AUSTRALIAN PRODUCT INFORMATION - TAFINLAR® (dabrafenib) capsules

1. NAME OF THE MEDICINE

Dabrafenib.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

TAFINLAR 50 mg capsules

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

TAFINLAR 75 mg capsules

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

Excipients

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

3. PHARMACEUTICAL FORM

TAFINLAR 50 mg capsules

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

TAFINLAR 75 mg capsules

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Unresectable or metastatic melanoma

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

TAFINLAR as monotherapy is indicated for the treatment of patients with BRAF V600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.

Adjuvant treatment of melanoma

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

4.2 Dose and method of administration

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

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

When TAFINLAR is used in combination with MEKINIST (trametinib), refer to the full MEKINIST product information, for dosing instructions.

TAFINLAR treatment should continue until disease progression or the development of unacceptable toxicity.

The efficacy and safety of TAFINLAR have not been established in patients with wild-type BRAF melanoma (see section 5.1 Clinical trials). TAFINLAR should not be used in patients with BRAF wild-type melanoma (see section 4.4 Special Warnings and Precautions for Use).

Adult Dose

Recommended Dosage for Unresectable or Metastatic Melanoma

The recommended dose of TAFINLAR used as monotherapy or in combination with trametinib is TAFINLAR 150 mg (two 75 mg capsules) taken twice daily (corresponding to a total daily dose of 300 mg).

Recommended Dosage for the Adjuvant Treatment of Melanoma

The recommended dosage of TAFINLAR is 150 mg orally taken twice daily in combination with trametinib until disease recurrence or unacceptable toxicity for up to 1 year.

Dose modifications

Monotherapy and in combination with MEKINIST

The management of adverse reactions when TAFINLAR is used as monotherapy or in combination with MEKINIST (trametinib) may require treatment interruption, dose reduction, or treatment discontinuation (see Table 1 and Table 2). Also refer to the full trametinib product information for dosing instructions and modifications.

Dose adjustments resulting in a dose lower than TAFINLAR 50 mg twice daily are not recommended.

Dose modifications are not recommended for TAFINLAR, when administered with trametinib, for the following adverse reactions of trametinib: retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED), interstitial lung disease (ILD)/pneumonitis, and uncomplicated venous thromboembolism.

Table 1 Recommended TAFINLAR dose level reductions

Dose Level	Dose/Schedule
Full dose	150 mg twice daily
First reduction	100 mg twice daily
Second reduction	75 mg twice daily
Third reduction	50 mg twice daily

Table 2 Recommended dose modifications for TAFINLAR

Severity of adverse reaction[a]	TAFINLAR[b]
FEBRILE DRUG REACTION	
Fever of 38.5°C-40.0°C	Evaluate patients for signs and symptoms of infection. Withhold TAFINLAR until the fever resolves. Resume TAFINLAR at same or lower dose level.
• Fever of > 40°C or • Fever is complicated with rigors, hypotension, dehydration, or renal failure	Evaluate patients for signs and symptoms of infection. Withhold TAFINLAR until the fever resolves. Then either: • resume TAFINLAR with appropriate anti-pyretic prophylaxis at a lower dose level if pyrexia is recurrent

Severity of adverse reaction[a]	TAFINLAR[b]
	and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure or • permanently discontinue TAFINLAR
CUTANEOUS	
• Intolerable Grade 2 skin toxicity • Grade 3 or 4 skin toxicity	Withhold TAFINLAR for up to 3 weeks. • If improved, resume at a lower dose level. • If not improved, permanently discontinue.
CARDIAC	
• Symptomatic congestive heart failure • Absolute decrease in LVEF of greater than 20 % from baseline that is below LLN	• Withhold TAFINLAR. If improved, resume at the same dose upon recovery of cardiac function
UVEITIS	
Uveitis including iritis and iridocyclitis	If mild or moderate uveitis does not respond to ocular therapy, or for severe uveitis, withhold TAFINLAR for up to 6 weeks. • If improved to Grade 0-1, then resume at the same or at a lower dose level. • If not improved, permanently discontinue.
OTHER	
Grade 2 (Intolerable) or Grade 3	Withhold TAFINLAR. • If improved to grade 0 – 1, resume at a lower dose level. • If not improved, permanently discontinue TAFINLAR.
First occurrence of any Grade 4 adverse reaction	• Withhold TAFINLAR until adverse reaction improves to Grade 0-1. Then resume at a lower dose level. Or • Permanently discontinue TAFINLAR.

[a] AE Intensity graded by the Common Terminology Criteria for Adverse Events (CTC-AE) v4.0

[b] See Table 2 for recommended dose reductions of TAFINLAR.

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 TAFINLAR dose should not exceed 150 mg twice daily.

If treatment related toxicities occur when TAFINLAR is used in combination with MEKINIST then both treatments should be simultaneously dose reduced, interrupted or discontinued with the following exceptions.

Detailed dosing modifications for selected adverse reactions

New Primary Cutaneous Malignancies

- No TAFINLAR dose modifications are required.

New Primary Non-Cutaneous Malignancies

- Permanently discontinue TAFINLAR in patients who develop RAS mutation-positive non-cutaneous malignancies.

Pyrexia Management

Follow the dose modifications in Table 2. Initiate treatment with anti-pyretics such as ibuprofen (preferred) or paracetamol. 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 (see section 4.4 Special Warnings and Precautions for Use). Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia.

Uveitis Management

No dose modifications are required as long as effective local therapies can control ocular inflammation.

Interstitial lung disease (ILD)/Pneumonitis

Do not modify the dose of TAFINLAR.

When receiving TAFINLAR in combination with MEKINIST, withhold MEKINIST in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Permanently discontinue MEKINIST for patients diagnosed with treatment-related ILD or pneumonitis.

Serious Skin Toxicity

For dosing modifications in intolerable or severe skin toxicity see Table 2.

Rash management should be considered whether TAFINLAR is given as monotherapy or in combination with MEKINIST, and if dose reduction, interruption or discontinuation is necessary it should be applied to both treatments.

Treatment of rash has not been formally studied and should be based on rash severity.

<u>Populations</u>

Paediatric use

The safety and efficacy of TAFINLAR have not been established in children and adolescents (< 18 years). Studies in juvenile animals have shown effects of TAFINLAR which had not been observed in adult animals (see Section 4.4 Special Warnings and Precautions for Use).

Use in the elderly

No dose adjustment is required in patients over 65 years (see section 5.2 – Pharmacokinetic properties).

Renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment. Based on the population pharmacokinetic analysis, mild and moderate renal impairment had no significant effect on TAFINLAR oral clearance or on the concentrations of its metabolites (see section 5.2 Pharmacokinetic properties). There are no clinical data in patients with severe renal impairment and the potential need for dose adjustment cannot be determined. 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 TAFINLAR oral

clearance or on the concentrations of its metabolites (see section 5.2 Pharmacokinetic properties). 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 TAFINLAR and its metabolites and patients with moderate to severe hepatic impairment may have increased exposure. TAFINLAR should be used with caution in patients with moderate or severe hepatic impairment.

Administration

TAFINLAR should be taken either at least one hour before, or at least two hours after a meal, leaving an interval of approximately 12 hours between doses. TAFINLAR should be taken at similar times every day.

Do not open, crush, or break TAFINLAR capsules.

Combination therapy

When TAFINLAR and MEKINIST are taken in combination, take the once-daily dose of MEKINIST at the same time each day with either the morning dose or the evening dose of TAFINLAR.

Missed dose

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

4.3 Contraindications

TAFINLAR is contraindicated in patients with hypersensitivity to the active substance dabrafenib mesilate or any of the excipients (see Section 6.1 List of excipients).

4.4 Special warnings and precautions for use

BRAF V600 testing

Before taking TAFINLAR, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test.

The efficacy and safety of TAFINLAR have not been established in patients with wild-type BRAF melanoma, and therefore TAFINLAR should not be used in patients with BRAF wild-type melanoma (see section 5.1 Clinical trials). Further around 40 % of BRAF wild-type metastatic melanomas have oncogenic NRAS mutations which may result in paradoxical activation of MAP-kinase signalling in the presence of BRAF inhibitors such as TAFINLAR and may lead to accelerated tumour growth.

Pyrexia and serious non-infectious febrile events

Pyrexia was reported in clinical trials with TAFINLAR monotherapy and in combination with MEKINIST (see section 4.8 Adverse Effects (Undesirable Effects)). In a Phase III clinical trial in patients with unresectable or metastatic melanoma, the incidence and severity of pyrexia were increased when TAFINLAR was used in combination with MEKINIST (57 % [119/209], 7 % Grade 3) as compared to TAFINLAR monotherapy (33 % [69/211], 2 % Grade 3). In a Phase III trial in the adjuvant treatment of melanoma, the incidence and severity of pyrexia were higher in the Tafinlar in combination with Mekinist arm (67% [292/435]; 6% Grade 3/4) as compared to the placebo arm (15% [66/432]; <1% Grade 3). In patients with unresectable or metastatic melanoma who received the combination dose of TAFINLAR 150 mg twice daily and MEKINIST 2 mg once daily developed pyrexia. Approximately one-third of the patients receiving combination therapy who experienced pyrexia had three or more events.

Monitor serum creatinine and other evidence of renal function during and following severe episodes of pyrexia (also see Section 4.4 Special warnings and precautions for use- Renal failure).

In 1 % of patients in clinical trials, serious non-infectious febrile events were identified defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency (See Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse Effects (Undesirable Effects)). 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.

Therapy with TAFINLAR should be interrupted if the patient's temperature is ≥ 38.5 ºC. Patients should be evaluated for signs and symptoms of infection. TAFINLAR 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 antipyretics are insufficient. If fever is associated with other severe signs or symptoms, TAFINLAR should be restarted at a reduced dose once fever resolves and as clinically appropriate.

No dose modification of MEKINIST is required when taken in combination with TAFINLAR.

For management of pyrexia also see Section 4.2 Dose and method of administration.

Renal failure

Renal failure has been identified in < 1 % of patients treated with TAFINLAR as monotherapy. Renal failure was reported in 7 % of patients who received the combination dose of TAFINLAR 150 mg twice daily and MEKINIST 2 mg once daily, a higher frequency than observed in TAFINLAR monotherapy patients (< 1 %). Observed cases were generally associated with pyrexia and dehydration and responded well to dose interruption and general supportive measures. Granulomatous nephritis has been reported. Patients should be routinely monitored for serum creatinine while on therapy. If creatinine increases, TAFINLAR may need to be interrupted as clinically appropriate. TAFINLAR has not been studied in patients with renal insufficiency (defined as creatinine > 1.5 x ULN) therefore caution should be used in this setting.

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 TAFINLAR as monotherapy and in combination with MEKINIST (see Section 4.8 Adverse Effects (Undesirable Effects)).). In a Phase III study in patients with unresectable or metastatic melanoma, 10 % (22/211) of patients receiving TAFINLAR as monotherapy developed cuSCC with a median time to onset of the first occurrence of approximately 8 weeks. In patients who received TAFINLAR with MEKINIST, 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 TAFINLAR who developed cuSCC, continued on treatment without dose modification. In a Phase III trial in the adjuvant treatment of melanoma, 1% (6/435) of patients receiving TAFINLAR in combination with MEKINIST as compared to 1% (5/432) of patients receiving placebo developed cuSCC. The median time to onset of the first occurrence of cuSCC in the combination arm was approximately 18 weeks.

Skin examination for cuSCC should be performed prior to initiation of TAFINLAR and every month throughout treatment with TAFINLAR and for up to six months after treatment. Monitoring should continue every two or three months for six months following discontinuation of TAFINLAR or until initiation of another anti-neoplastic therapy.

Cases of cuSCC should be managed by dermatological excision and 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 TAFINLAR. In clinical trials in unresectable or metastatic melanoma, these cases were identified within the first five months of

therapy, were managed with excision, and did not require treatment modification. In the Phase III clinical trial in the adjuvant treatment of melanoma, new primary melanomas occurred in <1% (1/435) of patients receiving the combination of Tafinlar and Mekinist as opposed to 1% (6/432) of patients receiving placebo. Monitoring for skin lesions should occur as described for cuSCC.

Non-cutaneous secondary/ recurrent malignancy

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signalling in BRAF wild type cells with RAS mutations when exposed to BRAF inhibitors. This may lead to an increased risk of non-cutaneous malignancies with TAFINLAR exposure, 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 TAFINLAR monotherapy (pancreatic adenocarcinoma, bile duct adenocarcinoma) and with TAFINLAR in combination with the MEK inhibitor MEKINIST (colorectal cancer, pancreatic cancer). In the Phase III trial in the adjuvant treatment of melanoma comparing combination of Tafinlar and Mekinist to placebo, non-cutaneous secondary malignancies or recurrent malignancies were observed in 1% (5/435) of patients receiving active therapy compared to 1% (3/432) of patients receiving placebo.

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. (See section 4.2 Dose and method of administration.)

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

Following discontinuation of TAFINLAR, 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.

Serious Skin Toxicity

Serious skin toxicity can occur with TAFINLAR. Across clinical trials of TAFINLAR administered with MEKINIST (N = 559), serious skin toxicity occurred in 0.7% (4/559) of patients. Withhold TAFINLAR for intolerable or severe skin toxicity. TAFINLAR may be resumed at the next lower dose level in patients with improvement or recovery from skin toxicity within three weeks (see section 4.2 Dose and method of administration).

Visual impairment

Treatment with TAFINLAR as monotherapy and in combination with MEKINIST has been associated with ophthalmologic reactions, including uveitis, iridocyclitis, and iritis. Monitor patients routinely for visual signs and symptoms (such as, change in vision, photophobia and eye pain) during therapy. (Also see section 4.2 Dose and method of administration.)

Uveitis

If uveitis does not respond to local ocular therapy, withhold TAFINLAR until resolution of ocular inflammation and then restart TAFINLAR reduced by one dose level. (See section 4.2 Dose and method of administration.)

No dose modification of MEKINIST is required when taken in combination with TAFINLAR following diagnosis of uveitis.

Retinal vein occlusion (RVO) and Retinal pigment epithelial detachment (RPED)

RPED and RVO may occur with dabrafenib in combination with MEKINIST (trametinib). No dose modification of TAFINLAR is required when taken in combination with trametinib following diagnosis of RVO or RPED.

Please refer to the MEKINIST Product Information.

Pancreatitis

Pancreatitis has been reported in < 1 % of TAFINLAR-treated patients in unresectable or metastatic melanoma clinical trials. One of the events occurred on the first day of dosing of a melanoma patient and recurred following re-challenge at a reduced dose. In the adjuvant treatment of melanoma trial, pancreatitis was reported in 1% of patients receiving TAFINLAR in combination with MEKINIST, and in <1% of patients receiving placebo.

Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when re-starting TAFINLAR after an episode of pancreatitis.

Hyperglycaemia

Hyperglycaemia requiring an increase in the dose of, or initiation of insulin or oral hypoglycaemic agent therapy can occur with TAFINLAR. In the pivotal study, five of 12 patients with a history of diabetes required more intensive hypoglycaemic therapy while taking TAFINLAR. The incidence of Grade 3 hyperglycaemia based on laboratory values was 6 % (12/187) in patients treated with TAFINLAR compared to none of the dacarbazine-treated patients. Monitor serum glucose levels as clinically appropriate during treatment with TAFINLAR in patients with pre-existing diabetes or hyperglycaemia. Advise patients to report symptoms of severe hyperglycaemia such as excessive thirst or any increase in the volume or frequency of urination.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

TAFINLAR, which contains a sulphonamide moiety, confers a potential risk of haemolytic anaemia in patients with G6PD deficiency. Monitor patients with G6PD deficiency for signs of haemolytic anaemia while taking TAFINLAR.

TAFINLAR in combination with MEKINIST® (trametinib)

When TAFINLAR is given in combination with trametinib, please refer to the full trametinib Product Information, prior to initiation of combination treatment.

Haemorrhage

Haemorrhagic events, including major haemorrhagic events have occurred in patients taking trametinib in combination with TAFINLAR. If patients develop symptoms of haemorrhage, they should immediately seek medical care.

Six (6) out of 559 unresectable or metastatic melanoma patients (1.1 %) receiving dabrafenib in combination with trametinib in a phase III trial had fatal intracranial haemorrhagic events. Three cases were from study MEK115306 (COMBI-d) and three cases were from study MEK116513 (COMBI-v). No fatal haemorrhagic events occurred in the Phase III study in the adjuvant treatment of melanoma (0/438). If patients develop symptoms of haemorrhage they should immediately seek medical care.

In Study BRF113220, treatment with TAFINLAR in combination with trametinib resulted in an increased incidence and severity of any haemorrhagic event: 16 % (9/55) of patients treated with trametinib in combination with TAFINLAR compared with 2 % (1/53) of patients treated with TAFINLAR as a single agent. The major haemorrhagic events of intracranial or gastric haemorrhage occurred in 5 % (3/55) of patients treated with MEKINIST in combination with

TAFINLAR compared with none of the 53 patients treated with dabrafenib as a single agent. Intracranial haemorrhage was fatal in two (4 %) patients receiving the combination of MEKINIST and TAFINLAR.

Cardiac Effects

LVEF reduction/Left ventricular dysfunction

Cardiomyopathy can occur with TAFINLAR (see section 4.8 Adverse Effects (Undesirable Effects)). In MEK115306 (COMBI-d), all patients were required to have an echocardiogram at baseline to document normal left ventricular ejection fraction (LVEF) and serial echocardiograms at Week 4, Week 12, and every 12 weeks thereafter. Cardiomyopathy, defined as a decrease in LVEF $\geq$ 10% from baseline and below the institutional lower limit of normal, occurred in 6% (12/206) of patients receiving TAFINLAR with MEKINIST and 2.9% (6/207) of patients receiving single-agent TAFINLAR. The median time to onset of cardiomyopathy on the TAFINLAR plus MEKINIST arm was 8.2 months (range: 28 days to 24.9 months), and was 4.4 months (range: 28 days to 19.1 months) on the TAFINLAR arm.

Cardiomyopathy was identified within the first month of initiation of TAFINLAR with MEKINIST in 2 of 12 patients, and in 2 of 6 patients receiving single-agent TAFINLAR in MEK115306. Development of cardiomyopathy in patients receiving TAFINLAR and trametinib resulted in dose interruption of TAFINLAR (4.4 %) or discontinuation of TAFINLAR (1.0 %). In patients receiving single-agent TAFINLAR, development of cardiomyopathy resulted in dose interruption (2.4 %), dose reduction (0.5 %), or discontinuation (1.0 %). Cardiomyopathy resolved in 10 of 12 patients receiving TAFINLAR with trametinib, and in 3 of 6 patients receiving single-agent TAFINLAR.

Assess LVEF by echocardiogram or multi-gated acquisition (MUGA) scan before initiation of TAFINLAR with MEKINIST, one month after initiation of TAFINLAR, and then at 2- to 3-month intervals while on treatment. Withhold TAFINLAR for symptomatic cardiomyopathy or asymptomatic LV dysfunction of > 20 % from baseline that is below institutional lower limit of normal (LLN). Resume TAFINLAR at the same dose level upon recovery of cardiac function to at least the institutional LLN for LVEF and absolute decrease $\leq$ 10 % compared to baseline (see section 4.2 Dose and method of administration).

QT prolongation

Worst-case QTc prolongation of > 60 millisecond (ms) was observed in 3 % of TAFINLAR-treated patients (one > 500 ms 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 ms; QTcB was increased more than 60 ms from baseline in 1% (3/209) of patients. In the Phase III study MEK116513 four patients (1 %) treated with MEKINIST in combination with TAFINLAR had a QTcB Grade 3 increase (> 500 ms). Two of these patients had a QTcB Grade 3 increase (>500 ms) that was also an increase > 60 ms from baseline. The potential effect of TAFINLAR on QT prolongation was assessed in a dedicated multiple dose QT study. A supra therapeutic dose of 300 mg TAFINLAR twice daily was administered in 32 patients with BRAF V600 mutation positive tumours. No clinically relevant effect of TAFINLAR or its metabolites on the QTc interval was observed.

Bradycardia

A dedicated cardiac study in solid tumour patients (n=30) confirmed early exploratory analyses in showing statistically significant changes in both PR interval (mean 21.68 ms increase, normal = 120 to 200) and heart rate (mean 8.12 bpm decrease) with MEKINIST versus placebo. The clinical significance of this small increase in PR interval is unclear, however in a large ongoing trial (n=704), heart rate decrease to < 60 bpm has been recorded in 23 % of 348 patients on MEKINIST and TAFINLAR combined therapy compared to 12 % of patients in the vemurafenib monotherapy control arm.

Hepatic events

Hepatic adverse events have been reported in clinical trials with dabrafenib in combination with trametinib (see section 4.8 Adverse effects (undesirable effects)). 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. Refer to the trametinib Product Information for additional information.

Brain metastases

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

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 Adverse Effects (Undesirable Effects)). Also refer to the MEKINIST Product Information for additional information.

Interstitial lung disease (ILD)/Pneumonitis

Cases of pneumonitis or ILD have been reported in clinical trials with TAFINLAR in combination with MEKINIST. Refer to the trametinib Product Information for additional information. If TAFINLAR is being used in combination with MEKINIST, then therapy with TAFINLAR may be continued at the same dose.

Rash

Rash has been observed in about 25 % of patients in clinical studies when TAFINLAR is used in combination with MEKINIST. Also refer to the MEKINIST Product Information for additional information.

Rhabdomyolysis

Rhabdomyolysis has been reported in patients taking TAFINLAR in combination with MEKINIST (see section 4.8 Adverse Effects (Undesirable Effects)). Also refer to the MEKINIST Product Information for additional information.

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

Pulmonary embolism or deep vein thrombosis can occur when TAFINLAR is used in combination with MEKINIST. 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 MEKINIST and TAFINLAR for life-threatening pulmonary embolism.

Use in hepatic impairment

See sections 4.2 Dose and method of administration, and 5.2 Pharmacokinetic properties.

Use in renal impairment

See sections 4.2 Dose and method of administration, 4.4 Special warnings and precautions for use (renal failure), 4.8 Adverse Effects (Undesirable Effects), and 5.2 Pharmacokinetic properties.

Use in the elderly

See sections 4.2 Dose and method of administration, 4.8 Adverse Effects (Undesirable Effects), and 5.2 Pharmacokinetic properties.

Paediatric use

See sections 4.2 Dose and method of administration, 4.8 Adverse Effects (Undesirable Effects) and 5.2 Pharmacokinetic properties.

Effects on laboratory tests

Treatment-emergent laboratory abnormalities may include any of the following: hyperglycaemia, hyperbilirubinemia, increased GGT, increased ALP, increased ALT, increased AST, increased CPK, hypophosphatemia, hyponatremia, serum albumin abnormalities, anaemia, neutropenia, thrombocytopenia, leukopenia, and lymphocytopenia. See section 4.8 Adverse Effects (Undesirable Effects).

4.5 Interactions with other medicines and other forms of interactions

In vitro evaluation of drug interaction potential

Effect of other medicines on TAFINLAR

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

Ketoconazole

Co-administration of ketoconazole (a CYP3A4 inhibitor) 400 mg once daily with TAFINLAR 75 mg twice daily, increased the AUC of dabrafenib by 71 %. Pharmacokinetic data showed an increase in repeat dose dabrafenib Cmax (33 %) and AUC (71 %) with ketoconazole, and increases of 82 % and 68 % respectively in hydroxy- and desmethyl-dabrafenib AUC with ketoconazole. A 16 % decrease in AUC was noted for carboxy-dabrafenib.

Gemfibrozil

Coadministration of TAFINLAR 75 mg twice daily and gemfibrozil (a CYP2C8 inhibitor) 600 mg twice daily resulted in an increase in repeat-dose TAFINLAR AUC (47 %) and no clinically relevant changes were noted in the AUC of the metabolites.

Drugs that affect gastric pH

Dabrafenib solubility is pH-dependent with decreased solubility at higher pH. Medicinal products that alter the pH of the upper GI tract (e.g. proton pump inhibitors, H2-receptor agonists, and antacids may decrease the solubility of TAFINLAR and reduce its bioavailability. However, no clinical study has been conducted to evaluate the effect of gastric pH-altering agents on the systemic exposure of TAFINLAR. Due to the theoretical risk that pH-elevating agents may decrease oral bioavailability and exposure to TAFINLAR, medicinal products that increase gastric pH should be used with caution when co-administered with TAFINLAR. The effect of these medicines on efficacy of TAFINLAR is unknown.

Effect of TAFINLAR on other medicines

Dabrafenib is an inducer of metabolising enzymes CYP3A4 and CYP2C9 and may induce other enzymes including CYP2B6, CYP2C8, CYP2C19, UDP glucuronosyl transferase (UGT) and transporters (e.g. P-glycoprotein [P-gp]).

Co-administration of TAFINLAR and medicinal products which are affected by the induction of

these enzymes or transporters such as hormonal contraceptives (see section 4.6 Fertility, pregnancy, and lactation), warfarin, dexamethasone, antiretroviral agents, or immunosuppressants may result in decreased concentrations and loss of efficacy. Concomitant use of TAFINLAR with these medicinal products should generally be avoided if monitoring for efficacy and dose adjustment is not possible. If co-administration of these medications is necessary with TAFINLAR, monitor patients for any potential loss of efficacy or consider substitutions of these medicinal products.

Onset of induction is likely to occur after 3 days of repeat dosing with TAFINLAR. Transient inhibition of CYP3A4 may be observed during the first few days of treatment. Upon discontinuation of TAFINLAR, concentrations of sensitive CYP3A4 substrates may increase and patients should be monitored for toxicity and dosage of these agents may need to be adjusted.

Midazolam

The single dose AUC of midazolam (CYP3A4 substrate) was decreased by 74 % with co-administration of TAFINLAR.

Warfarin

The single dose AUC of and S-warfarin (CYP2C9 substrate) was decreased by 37 % with co-administration of TAFINLAR. Exercise caution and additional INR (International Normalized Ratio) monitoring is recommended when TAFINLAR is used concomitantly with warfarin, and at discontinuation of TAFINLAR.

Digoxin

Concomitant administration of TAFINLAR 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 TAFINLAR and at discontinuation of TAFINLAR.

Effects of dabrafenib on substance transport systems

Dabrafenib is an *in vitro* inhibitor of human organic anion transporting polypeptide (OATP) 1B1 (OATP1B1) and OATP1B3 and clinical relevance cannot be excluded. Therefore caution is recommended at co-administration of TAFINLAR and OATB1B1 or OATP1B3 substrates such as statins.

Although TAFINLAR 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. TAFINLAR 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. Neither TAFINLAR nor its 3 metabolites were demonstrated to be inhibitors of P-gp *in vitro*.

Combination of TAFINLAR with MEKINIST

Co-administration of repeat dosing TAFINLAR 150 mg twice daily and MEKINIST 2 mg once daily resulted in no clinically meaningful changes in TAFINLAR or trametinib C_{max} and AUC (see section 5.2 Pharmacokinetic properties).

See Product Information for MEKINIST for guidelines on drug interactions associated with TAFINLAR combination therapy.

4.6 Fertility, pregnancy, and lactation

Effects on fertility

Infertility

There are no data in humans. TAFINLAR may impair male and female fertility as adverse effects

on male and female reproductive organs have been seen in animals. Male patients should be informed of the potential risk for impaired spermatogenesis, which may be irreversible.

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.

Males taking TAFINLAR in combination with MEKINIST

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

Use in Pregnancy (Category D)

TAFINLAR can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of TAFINLAR in pregnant women. Reproductive studies in rats have shown embryofetal development toxicity, including teratogenic effects. In adult female rats dosed with dabrafenib before mating and during gestation embryofetal toxicities included embryo-lethality, variation in thymic shape, and fetal ventricular septal defects at 300 mg/kg/day, and delayed skeletal development and reduced fetal body weight at ≥ 20 mg/kg/day (≥ 0.5 times human clinical exposure based on AUC).

TAFINLAR should not be administered to pregnant women unless the potential benefit to the mother outweighs the possible risk to the foetus.

Contraception

Females of reproductive potential should be advised that animal studies have been performed showing TAFINLAR to be harmful to the developing fetus. Sexually-active females of reproductive potential are recommended to use effective methods of contraception during TAFINLAR therapy and for 4 weeks following discontinuation of TAFINLAR. TAFINLAR may decrease the efficacy of hormonal contraceptives and an alternate method of contraception (methods that result in less than 1 % pregnancy rates), such as barrier methods, should be used during treatment and for four weeks after stopping treatment with TAFINLAR (see section 4.5 Interactions with other medicines and other forms of interactions).

If TAFINLAR is used during pregnancy, or if the patient becomes pregnant while taking TAFINLAR, the patient should be informed of the potential hazard to the foetus.

Use in Lactation

There are no data on the effect of TAFINLAR on the breast-fed child, or on the effect of TAFINLAR on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from 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 TAFINLAR and any potential adverse effects on the breast-fed child from TAFINLAR or from the underlying maternal condition.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

Summary of the safety profile

Unresectable or metastatic melanoma

TAFINLAR Monotherapy

Safety data were integrated from five clinical monotherapy studies and included 578 patients with BRAF V600 mutant unresectable or melanoma. Approximately 30 % of patients received treatment with TAFINLAR for more than 6 months.

In the integrated TAFINLAR safety population, the most common (≥ 15 %) adverse reactions were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, skin papilloma, alopecia, rash and vomiting.

Adverse reactions are listed in Table 3 by MedDRA body system organ class. Within each system organ class, the adverse events are ranked by frequency, with the most frequent adverse events first. Within each frequency grouping, adverse events are presented in order of decreasing seriousness. The following convention has been utilised for the classification of frequency:

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

Table 3 Unresectable or metastatic melanoma - adverse reactions with TAFINLAR monotherapy

Neoplasms benign and malignant (including cysts and polyps)	
Very common	Papilloma
Common	Acrochordon (skin tags), cutaneous squamous cell carcinoma (SCC) including
Uncommon	New primary melanoma
Immune System Disorders	
Uncommon	Hypersensitivity, panniculitis
Infections and infestations	
Common	Nasopharyngitis
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	Skin effects (rash, hyperkeratosis), alopecia, palmar-plantar
Common	Skin effects (actinic keratosis, skin lesion, dry skin, erythema, pruritus),
Uncommon	Panniculitis
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, myalgia, pain in extremity

Renal disorders	
Uncommon	Renal failure, acute renal failure, nephritis
General disorders and administration site conditions	
Very common	Asthenia, chills, fatigue, pyrexia
Common	Influenza-like illness
Investigations	
Common	LVEF decrease
Uncommon	QT prolongation

[1]Photosensitivity cases were also observed in post-marketing experience. All cases reported in clinical trials were Grade 1 and no dose modification was required.

Table 4 lists the very common (≥ 10 % of patients) adverse events reported in the Phase III randomised, open-label study [BREAK-3].

Table 4 Adverse events reported ≥ 10 % of patients receiving TAFINLAR or dacarbazine in unresectable or metastatic melanoma - BREAK-3 (safety population) by maximum grade

Preferred term	Number (%) of Patients					
	TAFINLAR (N=187)			dacarbazine (N=59)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any event	185 (99)	55 (29)	7 (4)	54 (92)	16 (27)	8 (14)
Hyperkeratosis	69 (37)	1 (<1)	1 (<1)	0	0	0
Headache	59 (32)	0	0	5 (8)	0	0
Pyrexia	52 (28)	6 (3)	0	6 (10)	0	0
Arthralgia	51 (27)	2 (1)	0	1 (2)	0	0
Skin papilloma	45 (24)	0	0	1 (2)	0	0
Alopecia	41 (22)	0	0	1 (2)	0	0
Palmar-plantar	37 (20)	4 (2)	0	1 (2)	0	0
Fatigue	36 (19)	2 (1)	0	14 (24)	0	0
Nausea	35 (19)	0	1 (<1)	30 (51)	0	0
Asthenia	33 (18)	1 (<1)	0	9 (15)	1 (2)	0
Rash	31 (17)	0	0	0	0	0
Vomiting	23 (12)	1 (<1)	1 (<1)	15 (25)	0	0
Cough	23 (12)	0	0	3 (5)	0	0
Back pain	22 (12)	5 (3)	0	4 (7)	0	0
Constipation	21 (11)	2 (1)	1 (<1)	8 (14)	0	0
Diarrhoea	20 (11)	1 (<1)	0	7 (12)	0	0
Myalgia	20 (11)	0	0	0	0	0
Nasopharyngitis	19 (10)	0	0	2 (3)	0	0
Pain in extremity	16 (9)	1 (<1)	0	7 (12)	0	0
Abdominal pain	7 (4)	1 (<1)	0	8 (14)	0	1 (2)
Anaemia	7 (4)	1 (<1)	0	7 (12)	1 (2)	1 (2)
Neutropenia	2 (1)	1 (<1)	0	10 (17)	4 (7)	4 (7)
Leukopenia	1 (<1)	0	0	6 (10)	2 (3)	0

Table 5 Incidence of Laboratory abnormalities increased from baseline occurring at a higher incidence in patients treated with TAFINLAR in BRF113683 [Between arm difference of ≥ 5 % (all Grades) or ≥ 2 % (Grades 3 or 4)]

	TAFINLAR (n=187)		dacarbazine (n=59)	
	All Grades	Grades 3	All Grades	Grades 3
Hyperglycemia	50	6	43	0
Hypophosphatemia	37	6*	14	2
Increased Alkaline	19	0	14	2
Hyponatremia	8	2	3	0

*Grade 4 laboratory abnormality limited to hypophosphatemia (n=1).

Description of selected adverse reactions

Pyrexia

Fever has been reported in clinical trials with TAFINLAR as monotherapy and in combination with trametinib. The incidence and severity of pyrexia are increased with the combination therapy. In 1 % of patients in clinical trials, serious non-infectious febrile events were identified defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency or pre-renal origin in patients 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 section 4.2 Dose and method of administration).

Cutaneous squamous cell carcinoma

Cutaneous squamous cell carcinomas (including those classified as keratoacanthoma or mixed keratoacanthoma subtype) occurred in 9 % (52/578) of patients treated with TAFINLAR monotherapy in the integrated safety population and 3 % of patients treated with TAFINLAR in combination with MEKINIST in MEK115306. With TAFINLAR 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 TAFINLAR in combination with MEKINIST, events occurred later with the median time to onset of 22 weeks. Ninety-six percent of patients on TAFINLAR 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 TAFINLAR. Cases were managed with excision and did not require treatment modification (see section 4.4 Special warnings and precautions for use).

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 Special warnings and precautions for use). In clinical trials non-cutaneous malignancies were reported in 1% (6/586) of patients with TAFINLAR monotherapy, and 1% (3/209) of patients in study MEK115306 and < 1 % (3/350) of patients in study MEK116513 with TAFINLAR in combination with MEKINIST. Cases of RAS-driven malignancies have been seen with TAFINLAR. Patients should be monitored as clinically appropriate.

TAFINLAR and trametinib combination therapy

In addition to adverse reactions observed with monotherapy treatments (Table 6, and Table 7), the safety of TAFINLAR and MEKINIST combination therapy has been evaluated in two randomized Phase III studies and one small phase II study of patients with BRAF mutant unresectable or metastatic melanoma treated with TAFINLAR 150 mg orally twice daily and MEKINIST 2 mg orally once daily (see section 5.1- Clinical trials). The following tables list adverse reactions which are specific to TAFINLAR in combination with MEKINIST.

The following convention has been utilised for the classification of frequency. In Table 5, there were 55 patients in the study and hence the frequencies of uncommon or rare events could not be calculated.

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

The most common adverse reactions (≥ 20 %) for TAFINLAR and MEKINIST combination therapy include pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, vomiting, peripheral oedema, and cough.

Table 6 Study MEK115306 (COMBI-d) - Adverse events occurring in ≥ 10 % (all grades) or ≥ 2 % (grades 3 or 4) in unresectable or metastatic melanoma

	TAFINLAR 150 mg BID +		TAFINLAR 150 mg BID +	
	All grades	grades 3 & 4	All grades	grades 3 & 4
Neoplasms benign and malignant (including cysts and polyps)				
Skin papilloma	1	0	21	0
Squamous cell	<1	<1	4	2
Squamous cell	<1	<1	5	2
Metabolism and nutritional disorders				
Decreased appetite	11	<1	12	<1
Hyperglycaemia	3	2	<1	0
Hypophosphatemia	2	1	2	2
Nervous system disorders				
Headache	30	<1	29	1
Dizziness	10	0	6	0
Respiratory, thoracic, and mediastinal disorders				
Cough	16	0	17	0
Dyspnea	6	<1	9	2
Gastrointestinal disorders				
Nausea	30	0	26	1
Diarrhoea	24	<1	14	<1
Vomiting	20	<1	14	<1
Constipation	11	<1	9	0
Abdominal pain	11	<1	7	1
Skin and subcutaneous tissue disorders				
Rash	23	0	22	<1
Dry skin	9	0	13	0
Hyperkeratosis	3	0	32	<1
Pruritus	8	0	12	0
Alopecia	7	0	26	0

	TAFINLAR 150 mg BID +		TAFINLAR 150 mg BID +	
	All grades	grades 3 & 4	All grades	grades 3 & 4
PPE[a]	4	0	18	<1
Palmoplantar	<1	0	11	0
Musculoskeletal, connective tissue and bone disorders				
Arthralgia	24	<1	27	0
Pain in extremity	14	1	16	<1
Myalgia	11	<1	11	0
General disorders and administrative site conditions				
Pyrexia	51	6	28	2
Fatigue	35	2	35	<1
Chills	30	0	16	0
Asthenia	10	<1	13	<1
Edema peripheral	14	<1	5	<1
Infections and infestations				
Nasopharyngitis	10	0	7	0
Vascular disorders				
Hypertension	22	4	14	5
Hypotension	6	2	3	<1
Blood and Lymphatic System Disorders				
Neutropenia	9	3	<1	0
Anemia	6	2	7	3
Investigations				
ALT increased	11	2	5	<1
AST increased	11	3	3	<1
Lymphocyte count	2	2	1	1

[a] PPE = Palmar-plantar erythrodysesthesia.

Table 7 Study MEK115306 (COMBI-d) - Treatment emergent Liver function test abnormalities (worst case on therapy) occurring in patients treated with TAFINLAR in combination with MEKINIST or placebo

Test	TAFINLAR 150 mg BID plus placebo			TAFINLAR 150 mg BID + MEKINIST 2 mg		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Increased ALP	20	<1	0	45	<1	0
Increased AST	17	<1	0	53	2	<1
Increased ALT	25	<1	0	38	24	<1
Hyperbilirubinemia	2	0	0	4	<1	<1

ALP = Alkaline phosphatase; AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase

Table 8 Adverse reactions for TAFINLAR in combination with MEKINIST in melanoma randomized Phase III studies MEK115306 (COMBI-d), and integrated safety data (ISD) from MEK115306 and MEK116513 (COMBI-v)

	Frequency category	
	COMBI-d n=209	COMBI-d &
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	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
Hyperglycemia	Common	Common
Hyponatraemia	Common	Common
Hypophosphataemia	Common	Common
Nervous system disorders		
Headache	Very common	Very common
Dizziness	Very common	Very common
Eye disorders		
Vision blurred	Common	Common
Visual impairment	Common	Common
Chorioretinopathy	Uncommon	Uncommon
Uveitis	Uncommon	Uncommon
Retinal detachment	Uncommon	Uncommon
Periorbital oedema	Uncommon	Uncommon
Cardiac disorders		
Ejection fraction decreased	Common	Common
Left ventricular dysfunction	NR	Uncommon
Cardiac failure	NR	Uncommon
Bradycardia	Common	Common
Vascular disorders		
Hypertension	Very common	Very common
Haemorrhage[1]	Very common	Very common
Hypotension	Common	Common

	Frequency category	
	COMBI-d n=209	**COMBI-d &**
Lymphoedema	Uncommon	Common
Respiratory, thoracic and mediastinal disorders		
Cough	Very common	Very common
Dyspnoea	Common	Common
Pneumonitis	Uncommon	Uncommon
Interstitial lung disease	NR	Uncommon
Gastrointestinal disorders		
Abdominal pain	Very common	Very common
Constipation	Very common	Very common
Diarrhoea	Very common	Very common
Nausea	Very common	Very common
Vomiting	Very common	Very common
Dry mouth	Common	Common
Stomatitis	Common	Common
Pancreatitis	Uncommon	Uncommon
Investigations		
Alanine aminotransferase increased	Very common	Very common
Aspartate aminotransferase increased	Very common	Very common
Blood alkaline phosphatase increased	Common	Common
Gamma-glutamyltransferase increased	Common	Common
Skin and subcutaneous tissue disorders		
Dry skin	Very common	Very common
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 reaction[2]	Common	Common
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Very common
Myalgia	Very common	Very common
Pain in extremity	Very common	Very common
Muscle spasms	Common	Common
Blood creatine phosphokinase increased	Common	Common
Rhabdomyolysis	NR	Uncommon
Renal disorders		
Renal failure	Uncommon	Common
Nephritis	Uncommon	Uncommon
Renal failure acute	NR	Uncommon
General disorders and administration site disorders		

	Frequency category	
	COMBI-d n=209	**COMBI-d &**
Fatigue	Very common	Very common
Oedema peripheral	Very common	Very common
Pyrexia	Very common	Very common
Chills	Very common	Very common
Asthenia	Very common	Very common
Mucosal inflammation	Common	Common
Influenza-like illness	Common	Common
Face oedema	Common	Common

NR= Not reported;

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

[2] Photosensitivity cases were also observed in post-marketing experience. All cases reported in clinical trials were Grade 1 and no dose modification was required.

Table 9 Adverse reactions specific for TAFINLAR in combination with MEKINIST in Part C of Phase II study BRF113220 (n=55) (data cut-off 31 May 2012)

Infections and infestations	
Very common	Urinary tract infection
Blood and lymphatic system disorders	
Very common	Neutropenia
Common	Thrombocytopenia
Metabolism and nutrition disorders	
Common	Hyponatraemia
Nervous system disorders	
Very common	Dizziness
Vascular disorders	
Very Common	Haemorrhage[a]
Common	Hypotension
Hepatobiliary disorders	
Common	Gamma-glutamyl transferase increased
Skin and subcutaneous tissue disorders	
Very common	Night sweats
Common	Hyperhidrosis
Musculoskeletal and connective tissue disorders	
Very Common	Muscle spasms
Common	Rhabdomyolysis

[a]Events include: brain stem haemorrhage, cerebral haemorrhage, gastric haemorrhage, epistaxis, gingival haemorrhage, haematuria, vaginal haemorrhage, haemorrhage intracranial, eye haemorrhage, and vitreous haemorrhage

Adjuvant treatment of melanoma

Tafinlar in combination with Mekinist

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

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

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

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

Very common:	≥1/10)
Common:	≥1/100 and <1/10
Uncommon:	≥1/1,000 and <1/100
Rare:	≥1/10,000 and <1/1,000
Very rare	<1/10,000.

Table 10 Adjuvant treatment of melanoma - Adverse drug reactions for Tafinlar in combination with Mekinist vs. placebo (Study BRF115532 [COMBI-AD])

Adverse drug reactions	Tafinlar in combination with Mekinist N=435 %		Placebo N=432 %		Frequency category (combination arm, all grades)
	All Grades	Grade 3/4	All Grades	Grade 3/4	
Infections and infestations					
Nasopharyngitis[1)]	12	<1	12	NR	Very common
Blood and lymphatic system disorders					
Neutropenia[2)]	10	5	<1	NR	Very common
Metabolism and nutrition disorders					
Decreased appetite	11	<1	6	NR	Very common
Nervous system disorders					
Headache[3)]	39	1	24	NR	Very common
Dizziness[4)]	11	<1	10	NR	Very common
Eye disorders					
Uveitis	1	<1	<1	NR	Common
Chorioretinopathy[5)]	1	<1	<1	NR	Common
Retinal detachment[6)]	1	<1	<1	NR	Common
Vascular disorders					
Haemorrhage[7)]	15	<1	4	<1	Very common
Hypertension[8)]	11	6	8	2	Very common
Respiratory, thoracic, and mediastinal disorders					
Cough[9)]	17	NR	8	NR	Very common
Gastrointestinal disorders					
Nausea	40	<1	20	NR	Very common
Diarrhoea	33	<1	15	<1	Very common
Vomiting	28	<1	10	NR	Very common
Abdominal pain[10)]	16	<1	11	<1	Very common
Constipation	12	NR	6	NR	Very common
Skin and subcutaneous tissue disorders					
Rash[11)]	37	<1	16	<1	Very common

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

1) Nasopharyngitis also includes pharyngitis.

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

3) Headache also includes tension headache.

4) Dizziness also includes vertigo.

5) Chorioretinopathy also includes chorioretinal disorder.

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

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

8) Hypertension also includes hypertensive crisis.

9) Cough also includes productive cough.

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

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

12) Dry skin also includes xerosis and xeroderma.

13) Erythema also includes generalized erythema.

14) Pruritus also includes puritus generalized and pruritus genital.

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

16) Muscle spasms also includes musculoskeletal stiffness.

17) Pyrexia also includes hyperpyrexia.

18) Fatigue also includes asthenia and malaise.

19) Oedema peripheral also includes peripheral swelling.

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

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

NR: not reported

Table 11 Treatment-emergent laboratory abnormalities (all grades) occurring with between arm difference ≥ 10 % (Study BRF115532 [COMBI-AD])

Test result	TAFINLAR in combination with MEKINIST (N=435)	Placebo (N=432)
Serum albumin abnormalities	25 %	<1 %
Hyponatraemia	16 %	3 %
Hyperglycaemia	63 %	47 %
Serum phosphate abnormalities	42 %	10 %

Paediatric use

The safety and efficacy of TAFINLAR has not been yet established in children and adolescents (< 18 years). 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), thymus toxicity (lymphoid apoptosis) and testicular toxicity (degeneration and tubular dilation) were observed.

Use in the elderly

No initial dose adjustment is required in patients over 65 years of age (see section 4.2 Dose and method of administration and section 5.2 Pharmacokinetic properties).

For clinical trials of TAFINLAR monotherapy, compared with younger patients (< 65 years of age), more patients over 65 years old had adverse reactions that lead 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 patients and younger patients.

Across clinical trials of TAFINLAR administered in combination with MEKINIST (n = 202), adverse events resulting in dose interruption were reported for 71 % of those aged ≥ 65 years as compared to 60 % of those < 65 years, while adverse events resulting in dose reduction occurred in 64 % of those aged ≥ 65 years as compared to 44 % of those < 65 years of age.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Symptoms and Signs

There is currently very limited experience with overdosage with TAFINLAR. The maximum dose of TAFINLAR administered during clinical trials was 600 mg (300 mg twice daily).

Treatment

There is no specific antidote for overdosage of TAFINLAR. Patients who develop adverse reactions should receive appropriate symptomatic treatment. In case of suspected overdose, TAFINLAR should be withheld and supportive care instituted. For information on the management of overdose contact the Poison Information Centre on 13 11 26.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors
Anatomical Therapeutic Chemical (ATC Code): L01XE23

5.1 Pharmacodynamic properties

Mechanism of action in all indications

TAFINLAR monotherapy

The active ingredient in TAFINLAR, dabrafenib, is an ATP-competitive inhibitor of RAF kinases with IC_{50} values of 0.65, 0.5 and 1.84 nM for BRAF V600E, BRAF V600K and BRAF V600D enzymes respectively. TAFINLAR also inhibits a small number of other kinases, including wild-type BRAF and CRAF with IC_{50} values of 3.2 and 5.0 nM, respectively. Mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway and stimulation of tumour cell growth. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50 % of melanoma. The most commonly observed BRAF mutation, V600E, and the next most common, V600K, account for 95 % of the BRAF mutations found in these cancers. A number of rare mutations also occur including V600D, V600G and V600R. Clinical inhibition of the MAPK pathway signalling depends on cellular and genotypic context (See section 4.4 Special warnings and precautions for use - Non-cutaneous malignancy).

TAFINLAR inhibits BRAF V600 mutant melanoma cell growth *in vitro* and *in vivo*.

TAFINLAR in combination with MEKINIST in all indications

The active ingredient in MEKINIST, trametinib, is a reversible 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. TAFINLAR and MEKINIST inhibit two critical kinases in this pathway, BRAF and MEK, and the combination provides concomitant inhibition of the pathway. The combination of TAFINLAR with MEKINIST is synergistic 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.

Pharmacodynamic effects

TAFINLAR 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 TAFINLAR resulted in inhibition of tumour phosphorylated ERK relative to baseline.

Determination of BRAF mutation status

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

Clinical Trials

Unresectable or metastatic melanoma

TAFINLAR monotherapy - open label studies

The efficacy of TAFINLAR in the treatment of adult patients with BRAF V600 mutation positive unresectable or metastatic melanoma has been evaluated in 3 open label studies:

1. Phase III Study BRF113683 [BREAK-3]
2. Phase II Study BRF113929 [BREAK-MB], and
3. Phase II Study BRF113710 [BREAK-2].

Included in these studies were 402 patients with BRAF V600E and 49 patients with BRAF V600K mutation.

Patients with evidence of active CNS disease (e.g. radiographically unstable or with symptomatic lesions) and those with disease progression in the brain in the last three months were excluded from the pivotal Phase III study.

Phase III study BREAK-3 in previously untreated melanoma patients

The efficacy and safety of TAFINLAR were evaluated in this Phase III randomised, open-label study [BREAK-3] comparing TAFINLAR 150 mg twice daily to IV dacarbazine (DTIC) 1000 mg/m2 every 3 weeks in previously untreated patients with BRAF V600E mutation positive unresectable or 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 tumour sample available. Two hundred and fifty patients were randomised 3:1 to receive either TAFINLAR or intravenous DTIC. The primary objective was to evaluate the efficacy of TAFINLAR compared to DTIC with respect to progression-free survival (PFS) per investigator assessment for patients with BRAF V600E mutation positive metastatic melanoma. Patients on the DTIC arm were allowed to cross over and receive 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 Caucasian; 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.

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 % CI 0.18, 0.51; p < 0.0001) was achieved. PFS from the primary analysis is shown in Figure 1. Efficacy results from a post-hoc analysis with 6-months additional follow-up are summarised in Table 12. Overall survival data from a further post-hoc analysis based on an 18 December 2012 data cut is provided in Table 13 and shown in Figure 1. As of 25 June 2012, thirty-five patients (55.6 %) of the 63 randomised to DTIC crossed over to TAFINLAR. Median PFS after cross-over was 4.4 months.

Table 12 Investigator assessed efficacy in previously untreated patients (BREAK-3 study, 25 June 2012)

	Intention-to-Treat Population	
Endpoints/ Assessment	**TAFINLAR (N=187)**	**dacarbazine (N=63)**
Progression-free survival		
Median, months (95 % CI)	6.9 (5.2, 9.0)	2.7 (1.5, 3.2)
HR (95 % CI)	0.37 (0.24, 0.58)	
Overall response[a]		
% (95 % CI)[b]	59 (51.4, 66.0)	24 (21.4, 36.2)
	p < 0.0001	
Duration of response		
Median, months (95 % CI)	8.0 (6.6, 11.5)	7.6 (5.0, 9.7)

Abbreviations: CI: confidence interval; HR: hazard ratio; NR-not reached; [a] Defined as complete response + partial response; [b] Confirmed response.

Table 13 Survival data from a post-hoc analysis (18 December 2012)

Treatment	Number of deaths	12-month OS rate	Hazard Ratio
dacarbazine	28 (44 %)	63 %	0.76 (0.48, 1.21) [(a)]
TAFINLAR	78 (42 %)	70 %	

Patients were not censored at the time of cross-over.

Figure 1 Investigator-assessed PFS in previously untreated melanoma patients (BREAK 3 ITT population, 19 December 2011)

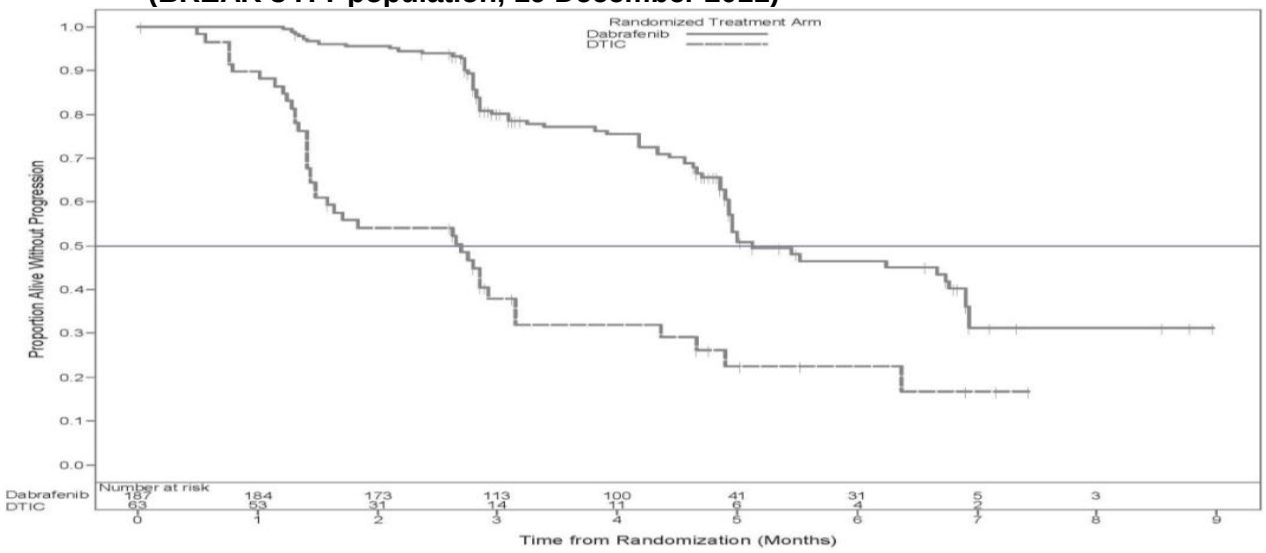
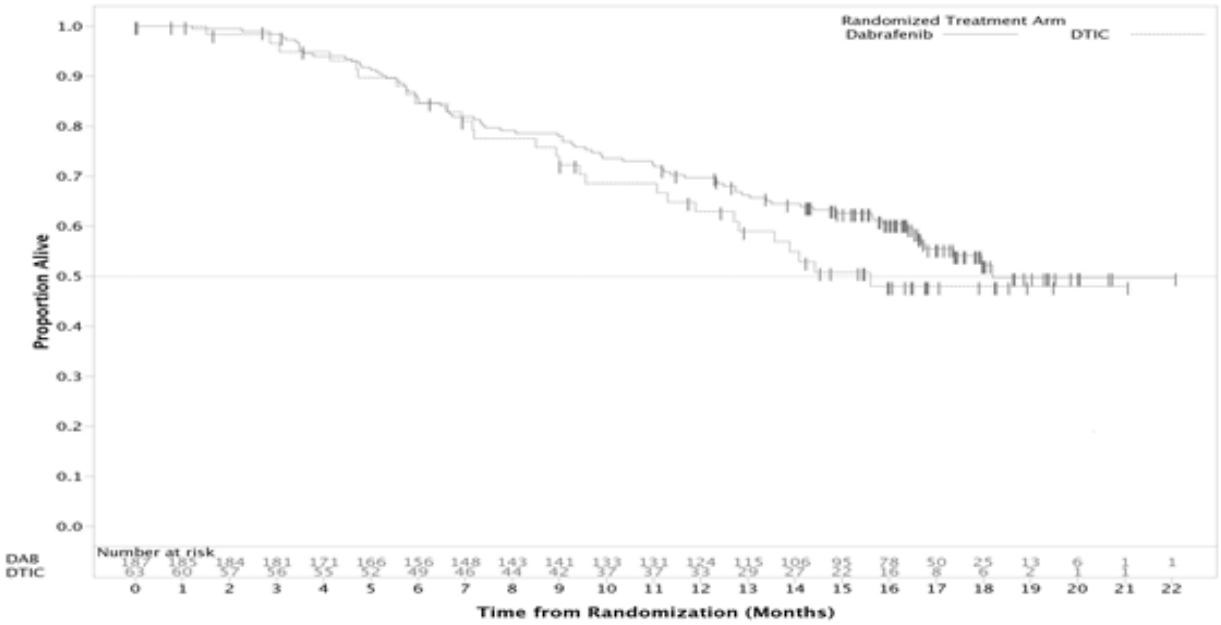


Figure 2 Investigator-assessed Kaplan-Meier curves of overall survival (BREAK-3) (18 December 2012)



Phase II Study BREAK-MB in patients with Stage IV BRAF-mutation positive (V600E or V600K) brain metastases

This multi-centre, open-label, two-cohort, Phase II study was designed to evaluate the intracranial response of 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 primary endpoint of the study was overall intracranial response rate (OIRR), which is a measure of response (CR + PR) of intracranial lesions using modified RECIST criteria as assessed by investigators. The results are summarised in Table 14. Of note, the benefit risk, in terms of intracranial response, relative to surgery or stereotactic radio-surgery has not been studied directly however evidence from cohort B below suggests that prior local treatment does not preclude subsequent benefit from BRAF inhibition.

Table 14 TAFINLAR efficacy data in patients with brain metastases (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)	31 % (19.9, 43.4)	7 % (0.2, 31.9)	22 % (6.4, 47.6)
	P<0.001	P<0.001[b]		
Duration of intracranial response, median months (95% CI)				
	N=29	N=20	N=1	N=4
	4.6 (2.8, NR)	6.5 (4.6, 6.5)	2.9 (NR, NR)	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	N=20	NA	N=5
	5.1 (3.7, NR)	4.6 (4.6, 6.5)		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)				
	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} positive patients.

Phase II study BREAK-2 in Stage IV metastatic patients who were previously untreated or failed at least one prior systemic therapy

This was a multi-centre, 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, etc.).

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. Although the evidence for the efficacy of TAFINLAR is limited by the low number of patients, median OS appeared consistent with data in patients with BRAF V600E positive tumours.

TAFINLAR in combination with MEKINIST

The efficacy and safety of the recommended dose of TAFINLAR (150 mg twice daily) in

combination with MEKINIST (2 mg once daily) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation was studied in Phase I/II study BRF113220 and two pivotal Phase III studies, MEK116513 and MEK115306.

Randomised open label studies

BRF113220 (Phase I/II Studies)

In an open-label study, the safety, PK, PD, and clinical activity of TAFINLAR and MEKINIST combination therapy were evaluated in patients with BRAF V600E, V600K, or V600D mutation-positive melanoma. This study had four parts, A-D:

- Part A was a drug/drug interaction (DDI) study to determine the effect of repeat doses of MEKINIST on the PK of a single dose of TAFINLAR and its metabolites (n = 8),
- Part B was a dose escalation and expansion study to determine optimal doses and safety of MEKINIST when administered in combination with TAFINLAR (n = 135).
- Part C was an open-label randomised three-arm phase II study determine the efficacy, safety, and tolerability of MEKINIST and TAFINLAR in patients with BRAF mutant metastatic melanoma (n=162) and is described below;
- Part D was a PK and safety evaluation of MEKINIST and TAFINLAR capsules (n = 110).

The determination of BRAF mutation positive status was required and was established by institutional laboratory for all patients enrolled in Parts A-D.

Prior BRAF inhibitor (BRAFi) therapy

There are limited data in patients taking the combination of TAFINLAR with MEKINIST who have progressed on a prior BRAF inhibitor.

Part B of open-label study BRF113220 included a cohort of 26 patients that had progressed on a BRAFi. The combination of 150 mg TAFINLAR with 2 mg MEKINIST demonstrated limited clinical activity in patients who had progressed on a BRAFi. The Investigator-assessed ORR 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 43 patients who crossed over from TAFINLAR monotherapy to the combination of 150 mg TAFINLAR plus 2 mg MEKINIST in Part C of this study. In these patients a 9 % (95 % CI: 2.6, 22.1) ORR was observed with a median PFS of 3.6 months (95 % CI: 1.8, 3.9).

Part C

Part C of this open-label, randomised, three-arm phase II study assessed the safety and efficacy of TAFINLAR at 150 mg given twice daily in combination with two different doses of MEKINIST (1 mg once daily and 2 mg once daily) relative to TAFINLAR alone (150 mg twice daily) in 162 patients. The primary efficacy endpoints were PFS, ORR, and DoR. Patients on the TAFINLAR monotherapy arm were permitted to cross-over to the full-dose combination arm (150 mg TAFINLAR plus 2 mg MEKINIST) upon progression. A total of 43 patients (81 %) in the TAFINLAR monotherapy arm with disease progression crossed over to receive TAFINLAR 150 mg and MEKINIST 2 mg combination.

Baseline characteristics were balanced between treatment groups. Most patients (85 %) in all treatment arms had BRAF V600E mutation and 15 % of patients had BRAF V600K. Investigator assessed median PFS for TAFINLAR 150 mg twice daily plus MEKINIST 2 mg once daily was 9.4 months (95 % CI: 8.6, 16.7) compared to 5.8 months (95 % CI: 4.6, 7.4 months) for TAFINLAR 150 mg twice daily monotherapy. The hazard ratio was 0.39 (95 % CI 0.25, 0.62, $p < 0.0001$). Overall response rate for TAFINLAR 150 mg twice daily plus MEKINIST 2 mg once daily was 76 % (95 % CI: 62.4, 86.5, $p = 0.0264$) compared to 54 % (95 % CI: 39.6, 67.4) for TAFINLAR 150 mg twice daily monotherapy.

The investigator-assessed ORR, DoR, and PFS were consistent in the subgroup of patients with BRAF V600E and BRAF V600K mutation positive melanoma receiving 150 mg TAFINLAR plus 2 mg MEKINIST combination.

A retrospective blinded independent committee review (BICR) was conducted and had the following results:

- 61 % ORR (95 CI: 46.9 %, 74.1 %; P = 0.1486) for patients treated with 150 mg TAFINLAR plus 2 mg MEKINIST combination,
- 39 % (95 % CI: 25.9, 53.1; P = 0.5008) for patients treated with 150 mg TAFINLAR plus 1 mg MEKINIST combination, and
- 46 % (95 % CI: 32.6 %, 60.4 %) for patients treated with 150 mg TAFINLAR monotherapy.
- Median PFS was 9.2 months (95 % CI: 7.6, NR; P = 0.0121) for patients treated with TAFINLAR 150 mg plus 2 mg MEKINIST combination,
- Median PFS was 8.3 months (95 % CI: 5.6, 11.3; P = 0.1721) for patients treated with 150 mg TAFINLAR plus 1 mg MEKINIST combination, and
- Median PFS was 7.3 months (95 % CI: 5.5, 9.4) for patients treated with 150 mg TAFINLAR monotherapy.

Randomised open label study in BRAFi-treatment-naïve patients

MEK116513 (COMBI-v, Phase III Study)

Study MEK116513 was a 2-arm, randomized, open-label, Phase III study comparing TAFINLAR and MEKINIST combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive unresectable or metastatic melanoma. The primary endpoint of the study was OS (see Figure 3) and the key secondary endpoint was PFS. Other secondary objectives included ORR, DoR, and safety. Patients were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ ULN) and BRAF mutation (V600E versus V600K).

Seven hundred and four patients were randomized 1:1 to either the combination therapy arm (TAFINLAR 150 mg twice daily and MEKINIST 2 mg once daily) or the vemurafenib monotherapy arm (960 mg twice daily). Most patients were white (> 96 %) and male (55 %), with a median age of 55 years (24 % were ≥ 65 years). The majority of 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 %).

The OS analysis for Study MEK116513 was conducted when 222 total deaths (77 % of the required events for the final analysis) occurred. The Independent Data Monitoring Committee (IDMC) recommended stopping the study since the OS results crossed the pre-specified efficacy boundary. As a consequence the interim OS summary was considered the final comparative OS analysis.

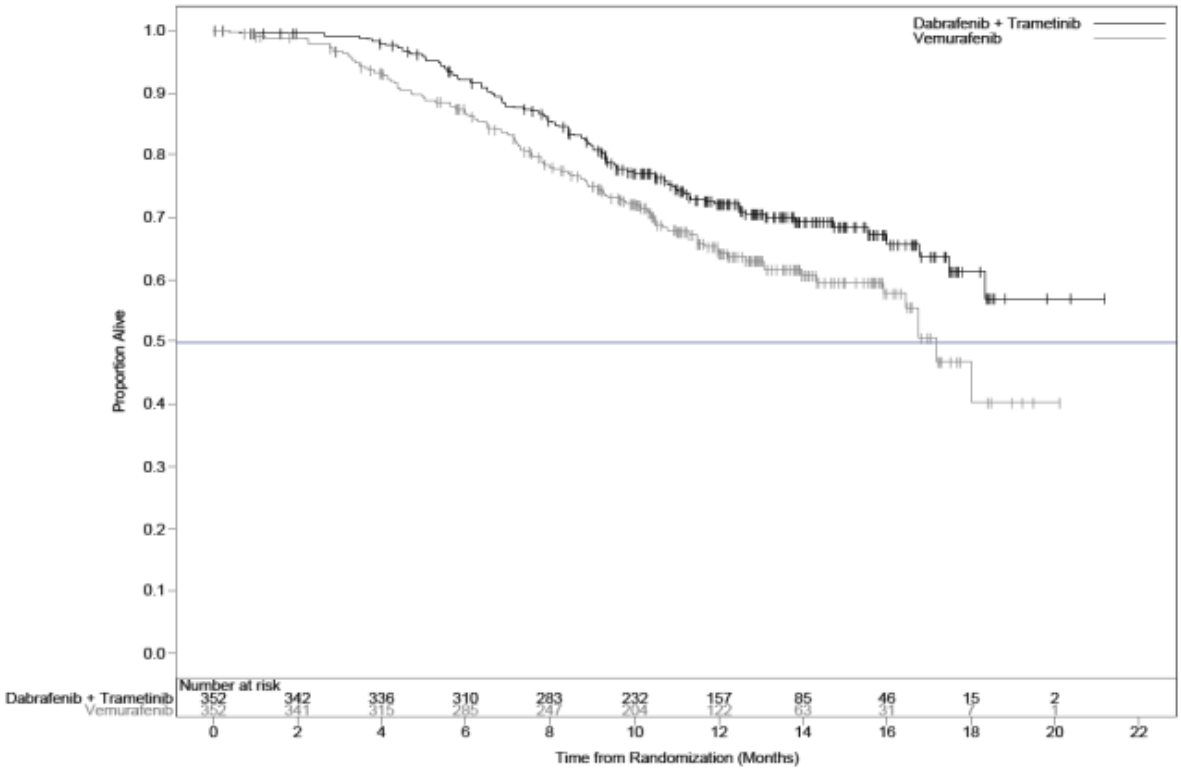
The OS analysis was based on 222/704 (32 %) deaths in the study [TAFINLAR and MEKINIST combination therapy: 100 deaths (28 %) and vemurafenib monotherapy: 122 deaths (35 %)]. The median follow up time on study treatment was 11 months for the combination arm and 9 months in the vemurafenib arm. Study MEK116513 showed a statistically significant 31 % reduction in the risk of death for the MEKINIST and TAFINLAR combination therapy compared with vemurafenib monotherapy (HR = 0.69, 95 % CI: 0.53, 0.89; p = 0.005). The median OS was not yet reached for the combination arm, and was 17.2 months for vemurafenib monotherapy. The results of the secondary efficacy endpoints for PFS, ORR and DoR are summarized in Table 15.

Table 15 Investigator-Assessed Efficacy results for MEK116513 (COMBI-v) study

Endpoint	TAFINLAR + MEKINIST (N=352)	Vemurafenib (N=352)
Investigator Assessed PFS		
Progressive disease or death, n (%)	166 (47)	217 (62)
Median, 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	
Overall Response Rate, n (%)	226 (64)	180 (51)
95 % CI	(59.1, 69.4)	(46.1, 56.8)
Difference in response rate (CR+PR), %	13	
95 % CI for difference	(5.7, 20.2)	
p value	0.005	
Duration of Response (months)		
Median	13.8	7.5
95 % CI	(11.0, NR)	(7.3, 9.3)

PFS= Progression Free Survival; NR= Not reached

Figure 3 Kaplan-Meier Overall Survival Curves (ITT Population)



Randomised double-blind study in BRAFi-treatment-naïve patients

MEK115306 (COMBI-d, Phase III Study)

MEK115306 (COMBI-d) was a Phase III, randomized, double-blind study comparing the combination of TAFINLAR and MEKINIST to 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).

Four hundred and twenty three patients were randomized 1:1 to either the combination therapy arm (TAFINLAR 150 mg twice daily and MEKINIST 2 mg once daily) (N = 211) or 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 (28% were ≥65 years). The majority of patients had an ECOG performance score of 0 (72 %) and had Stage IVM1c disease (66 %). Most patients had the BRAF V600E mutation (85 %); the remaining 15 % of patients had the BRAF V600K mutation. Patients with brain metastases were not included in the trial.

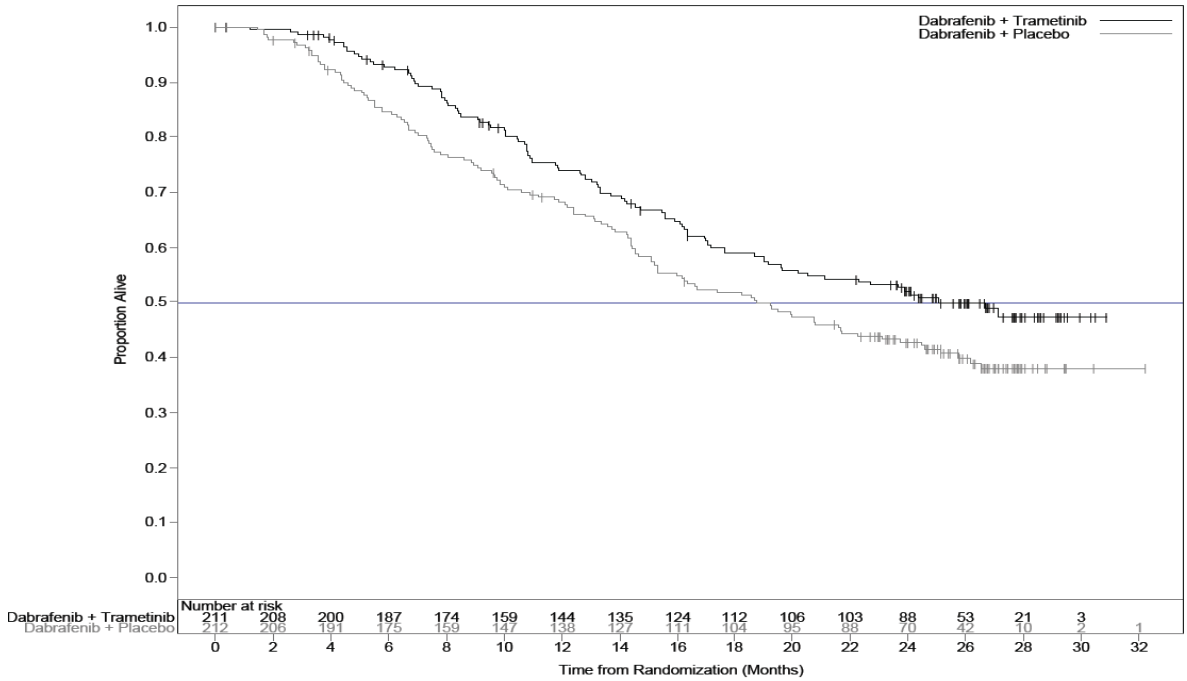
At the time of final OS analysis, a total of 222 deaths (52.5 %) [TAFINLAR and MEKINIST combination therapy: 99 deaths (47 %) and TAFINLAR monotherapy: 123 deaths (58 %)] out of the randomized (or ITT) population were reported. The median follow up time on study treatment was 20 months in the combination therapy arm and 16 months in the TAFINLAR monotherapy arm. Study MEK115306 showed a statistically significant 29 % reduction in the risk of death for the combination therapy arm compared with the TAFINLAR monotherapy arm (HR=0.71, 95 % CI: 0.55, 0.92; p=0.011). The median OS was 25.1 months for the combination therapy arm and 18.7 months for the TAFINLAR monotherapy arm. The 12-month (74 %) and 24-month (51.4 %) OS estimates for the combination were also greater than those for TAFINLAR monotherapy (67.6 % and 42.1 %, respectively). Efficacy results of PFS, ORR and Duration of Response are summarized in Table 16.

Table 16 Investigator-Assessed efficacy results for MEK115306 (COMBI-d) study (primary data cut and final data cut)

	Primary analysis*		Final analysis*	
Endpoints	**TAFINLAR plus MEKINIST**	**TAFINLAR**	**TAFINLAR plus MEKINIST**	**TAFINLAR**
Investigator Assessed PFS	**(N=211)**	**(N=212)**	**(N=211)**	**(N=212)**
Progressive disease or death, n (%)	102 (48)	109 (51)	139 (66)	162 (76)
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)
Hazard Ratio (95 % CI)	0.75 (0.57,0.99)		0.67 (0.53, 0.84)	
p value (log-rank test)	0.035		< 0.001	
	(N=210)	**(N=210)**	**(N=210)**	**(N=210)**
Overall Response Rate[b] % (95 % CI)	67 (59.5,73.0)	51 (44.5,58.4)	69 (61.8, 74.8)	53 (46.3, 60.2)
% Difference in response rate (CR[c]+PR[c])	15[d]		15[d]	
95 % CI for difference	(5.9, 24.5)		(6.0, 24.5)	
p value	0.0014		0.0014	
Median duration of response (months) (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)

*Primary data cut: 26 August 2013, Final data cut: 12 January 2015
[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
NR = Not reached

Figure 4 Kaplan-Meier Overall Survival Curves (Combi-d ITT Population)



Adjuvant treatment of melanoma

Study BRF115532 / CDRB436F2301 (COMBI-AD)

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

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

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

Results for the primary analysis of RFS are presented in Figure 5 and in Table 17. The study showed a statistically significant difference for the primary outcome of RFS between treatment arms, with an estimated 53% risk reduction in the dabrafenib and trametinib combination arm

as compared to the placebo arm (HR=0.47; 95% CI: 0.39, 0.58; p=1.53×10-14). Results were consistent across subgroups, including stratification factors for disease stage and BRAF V600 mutation type. Median RFS was 16.6 months for the placebo arm, and has not yet been reached for the combination arm.

Based on 153 events (60 (14%) in the combination arm and 93 (22%) in the placebo arm) corresponding to a 26% information fraction of the total target of 597 OS events, the estimated hazard ratio for OS was 0.57 (95% CI: 0.42, 0.79; p=0.0006). These results did not meet the pre-specified boundary to claim statistical significance at this first OS interim analysis (HR=0.50; p=0.000019). Survival estimates at 1 and 2 years from randomization were 97% and 91% in the combination arm and 94% and 83% in the placebo arm, respectively. The Kaplan-Meier curve for this OS interim analysis is shown in Figure 6.

Figure 5 COMBI-AD - Relapse-free survival Kaplan-Meier curves (ITT population)

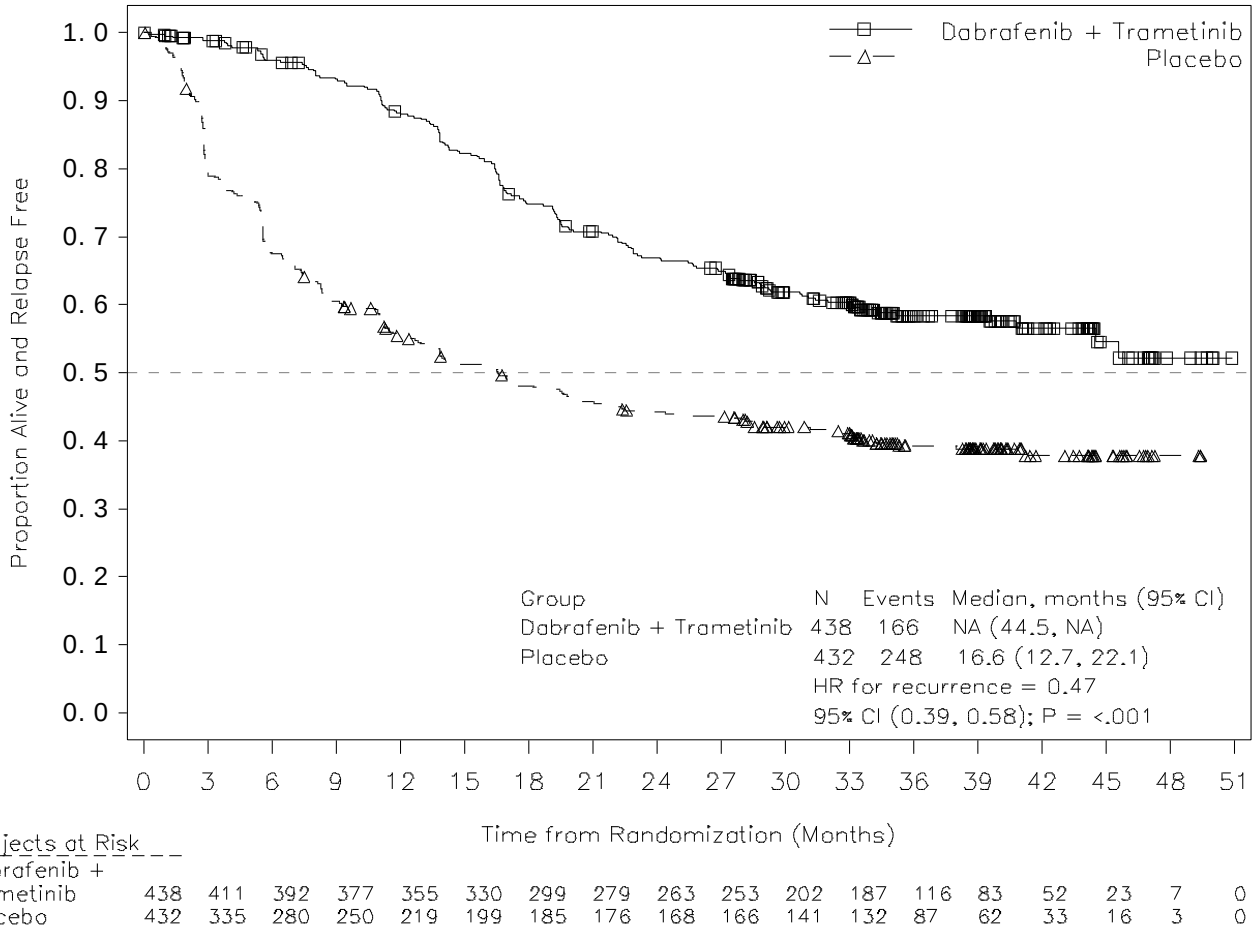


Table 17 COMBI-AD – Relapse-free survival results

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

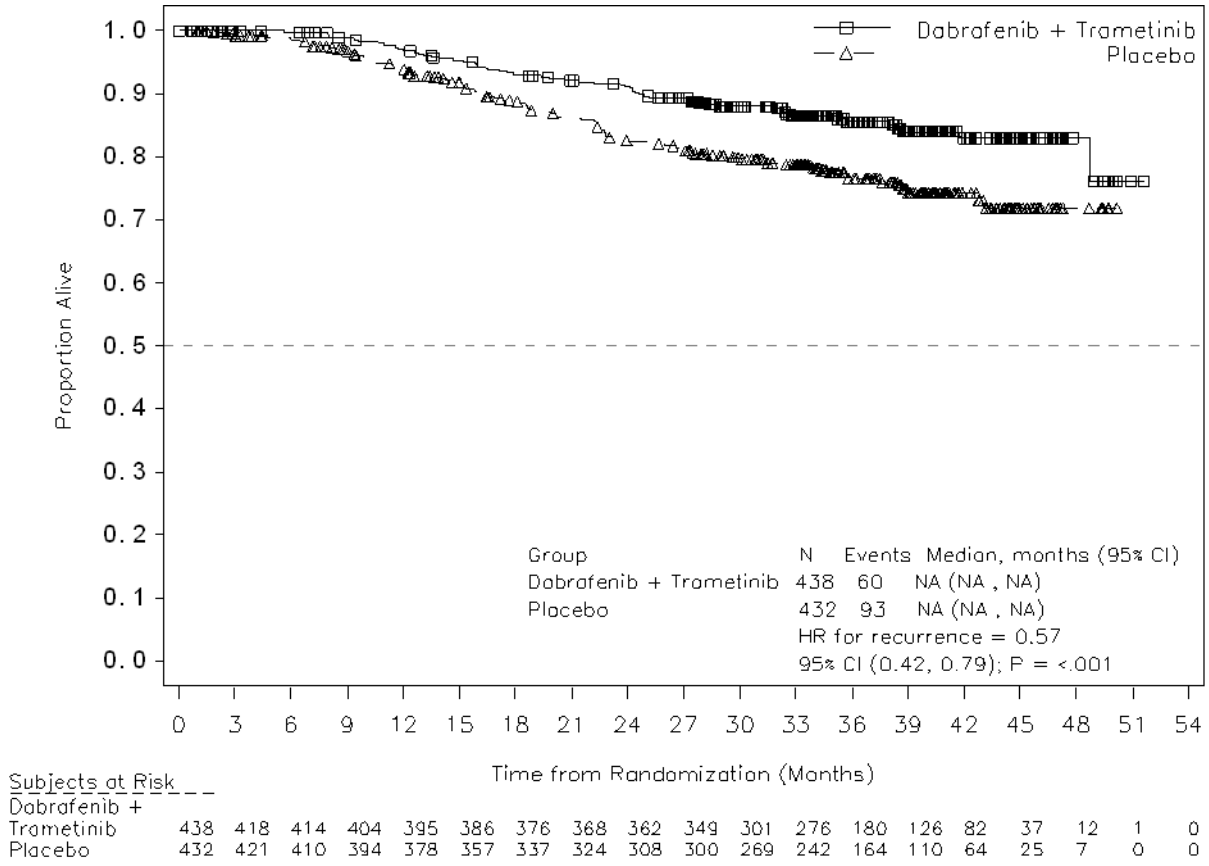
RFS parameter	Dabrafenib + Trametinib N=438	Placebo N=432
(95% CI)	(0.39, 0.58)	
p-value[2]	1.53×10^{-14}	
1-year rate (95% CI)	0.88 (0.85, 0.91)	0.56 (0.51, 0.61)
2-year rate (95% CI)	0.67 (0.63, 0.72)	0.44 (0.40, 0.49)
3-year rate (95% CI)	0.58 (0.54, 0.64)	0.39 (0.35, 0.44)

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

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

NE = not estimable

Figure 6 COMBI-AD – Overall survival Kaplan-Meier curves (ITT Population)



5.2 Pharmacokinetic properties

The pharmacokinetics of TAFINLAR were determined in patients with BRAF mutation-positive metastatic melanoma after single dose and after repeat dosing at 150 mg twice daily with dosing approximately 12 hours apart.

Absorption

TAFINLAR is absorbed orally with median time to achieve peak plasma concentration of 2 hours post-dose. Mean absolute bioavailability of oral TAFINLAR is 95 % (90 % CI: 81, 110 %). TAFINLAR exposure (C_{max} and AUC) increased in a dose proportional manner between 75 and 150 mg following single-dose administration, but the increase was slightly 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 averaged 0.73. Following administration of 150 mg twice daily, geometric mean C_{max}, $AUC_{(0-\tau)}$ and predose concentration ($C\tau$) at steady state were 1,478 ng/mL, 4,341 ng*hour/mL and

26 ng/mL, respectively.

Effect of food on TAFINLAR

Administration of TAFINLAR with food reduced the bioavailability (C_{max} and AUC decreased by 51 % and 31 % respectively) and delayed absorption of TAFINLAR capsules when compared to the fasted state. Patients should take TAFINLAR as monotherapy or in combination with MEKINIST at least one hour prior to or two hours after a meal due to the effect of food on TAFINLAR absorption (see section 4.2 Dose and method of administration).

Distribution

The active in TAFINLAR binds to human plasma protein and is 99.7 % bound. The steady-state volume of distribution following intravenous microdose administration is 46 L.

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

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

Metabolism

The metabolism of TAFINLAR 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 metabolised 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 TAFINLAR; while the activity of carboxy-dabrafenib is not likely to be significant.

Excretion

Terminal half-life following IV microdose is 2.6 hours. TAFINLAR terminal half-life is 8 hours due to a prolonged terminal phase after oral administration. IV plasma clearance after single dose is 12 L/hour. Following repeat oral dose administration, the oral clearance (CL/F) is 35 L/hour.

Faecal excretion mediated via CYP3A4 and CYP2C8 metabolism is the major route of elimination after oral dose, accounting for 71 % of a radioactive dose while urinary excretion accounted for 23 % of radioactivity as metabolites.

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 TAFINLAR oral clearance. In addition, mild hepatic impairment as defined by bilirubin and AST did not have a significant effect on TAFINLAR 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 TAFINLAR and its metabolites, administration of TAFINLAR should be undertaken with caution in patients with moderate to severe hepatic impairment (see section 4.2 Dose and method of administration).

Renal Impairment

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

Paediatric use

No studies have been conducted to investigate the pharmacokinetics of TAFINLAR in paediatric patients.

Use in the elderly

Based on the population pharmacokinetic analysis, age had no significant effect on TAFINLAR pharmacokinetics. Age greater than 75 years was a significant predictor of carboxy- and desmethyl-dabrafenib plasma concentrations with a 40 % greater exposure in patient's $\geq$ 75 years of age, relative to patients < 75 years old.

Body Weight and Gender

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

Race/Ethnicity

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

5.3 Preclinical Safety Data

Genotoxicity

TAFINLAR was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay.

Carcinogenicity

Carcinogenicity studies with TAFINLAR have not been conducted. An increase in cutaneous malignancies has been observed with BRAF inhibitors with preliminary evidence suggesting this occurs in patients harbouring other MAPK pathway mutations, including RAS, in skin (see section 4.4 Special warnings and precautions for use for cuSCC, new primary melanoma and non-cutaneous malignancy).

6. PHARMACEUTICAL PARTICULARS

6.1 List Of Excipients

TAFINLAR capsules contain the following inactive ingredients: microcrystalline cellulose, magnesium stearate (vegetable source), colloidal anhydrous silica, iron oxide red, titanium dioxide, hypromellose, iron oxide black, shellac, butan-1-ol, isopropyl alcohol, propylene glycol, and ammonium hydroxide.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf-life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for Storage

Store TAFINLAR capsules below 30°C.

6.5 Nature and contents of the container

TAFINLAR capsules are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures. The packs contain either 28* or 120 capsules.

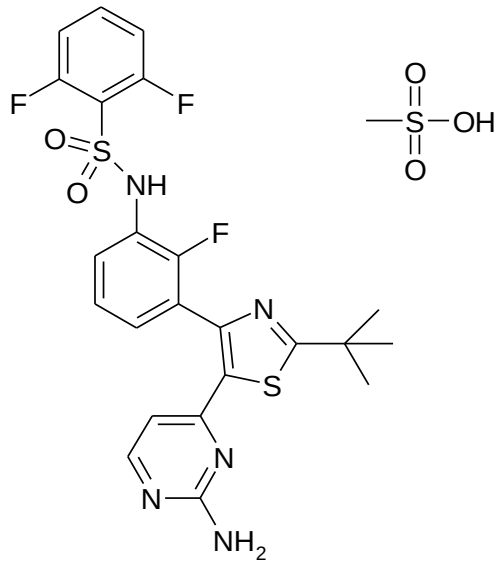
*Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

6.7 Physicochemical properties

Chemical structure



Chemical Abstracts Service (CAS) number 1195768-06-9

Chemical name	N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methane sulfonate salt
Molecular formula	$C_{23}H_{20}F_3N_5O_2S_2$. CH_4O_3S
Molecular weight	615.68

Dabrafenib mesilate is a nitrogen- and sulphur- containing heterocycle possessing an aromatic sulphonamide. It is a white to slightly coloured solid. In aqueous media, dabrafenib mesilate is very slightly soluble at pH 1, and practically insoluble above pH 4. The pKa of the sulphonamide moiety is 6.6, the pKa of the pyrimidine moiety is 2.2 and the pKa of the thiazole moiety is -1.5. The partition coefficient (log P) is 2.9.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

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Web site: www.novartis.com.au
® = Registered Trademark

9. DATE OF FIRST APPROVAL

21 August 2013

10. DATE OF REVISION

06 June 2018

Summary table of changes

Section changed	Summary of new information
All	Product Information has been reformatted according to TGA guidance and includes the adjuvant melanoma indication