402 subjects with BRAF V600E and 49 subjects with BRAF V600K mutation. Patients with melanoma driven by BRAF mutations other than V600E were excluded from the confirmatory trial and with respect to patients with the V600K mutation in single arm studies the activity appears lower than in V600E tumours.

No data is available in patients with melanoma harbouring BRAF V600 mutations others than V600E and V600K. Efficacy of dabrafenib in subjects previously treated with a protein kinase inhibitor has not been investigated.

*Previously untreated patients (Results from the Phase III study [BREAK-3])*
The efficacy and safety of dabrafenib were evaluated in a Phase III randomised, open-label study [BREAK 3] comparing dabrafenib to dacarbazine (DTIC) in previously untreated patients with BRAF V600E mutation positive advanced (unresectable Stage III) or metastatic (Stage IV) melanoma. Patients with melanoma driven by BRAF mutations other than V600E were excluded.

The primary objective for this study was to evaluate the efficacy of dabrafenib compared to DTIC with respect to progression-free survival (PFS) per investigator assessment. Patients on the DTIC arm were allowed to cross over to dabrafenib after independent radiographic confirmation of initial progression. Baseline characteristics were balanced between treatment groups. Sixty percent of patients were male and 99.6% were Caucasian ; the median age was 52 years with 21% of patients being ≥65 years, 98.4% had ECOG status of 0 or 1, and 97% of patients had metastatic disease.

At the pre-specified analysis with a 19 December 2011 data cut, a significant improvement in the primary endpoint of PFS (HR = 0.30; 95% Cl 0.18, 0.51; p < 0.0001) was achieved. Efficacy results from the primary analysis and a post-hoc analysis with 6-months additional follow up are summarised in Table 8. Overall survival data from a further post-hoc analysis based on a 18 December 2012 data cut are shown in Figure 3.

Table 8 Efficacy in previously untreated patients (BREAK-3 Study, 25 June 2012)

| | **Data as of December 19, 2011** | | **Data as of June 25, 2012** | |
|---|---|---|---|---|
| | **Dabrafenib N=187** | **DTIC N=63** | **Dabrafenib N=187** | **DTIC N=63** |
| **Progression-free survival** | | | | |
| Median, months (95% CI) | 5.1 (4.9, 6.9) | 2.7 (1.5, 3.2) | 6.9 (5.2,9.0) | 2.7 (1.5,3.2) |
| HR (95% CI) | 0.30 (0.18, 0.51) P < 0.0001 | | 0.37 (0.24, 0.58) P < 0.0001 | |
| **Overall response**[a] | | | | |
| % (95% CI) | 53 (45.5, 60.3) | 19 (10.2, 30.9) | 59 (51.4, 66.0) | 24 (14, 36.2) |
| **Duration of response** | | | | |
| Median, months (95% CI) | N=99 5.6 (4.8, NR) | N=12 NR (5.0, NR) | N=110 8.0 (6.6, 11.5) | N=15 7.6 (5.0, 9.7) |

Abbreviations: CI: confidence interval; DTIC: dacarbazine; HR: hazard ratio; NR: not reached
[a] Defined as confirmed complete +partial response.

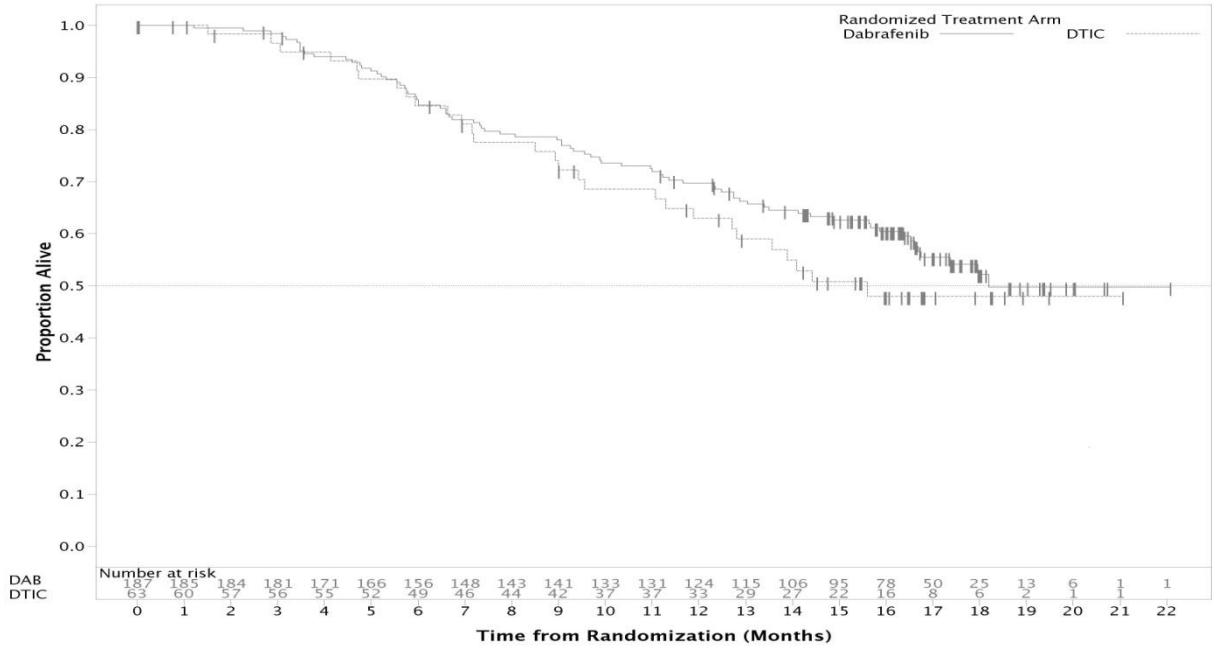
As of 25 June 2012 cut-off, thirty five subjects (55.6%) of the 63 randomised to DTIC had crossed over to dabrafenib and 63% of subjects randomised to dabrafenib and 79% of subjects randomised to DTIC had progressed or died. Median PFS after cross-over was 4.4 months.

Table 9 Survival data from the primary analysis and post-hoc analyses

| **Cut-off date** | **Treatment** | **Number of deaths (%)** | **Hazard Ratio (95% CI)** |
|---|---|---|---|
| December 19, 2011 | DTIC | 9 (14%) | 0.61 (0.25, 1.48) [(a)] |
| | dabrafenib | 21 (11%) | |
| June 25, 2012 | DTIC | 21 (33%) | 0.75 (0.44, 1.29) [(a)] |
| | dabrafenib | 55 (29%) | |
| December 18, 2012 | DTIC | 28 (44%) | 0.76 (0.48, 1.21) [(a)] |
| | dabrafenib | 78 (42%) | |
| [(a)] Patients were not censored at the time of cross-over | | | |

Overall survival data from a further post-hoc analysis based on the 18 December 2012 data cut demonstrated a 12-month OS rate of 63% and 70% for DTIC and dabrafenib treatments, respectively.

Figure 3 Kaplan-Meier curves of overall survival (BREAK-3) (18 December 2012)




*Patients with brain metastases (Results from the Phase II study (BREAK-MB)*
BREAK-MB was a multicentre, open-label, two-cohort, Phase II study designed to evaluate the intracranial response of dabrafenib in subjects with histologically confirmed (Stage IV) BRAF-mutation positive (V600E or V600K) melanoma metastatic to the brain. Subjects were enrolled into Cohort A (subjects with no prior local therapy for brain metastasis) or Cohort B (subjects who received prior local therapy for brain metastasis).

The primary endpoint of the study was overall intracranial response rate (OIRR) in the V600E patient population, as assessed by investigators. The confirmed OIRR and other efficacy results per investigator assessment are presented in Table 10.

Table 10 Efficacy data in patients with brain metastases (BREAK-MB Study)

| | All Treated Subjects Population | | | |
|---|---|---|---|---|
| | BRAF V600E (Primary) | | BRAF V600K | |
| | 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) |
| **Overall response,% (95% CI)[a]** | | | | |
| | 38% (26.8, 49.9) | 31% (19.9, 43.4) | 0 (0, 21.8) | 28% (9.7, 53.5) |
| **Duration of response, 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) |
| **Progression-free survival, 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) |
| **Overall survival, 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; NR: not reached; NA: not applicable

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 mutation positive subjects.

*Patients who were previously untreated or failed at least one prior systemic therapy (Results from the Phase II [BREAK-2])*

BRF113710 (BREAK-2) was a multicentre, single-arm study that enrolled 92 subjects with metastatic melanoma (Stage IV) with confirmed BRAF V600E or V600K mutation-positive melanoma.

The investigator assessed confirmed response rate in patients with BRAF V600E metastatic melanoma (n=76) was 59% (95% CI: 48.2, 70.3) and the median duration of response was 5.2 months (95% CI: 3.9, not calculable) based on a median follow-up time of 6.5 months. In patients with BRAF V600K mutation positive metastatic melanoma (n=16) the response rate was 13% (95% CI: 0.0, 28.7) with a median duration of response of 5.3 months (95% CI: 3.7, 6.8). Although limited by the low number of patients, median OS appeared consistent with data in patients with BRAF V600E positive tumours.

QT prolongation

Worst-case QTc prolongation of >60 millisecond (msec) was observed in 3% of dabrafenib-treated subjects (one >500 msec in the integrated safety population). In the Phase III study MEK115306 no patients treated with trametinib in combination with dabrafenib had worst-case QTcB prolongation to >500 msec; QTcB was increased more than 60 msec from baseline in 1% (3/209) of patients. In the Phase III study MEK116513 four patients (1%) treated with trametinib in combination with dabrafenib had a QTcB Grade 3 increase (>500 msec). Two of these patients had a QTcB Grade 3 increase (>500 msec) that was also an increase >60 msec from baseline.

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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with dabrafenib in one or more subsets of the paediatric population in melanoma (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

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. A decrease in exposure was 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 $C_{max}$, AUC(0-$\tau$) and predose concentration (C$\tau$) were 1478 ng/ml, 4341 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 capsules 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 microdose administration is 46 L.

Dabrafenib is a substrate of human P-glycoprotein (Pgp) and murine BCRP *in vitro*. However, these transporters have minimal impact on dabrafenib oral bioavailability and elimination and the risk for clinically relevant drug-drug interactions with inhibitors of Pgp or BCRP is low. Dabrafenib is not an *in vitro* substrate of OATP1B1, OATP1B3 or OATP2B1 transporters.

Neither dabrafenib nor its 3 main metabolites were demonstrated to be inhibitors of Pgp *in vitro*.

Biotransformation

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidised 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 metabolised by CYP3A4 to oxidative metabolites. Hydroxy-dabrafenib terminal half-life parallels that of parent with a half-life of 10 hrs while the carboxy- and desmethyl-metabolites exhibited longer half-lives (21-22 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 an intravenous single microdose is 2.6 hours. Dabrafenib terminal half-life after a single dose is 8 hours due to absorption-limited elimination after oral administration (flip-flop pharmacokinetics). IV plasma clearance is 12 l/hr.

After an oral dose, the major route of elimination of dabrafenib is metabolism, mediated via CYP3A4 and CYP2C8. Dabrafenib related material is excreted primarily in faeces, with 71% of an oral dose recovered in faeces and 23% in urine as metabolites only.

Special patient populations

*Hepatic impairment*

A population pharmacokinetic analysis indicates that mildly elevated bilirubin and/or AST levels (based on National Cancer Institute [NCI] classification) do not significantly affect dabrafenib oral clearance. In addition, mild hepatic impairment as defined by bilirubin and AST did not have a significant effect on dabrafenib metabolite plasma concentrations. No data are available in patients with moderate to severe hepatic impairment. As hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites, administration of dabrafenib should be undertaken with caution in patients with moderate to severe hepatic impairment (see section 4.2).

*Renal impairment*

A population pharmacokinetic analysis suggests that mild renal impairment does not affect oral clearance of dabrafenib. Although data in moderate renal impairment are limited these data may indicate no clinically relevant effect. No data are available in subjects with severe renal impairment (see section 4.2).

*Elderly*

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 subjects ≥75 years of age, relative to subjects <75 years old.

*Body weight and gender*

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*

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

*Paediatric population*

No studies have been conducted to investigate the pharmacokinetics of dabrafenib in

paediatric patients.

## 5.3 Preclinical safety data

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.

In combined female fertility, early embryonic and embryofoetal 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 oestrous cycle, mating or fertility indices. Developmental toxicity including embryo-lethality and ventricular septal defects 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).

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 (see section 4.6).

Cardiovascular effects, including coronary arterial degeneration/necrosis and/or haemorrhage, cardiac atrioventricular valve hypertrophy/haemorrhage 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 haematological 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).

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).

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.

<u>Combination with trametinib</u>

In a study in dogs in which trametinib and dabrafenib were given in combination for 4 weeks, signs of gastrointestinal toxicity and decreased lymphoid cellularity of the thymus were observed at lower exposures than in dogs given trametinib alone. Otherwise, similar toxicities were observed as in comparable monotherapy studies.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content
Microcrystalline cellulose
Magnesium stearate
Colloidal silicone dioxide

Capsule shell
Red iron oxide (E172)
Titanium dioxide (E171)
Hypromellose (E464)

Printing ink:
Black iron oxide (E172)
Shellac
Propylene glycol

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

The expiry date of the product is indicated on the label and packaging.

Use within 6 months after opening.

### 6.4 Special precautions for storage

Do not store above 30°C.

### 6.5 Nature and contents of container

Opaque white high density polyethylene (HDPE) bottle with polypropylene screw cap and a silica gel desiccant.

Each bottle contains 28 capsules.

## 7. MANUFACTURER

Glaxo Wellcome S.A., Burgos, Spain.

## 8. REGISTRATION HOLDER

**Novartis Israel Ltd.**
**36 Shacham St., Petach-Tikva.**

## 9. LICENSE NUMBER

Tafinlar 50mg: 151 42 33976
Tafinlar 75mg: 151 43 33977