NEW ZEALAND DATA SHEET

TAFINLAR® capsules

Dabrafenib mesilate

1. PRODUCT NAME

TAFINLAR 50 mg hard capsules
TAFINLAR 75 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TAFINLAR 50 mg capsule
Each hard capsule contains 50mg of dabrafenib (as mesilate).

TAFINLAR 75 mg capsule
Each hard capsule contains 75mg of dabrafenib (as mesilate).

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

3. PHARMACEUTICAL FORM

Hard capsules.

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

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Unresectable or metastatic melanoma

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

TAFINLAR in combination with MEKINIST is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Adjuvant treatment of melanoma

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

Anaplastic thyroid cancer (ATC)

TAFINLAR in combination with MEKINIST is indicated for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with a BRAF V600 mutation.

Non-small cell lung cancer (NSCLC)

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

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 therapy and in combination with trametinib (see section 5.1).

When TAFINLAR is used in combination with trametinib (MEKINIST), please also refer to the full MEKINIST Data Sheet: Dose and method of administration, for trametinib dosing instructions.

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

Adult Dosage

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

TAFINLAR treatment should continue until disease progression or the development of unacceptable toxicity (see Table 1), except for the adjuvant treatment of melanoma. For adjuvant melanoma, TAFINLAR treatment should continue until disease recurrence or unacceptable toxicity for up to 1 year.

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.

Dose modifications

Monotherapy and in combination with trametinib

The management of adverse events/adverse drug reactions may require treatment interruption, dose reduction, or treatment discontinuation (see Table 1, Table 2 and Table 3).

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

Therapy should be interrupted if the patient's temperature is ≥ 38.0°C. Patients should be evaluated for signs and symptoms of infection (see section 4.4).

Recommended dose level reductions and recommendations for dose modifications are provided in Table 1 and Table 2, respectively. Doses below 50 mg twice daily are not recommended.

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

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

Table 2 Recommended dose modifications for TAFINLAR (excluding pyrexia)

Grade (CTC-AE)*	Recommended TAFINLAR Dose Modifications
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is grade 0 – 1 and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until grade 0 – 1 and reduce by one dose level when resuming therapy.

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

Exceptions where dose modifications are necessary for only TAFINLAR:
- Pyrexia
- Uveitis

Refer to the full data sheet of trametinib for dose modification guidelines.

Detailed dosing modifications for selected adverse reactions
New Primary Malignancies:
For New Primary Cutaneous Malignancies no dose modifications are required. For New Primary Non-Cutaneous Malignancies in patients who develop RAS mutation-positive non-cutaneous malignancies, permanently discontinue TAFINLAR.

Haemorrhagic events:
Permanently discontinue TAFINLAR, and also permanently discontinue trametinib if administered in combination, for all Grade 4 haemorrhagic events and for any Grade 3 haemorrhagic events that do not improve.

Withhold TAFINLAR for up to 3 weeks for Grade 3 haemorrhagic events; if improved resume at a lower dose level.

If used in combination, withhold trametinib for Grade 3 haemorrhagic events; if improved resume at a lower dose level.

Pyrexia Management
Follow the dose modifications below. Therapy should be interrupted (TAFINLAR when used as monotherapy, and both TAFINLAR and MEKINIST when used in combination) if the patient's temperature is ≥38.0°C, or at the first symptom of pyrexia/pyrexia syndrome. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia/pyrexia syndrome. Initiate treatment with anti-pyretics such as ibuprofen 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). TAFINLAR when used as monotherapy, or both TAFINLAR and MEKINIST when used in combination, should be restarted if patient is symptom free for at least 24 hours either (1) at the same dose level, or (2) reduced by one dose level, if pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient (see table 3). Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia.

If treatment related toxicities occur when dabrafenib is used in combination with trametinib then both treatments should be simultaneously dose reduced, interrupted or discontinued with the exceptions shown below.

Table 3 Recommended dose modifications for TAFINLAR

Severity of adverse reaction[a]	**TAFINLAR**[b]
FEBRILE DRUG REACTION	
Fever of 38.0°C-40.0°C	Withhold TAFINLAR (and MEKINIST when used in combination) if patient's temperature is 38.0ºC - 40ºC or at the first sign of pyrexia/pyrexia syndrome (i.e. chills, rigors, night sweats, or flu-like symptoms). TAFINLAR (and MEKINIST when used in combination) should be restarted if patient is symptom free for at least 24 hours either at the same dose level, or reduced by one dose level, if pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure.
• Fever of > 40°C or • Fever is complicated with rigors, hypotension, dehydration, or renal failure	Withhold TAFINLAR (and MEKINIST when used in combination) if patient's temperature is >40ºC or at the first sign of pyrexia/pyrexia syndrome (i.e. chills, rigors, night sweats, or flu-like symptoms). TAFINLAR (and MEKINIST when used in combination) should be restarted if patient is symptom free for at least 24 hours either at the same or lower dose level, or permanently discontinue.

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

If uveitis does not respond to local ocular therapy, withhold TAFINLAR until resolution of ocular inflammation and then restart TAFINLAR reduced by one dose level. No dose modification of MEKINIST is required when taken in combination with TAFINLAR.

Refer to the full MEKINIST (trametinib) data sheet for MEKINIST dosing instructions and modifications.

Special populations

Paediatric patients (< 18 years of age)
The safety and efficacy of TAFINLAR have not been established in children and adolescents (< 18 years). TAFINLAR is not recommended in this age group.

Studies in juvenile animals have shown effects of dabrafenib which had not been observed in adult animals (see section 4.4).

Patients > 65 years of age

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

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 dabrafenib oral clearance or on the concentrations of its metabolites (see section 5.2). 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 dabrafenib oral clearance or on the concentrations of its metabolites (see section 5.2) There are no clinical data in patients with moderate to severe hepatic impairment and the potential need for dose adjustment cannot be determined. Hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib 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.

Swallow the capsules whole with a full glass of water. 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 TAFINLAR dose is missed, it should not be taken if it is less than six 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).

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 (see section 5.1). 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 dabrafenib and may lead to accelerated tumour growth. TAFINLAR should not be used in patients with BRAF wild-type melanoma.

Pyrexia and serious non-infectious febrile events

Pyrexia was reported in clinical trials with dabrafenib monotherapy and in combination with MEKINIST (see section 4.8). 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 dabrafenib 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 a Phase II trial in patients with rare cancers including ATC, the incidence and severity of pyrexia was 35% (35/100), 4% Grade 3 or 4 across all cohorts. In a Phase II trial in patients with NSCLC the incidence and severity of pyrexia were increased slightly when TAFINLAR was used in combination with MEKINIST (55% [51/93], 5% Grade 3) as compared to TAFINLAR monotherapy (37% [31/84], 2% Grade 3). In patients with unresectable or metastatic melanoma who received the combination dose of TAFINLAR 150 mg twice daily and trametinib 2 mg once daily and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy. About one-third of the patients receiving combination therapy who experienced pyrexia had three or more events. Pyrexia may be accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency (see sections 4.4 and 4.8).

Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia (see section 4.4 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.

A cross-study comparison in 1,810 patients treated with combination therapy demonstrated a reduction in the incidence of high-grade pyrexia and other pyrexia-related adverse outcomes when both TAFINLAR and MEKINIST were interrupted, compared to when only TAFINLAR was interrupted.

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

Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. Patients should be evaluated for signs and symptoms of infection (see section 4.4 Special warnings and precautions for use).

TAFINLAR (or both TAFINLAR and MEKINIST when used in combination should be restarted if patient is symptom free for at least 24 hours either (1) at the same dose level, or (2) reduced by one dose level, if pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient.

For management of pyrexia, see Dosage and Administration, Dose Modification Guidelines and the full data sheet for MEKINIST.

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). In a Phase III study in patients with unresectable or metastatic melanoma, 10 % (22/211) of patients receiving TAFINLAR monotherapy developed cuSCC with a median time to the first occurrence of approximately 8 weeks. In patients who received the combination dose of TAFINLAR in combination 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 II trial in patients with NSCLC, 18 % (15/84) of patients receiving TAFINLAR monotherapy developed cuSCC, with a median time to onset of the first occurrence of approximately 11 weeks. In patients who received TAFINLAR in combination with MEKINIST, only 2% (2/93) of patients developed cuSCC. 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 be performed prior to initiation of TAFINLAR and every month throughout treatment with TAFINLAR and for up to 6 months after treatment for cuSCC. Monitoring should continue for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy.

Cases of cuSCC should be managed by dermatological excision and TAFINLAR treatment should be continued without any dose adjustment. Patients should be instructed to immediately inform their physician if new lesions develop.

New primary melanoma

New primary melanomas have been reported in patients treated with dabrafenib. In clinical trials in unresectable or metastatic melanoma, these were identified within the first 5 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 malignancies

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signalling in BRAF wild type cells with RAS mutations when exposed to BRAF inhibitors, which may lead to increased risk of non-cutaneous malignancies in patients treated with TAFINLAR. Cases of RAS-driven malignancies have seen with BRAF inhibitors. 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.

Patients should be monitored as clinically appropriate. In patients with a non-cutaneous malignancy that has a RAS mutation the benefits and risks should be considered before continuing treatment with TAFINLAR. 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.

Uveitis

Treatment with TAFINLAR has been associated with the development of uveitis (including iritis). Patients should be routinely monitored during therapy for visual signs and symptoms (such as, change in vision, photophobia and eye pain). See section 4.2.

Pancreatitis

Pancreatitis has been reported in <1% of dabrafenib-treated patients in unresectable or metastatic melanoma clinical trials, and acute pancreatitis has been reported in 1% of Tafinlar-treated patients in the NSCLC trial. One of the events occurred on the first day of dosing of a metastatic 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 68 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.

Renal failure
Renal failure has been identified in <1% of patients treated with TAFINLAR. 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, dabrafenib may need to be interrupted as clinically appropriate. Dabrafenib has not been studied in patients with renal insufficiency (defined as creatinine >1.5 x ULN) therefore caution should be used in this setting.

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

Haemorrhage
Haemorrhagic events, including major haemorrhagic events have occurred in patients taking trametinib in combination with TAFINLAR (see section 4.8). Six out of the 559 unresectable or metastatic melanoma patients (1.1 %) treated with TAFINLAR 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. Two out of 93 patients (2 %) receiving TAFINLAR in combination with trametinib in a Phase II trial in patients with metastatic NSCLC had fatal intracranial haemorrhagic events. If patients develop symptoms of haemorrhage they should immediately seek medical care.

Haemophagocytic lymphohistiocytosis (HLH)
In post-marketing experience, HLH has been observed with TAFINLAR in combination with MEKINIST. If HLH is suspected, treatment should be interrupted. If HLH is confirmed, treatment should be discontinued and appropriate management of HLH should be initiated.

Tumour Lysis Syndrome (TLS)
Cases of TLS, including fatal cases, have been reported in patients treated with TAFINLAR in combination with Mekinist (see section 4.8 Undesirable effects). Risk factors for TLS include rapidly growing tumours, a high tumour burden, renal dysfunction, and dehydration. Patients with risk factors for TLS should be closely monitored, prophylaxis should be considered (e.g., intravenous hydration and treatment of high uric acid levels prior to initiating treatment) and treated as clinically indicated.

Skin toxicity
Severe cutaneous adverse reactions

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

Venous thromboembolism (VTE)
VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE) can occur when TAFINLAR is used in combination with trametinib. Patients should be advised to immediately seek medical care if they develop symptoms of VTE (see section 4.8).

Use in paediatrics (< 18 years of age)
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) and testicular toxicity (degeneration and tubular dilation) were observed.

Use in patients ≥ 65 years of age
No dose adjustment is required in patients over 65 years (see sections 4.2 and 5.2).

Compared with younger patients (< 65), more patients over 65 years old had adverse reactions that led to study drug dose reductions (22% versus 12%) or interruptions (39% versus 27%). In addition, older patients experienced more serious adverse reactions compared to younger patients (41% versus 22%). No overall differences in efficacy were observed between these patients and younger patients.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on TAFINLAR

Based on *in vitro* studies, dabrafenib was shown to be primarily metabolised by cytochrome P450 (CYP) 2C8 and CYP3A4 (see section 5.2). Dabrafenib's 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
Pharmacokinetic data showed an increase in repeat-dose dabrafenib Cmax (33%) and AUC (71%) upon co-administration with ketoconazole (CYP3A4 inhibitor), and increases of 82% and 68% of hydroxy- and desmethyl-dabrafenib AUC, respectively. A decrease in AUC was noted for carboxy-dabrafenib (decrease of 16%).

Gemfibrozil
Co-administration of dabrafenib and gemfibrozil (CYP2C8 inhibitor) resulted in an increase in repeat-dose dabrafenib AUC (47%) and no meaningful change in the concentrations of the metabolites.

Rifampin

Pharmacokinetic data showed a decrease in repeat-dose dabrafenib Cmax (27%) and AUC (34%) upon co-administration with rifampin (CYP3A4/CYP2C8 inducer). No relevant change in AUC was noted for hydroxy-dabrafenib, there was an increase in AUC of 73% for carboxy-dabrafenib and a decrease in AUC of 30% for desmethyl-dabrafenib.

Drugs that affect gastric pH
Co-administration of repeat dosing of dabrafenib 150 mg twice daily and a pH elevating agent, rabeprazole 40 mg once daily, resulted in a 3% increase in dabrafenib AUC and a 12% decrease in dabrafenib Cmax. These changes in dabrafenib AUC and Cmax are considered not clinically meaningful. Medicinal products that alter the pH of the upper gastrointestinal (GI) tract (e.g. proton pump inhibitors, H2-receptor antagonists, antacids) are not expected to reduce the bioavailability of dabrafenib.

Effect of TAFINLAR on other drugs

Dabrafenib induces CYP3A4- and CYP2C9-mediated metabolism (see sections 5.1 and 5.2) and may induce other enzymes, including CYP2B6, CYP2C8, CYP2C19 and UDP glucuronosyltransferases (UGT). Dabrafenib may also induce transporters (e.g. P-glycoprotein (Pgp)). In human hepatocytes, dabrafenib produced dose-dependent increases in CYP2B6 and CYP3A4 mRNA levels up to 32 times the control levels. Co-administration of dabrafenib and medicinal products which are affected by the induction of these enzymes or transporters such as hormonal contraceptives (see sections 4.4 and 4.6), dexamethasone, antiretroviral agents, or immunosuppressants may result in decreased concentrations and loss of efficacy. Concomitant use of dabrafenib 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, monitor subjects for loss of efficacy or consider substitutions of these medicinal products.

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

Midazolam
In a clinical study in 16 patients using a single dose of midazolam, a CYP3A4 substrate, Cmax and AUC were decreased by 47% and 65%, respectively, with co-administration of repeat-dose TAFINLAR 150 mg twice daily.

Warfarin
In a separate trial in 14 patients, repeat-dose TAFINLAR decreased the single-dose AUC of S-warfarin (a substrate of CYP2C9) and of R-warfarin (a substrate of CYP3A4/CYP1A2) by 37% and 33%, respectively, with a small increase in Cmax (18 % and 19 % respectively).

Exercise caution and consider additional INR (International Normalised Ratio) monitoring when dabrafenib is used concomitantly with warfarin.

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.

Rosuvastatin and other statins
Following co-administration of a single dose of rosuvastatin (OATP1B1 and OATP1B3 substrate) with repeat dose TAFINLAR 150 mg twice daily in 16 patients, AUC was minimally changed (7 % increase) and Cmax was increased by 156%. Therefore caution is recommended at co-administration of dabrafenib and OATB1B1 or OATP1B3 substrates such as statins.

Effects of TAFINLAR 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. Monitoring is recommended for adverse reactions if TAFINLAR is co-administered with drugs that are OATP1B1 or OATP1B3 substrates with a narrow therapeutic index with regards to high peak concentrations.

Although dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, were inhibitors of human organic anion transporter (OAT) 1 and OAT3 and dabrafenib and its desmethyl metabolite were found to be inhibitors of organic cation transporter 2 (OCT2), *in vitro*, the risk of a drug-drug interaction is minimal based on clinical exposure.

Dabrafenib and desmethyl-dabrafenib were also shown to be moderate inhibitors of human breast cancer resistance protein (BCRP); however, based on clinical exposure, the risk of a drug-drug interaction is minimal.

Neither dabrafenib nor its 3 metabolites were demonstrated to be inhibitors of P-glycoprotein (P-gp) *in vitro*.

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

See the full data sheet for MEKINIST for guidelines on drug interactions associated with MEKINIST.

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.

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 animals (rats) have demonstrated TAFINLAR-induced embryofetal development toxicity, including teratogenic effects. In adult female rats dosed with dabrafenib before mating and during gestation, embryofetal toxicities including embryo-lethality, fetal ventricular septal defects, and variation in thymic shape were observed 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.

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 fetus.

Contraception

Females

Women 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 (methods that result in less than 1% pregnancy rates) when taking TAFINLAR and for at least two weeks following discontinuation of TAFINLAR. If taking TAFINLAR in combination with Mekinist, sexually-active females of reproductive potential are recommended to use effective contraception and for at least 16 weeks after stopping treatment.

TAFINLAR may decrease the efficacy of oral or any other systemic hormonal contraceptives and an effective alternate method of contraception should be used (see section 4.5).

Males

Male patients (including those that have had a vasectomy) with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during sexual intercourse while taking TAFINLAR monotherapy and for at least 2 weeks after stopping treatment with TAFINLAR. If taking TAFINLAR in combination with Mekinist, male patients should use condoms during sexual intercourse, and for at least 16 weeks after stopping treatment.

Use in Lactation

There are no data on the effect of TAFINLAR on the breast-fed child, or the effect of TAFINLAR on milk production. Because many drugs are transferred into human milk and

because of the potential for adverse reactions in a suckling child from TAFINLAR, a nursing mother should be advised of 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 Undesirable effects

Adverse events are listed by MedDRA system organ class, using the following classifications for frequency:

Very common	≥ 1 in 10
Common	≥ 1 in 100 to < 1 in 10
Uncommon	≥ 1 in 1,000 to < 1 in 100
Rare	≥1 in 10,000 to <1 in 1,000
Very rare	<1 in 10,000.

Summary of the safety profile
Unresectable or metastatic melanoma

TAFINLAR monotherapy

Safety data for TAFINLAR monotherapy was integrated from five clinical monotherapy studies BRF113683 (BREAK-3), BRF113929 (BREAK-MB), BRF113710 (BREAK-2), BRF113220, and BRF112680, and included 578 patients with BRAF V600 mutant unresectable or metastatic melanoma. Approximately 30% of patients received treatment with dabrafenib for more than 6 months.

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

Table 4 Adverse reactions for TAFINLAR monotherapy in unresectable or metastatic melanoma

Neoplasms benign and malignant (including cysts and polyps)	
Very common	Papilloma
Common	Acrochordon (skin tags), cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma, seborrheic keratosis, basal cell carcinoma
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 erythrodysaesthesia syndrome
Common	Skin effects (actinic keratosis, skin lesion, dry skin, erythema), pruritus, photosensitivity reaction[1]
Uncommon	Panniculitis
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, myalgia, pain in extremity
Renal disorders	
Uncommon	Renal failure, acute renal failure, tubulointerstitial 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 (BRF113683 (BREAK-3), BRF113929 (BREAK-MB), BRF113710 (BREAK-2), BRF113220, and BRF112680) were Grade 1 and no dose modifications were required.

TAFINLAR and trametinib combination therapy

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

Table 5 lists adverse reactions when trametinib was used in combination with dabrafenib from the randomised double-blind Phase III study MEK115306 (n = 209, COMBI-d), and integrated safety data from MEK115306 (n = 209) and from the randomised open-label Phase III study MEK 116513 (n = 350, COMBI-v).

Table 5 **Adverse reactions for TAFINLAR in combination with MEKINIST in unresectable or metastatic melanoma – data from the randomised double-blind phase III combination study MEK115306 (COMBI-d), and integrated safety data from two randomised phase III combination studies, MEK115306 and MEK116513 (COMBI-d and COMBI-v)**

Adverse reactions	**Frequency classification**	
	COMBI-d (MEK115306) N=209	**COMBI-d (MEK115306) & COMBI-v (MEK116513) integrated data N=559**
Infections and Infestations		
Urinary tract infection	Very common	Common
Nasopharyngitis	Very common	Very common
Cellulitis	Common	Common
Folliculitis	Common	Common
Paronychia	Common	Common
Rash pustular	Common	Common
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma	Common	Common
Papilloma including skin papilloma	Common	Common
Seborrhoeic keratosis	Common	Common
Acrochordon (skin tags)	Common	Uncommon
New primary melanoma	Uncommon	Uncommon
Blood and lymphatic system disorders		
Neutropenia	Very Common	Common
Anaemia	Common	Common
Thrombocytopenia	Common	Common
Leukopenia	Common	Common
Immune system disorders		
Hypersensitivity	Uncommon	Uncommon
Metabolic and nutrition disorders		
Decreased appetite	Very common	Very common
Dehydration	Common	Common
Hyperglycaemia	Common	Common
Hyponatraemia	Common	Common
Hypophosphataemia	Common	Common
Nervous system disorders		
Headache	Very common	Very common
Dizziness	Very common	Very common
Eye disorders		
Vision blurred	Common	Common
Visual impairment	Common	Common
Chorioretinopathy	Uncommon	Uncommon
Uveitis	Uncommon	Uncommon
Retinal detachment	Uncommon	Uncommon
Periorbital oedema	Uncommon	Uncommon
Cardiac disorders		
Ejection fraction decreased	Common	Common

Adverse reactions	Frequency classification COMBI-d (MEK115306) N=209	COMBI-d (MEK115306) & COMBI-v (MEK116513) integrated data N=559
Left ventricular dysfunction	NR	Uncommon
Cardiac failure	NR	Uncommon
Bradycardia	Common	Common
Vascular disorders		
Cardiac failure	NR	Uncommon
Hypertension	Very common	Very common
Haemorrhage1	Very common	Very common
Hypotension	Common	Common
Lymphoedema	Uncommon	Common
Respiratory, thoracic and mediastinal disorders		
Cough	Very common	Very common
Dyspnoea	Common	Common
Pneumonitis	Uncommon	Uncommon
Interstitial lung disease	NR	Uncommon
Gastrointestinal disorders		
Gastrointestinal perforation	Not reported	Uncommon
Colitis	Uncommon	Uncommon
Abdominal pain	Very common	Very common
Constipation	Very common	Very common
Diarrhoea	Very common	Very common
Nausea	Very common	Very common
Vomiting	Very common	Very common
Dry mouth	Common	Common
Stomatitis	Common	Common
Pancreatitis	Uncommon	Uncommon
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[1)]	Common	Common

Adverse reactions	Frequency classification COMBI-d (MEK115306) N=209	COMBI-d (MEK115306) & COMBI-v (MEK116513) integrated data N=559
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Very common
Myalgia	Very common	Very common
Pain in extremity	Very common	Very common
Muscle spasms	Common	Common
Blood creatine phosphokinase increased	Common	Common
Rhabdomyolysis	NR	Uncommon
Renal disorders		
Renal failure	Uncommon	Common
Nephritis	Uncommon	Uncommon
Renal failure acute	NR	Uncommon
General disorders and administration site disorders		
Fatigue	Very common	Very common
Oedema peripheral	Very common	Very common
Pyrexia	Very common	Very common
Chills	Very common	Very common
Asthenia	Very common	Very common
Mucosal inflammation	Common	Common
Influenza-like illness	Common	Common
Face oedema	Common	Common

NR= Not reported
[1)] *Photosensitivity cases were also observed in post-marketing experience. All cases reported in COMBI-d and COMBI-v clinical trials were Grade 1 and no dose modification was required.*

Metastatic melanoma patients with brain metastases

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

Adjuvant treatment of melanoma

TAFINLAR in combination with MEKINIST

The safety of TAFINLAR in combination with MEKINIST was evaluated in a Phase III, randomised, 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).

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, diarrhoea, vomiting, arthralgia, and myalgia.

Table 6 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.

Table 6 Adverse reactions for TAFINLAR in combination with MEKINIST against placebo in adjuvant melanoma

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
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

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	
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 generalised, rash erythematous, rash papular, rash pruritic, nodular rash, rash vesicular, and rash pustular.
12) Dry skin also includes xerosis and xeroderma.
13) Erythema also includes generalised erythema.
14) Pruritus also includes pruritus generalised and pruritus genital.
15) Myalgia also includes musculoskeletal pain and musculoskeletal chest pain.
16) Muscle spasms also includes musculoskeletal stiffness.
17) Pyrexia also includes hyperpyrexia.
18) Fatigue also includes asthenia and malaise.
19) Oedema peripheral also includes peripheral swelling.
20) Alanine aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia.
21) Aspartate aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia.
NR: not reported

Locally advanced or metastatic anaplastic thyroid cancer

TAFINLAR in combination with MEKINIST

The efficacy and safety of TAFINLAR in combination with MEKINIST was studied in a Phase II, nine-cohort, multicenter, non-randomised, open-label study in patients with rare

cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC (see section 5.1 Clinical studies).

The 'All Treated Patients (ATS)' population was the primary safety population for the study and includes all patients who received at least one dose of TAFINLAR or MEKINIST from all the histologic cohorts. The safety profiles in the ATS population and in the ATC cohort are consistent.

At the time of safety analysis, the most common adverse events (≥ 20%) reported for TAFINLAR in combination with MEKINIST in the ATS population were fatigue, pyrexia, rash, nausea, chills, vomiting, cough, and headache.

Table 7 lists the adverse drug reactions for TAFINLAR in combination with MEKINIST occurring at an incidence ≥ 10% for all grade adverse drug reactions or at an incidence ≥ 2% for Grade 3 and Grade 4 adverse drug reactions or events which are medically significant in Study BRF117019.

Table 7 Adverse reactions for TAFINLAR in combination with MEKINIST in the locally advanced or metastatic anaplastic thyroid cancer ATS population

Adverse drug reactions	TAFINLAR in combination with MEKINIST		
	All grades n = 100 %	Grades 3/4 n = 100 %	Frequency category
Blood and lymphatic system disorders			
Neutropenia[1)]	15	6	Very common
Anaemia	14	2	Very common
Leukopenia[2)]	13	NR	Very common
Metabolism and nutrition disorders			
Hyperglycaemia	12	3	Very common
Decreased appetite	11	NR	Very common
Hypophosphataemia	6	3	Common
Hyponatremia	3	3	Common
Nervous system disorders			
Headache	20	2	Very common
Dizziness[3)]	13	NR	Very common
Eye disorders			
Detachment of retinal pigment epithelium	1	NR	Common
Vascular disorders			
Haemorrhage[4)]	16	NR	Very common
Hypertension	4	2	Common
Respiratory, thoracic and mediastinal disorders			
Cough[5)]	21	NR	Very common
Gastrointestinal disorders			
Nausea	31	1	Very common
Vomiting	22	1	Very common
Diarrhoea	17	1	Very common
Constipation	15	NR	Very common
Dry mouth	11	NR	Very common
Skin and subcutaneous tissue disorders			

Adverse drug reactions	TAFINLAR in combination with MEKINIST		
	All grades n = 100 %	Grades 3/4 n = 100 %	Frequency category
Rash[6)]	31	4	Very common
Musculoskeletal and connective tissue disorders			
Myalgia[7)]	11	1	Very common
Arthralgia	11	NR	Very common
Rhabdomyolysis	1	1	Common
General disorders and administration site conditions			
Fatigue[8)]	45	5	Very common
Pyrexia	35	4	Very common
Chills	25	1	Very common
Oedema[9)]	17	NR	Very common
Investigations			
Alanine aminotransferase increased	13	3	Very common
Aspartate aminotransferase increased	12	2	Very common
Blood alkaline phosphatase increased	11	3	Very common
Ejection fraction decreased	3	1	Common

[1)] Neutropenia includes neutropenia, neutrophil count decreased and febrile neutropenia. Neutrophil count decreased qualified as a neutropenia event.

[2)] Leukopenia includes leukopenia, white blood cell count decreased and lymphopenia.

[3)] Dizziness includes dizziness, vertigo and vertigo positional.

[4)] Haemorrhage includes haematuria, purpura, epistaxis, eye contusion, gingival bleeding, haemoptysis, melaena, petechiae, prothrombin time prolonged, rectal haemorrhage, retinal haemorrhage and vaginal haemorrhage.

[5)] Cough includes cough and productive cough.

[6)] Rash includes rash, rash maculo-papular, rash generalised and rash papular.

[7)] Myalgia includes myalgia and musculoskeletal pain.

[8)] Fatigue includes fatigue, asthenia and malaise.

[9)] Oedema includes oedema and peripheral oedema.

NR: not reported

Advanced non-small cell lung cancer

TAFINLAR monotherapy

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

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

TAFINLAR in combination with MEKINIST

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

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

Table 8 lists the adverse drug reactions for TAFINLAR in combination with MEKINIST occurring at an incidence ≥ 10% for all grade adverse drug reactions or at an incidence ≥ 2% for Grade 3 and Grade 4 adverse drug reactions or events which are medically significant in Cohorts B and C of study BRF113928.

Table 8 Adverse reactions for TAFINLAR in combination with MEKINIST in advanced NSCLC

Adverse drug reactions	TAFINLAR in combination with MEKINIST		
	All grades n = 93 %	Grades 3/4 n = 93 %	Frequency category
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Cutaneous squamous cell carcinoma	3	2	Common
Blood and lymphatic system disorders			
Neutropenia[1)]	15	8	Very common
Leukopenia	6	2	Common
Metabolism and nutrition disorders			
Hyponatraemia	14	9	Very common
Dehydration	8	3	Common
Eye disorders			
Detachment of retina/retinal pigment epithelium	2	NR	Common
Nervous system disorders			
Headache	16	NR	Very common
Dizziness	14	NR	Very common
Cardiac disorders			
Ejection fraction decreased	9	4	Common
Vascular disorders			
Haemorrhage[2)]	26	3	Very common
Hypotension	15	2	Very common
Hypertension	8	6	Common
Pulmonary embolism	4	2	Common
Gastrointestinal disorders			
Nausea	46	NR	Very common
Vomiting	37	3	Very common
Diarrhoea	33	2	Very common
Decreased appetite	28	NR	Very common
Constipation	16	NR	Very common
Pancreatitis acute	1	NR	Common
Skin and subcutaneous tissue disorders			
Erythema	10	NR	Very common
Dry skin	32	1	Very common
Rash[3)]	31	3	Very common

Adverse drug reactions	TAFINLAR in combination with MEKINIST		
	All grades n = 93 %	**Grades 3/4 n = 93 %**	**Frequency category**
Pruritus[4)]	15	2	Very common
Hyperkeratosis[5)]	13	1	Very common
Musculoskeletal and connective tissue disorders			
Muscle spasms	10	NR	Very common
Arthralgia	16	NR	Very common
Myalgia	13	NR	Very common
Renal and urinary disorders			
Renal failure	3	1	Common
Tubulointerstitial nephritis	2	2	Common
General disorders and administration site disorders			
Pyrexia	55	5	Very common
Asthenia[6)]	47	6	Very common
Oedema[7)]	35	NR	Very common
Chills	24	1	Very common
Investigations			
Blood alkaline phosphatase increased	12	NR	Very common
Aspartate aminotransferase increased	11	2	Very common
Alanine aminotransferase increased	10	4	Very common

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

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

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

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

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

6) Asthenia also includes fatigue and malaise.

7) Oedema includes generalised oedema and peripheral oedema.

NR: Not Reported

Post-marketing experience and pooled clinical trials

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

Table 9 Adverse reactions from post-marketing experience and pooled clinical trials across indications

Adverse reaction	TAFINLAR in combination with Mekinist frequency category	TAFINLAR monotherapy frequency category
Cardiac disorders		
Atrioventricular block[1]	Common	-
Bundle branch block[2]	Uncommon	-
Vascular disorders		
Venous thromboembolism (VTE)[3]	Common	-
Immune system disorders		
Sarcoidosis	Uncommon	-
Haemophagocytic lymphohistiocytosis	Not known	-
Metabolism and nutrition disorders		
Tumour lysis syndrome	Not known	-
Nervous system disorders		
Peripheral neuropathy	Common	Common

[1] Atrioventricular block includes atrioventricular block, atrioventricular block first degree, atrioventricular block second degree and atrioventricular block complete.
[2] Bundle branch block includes bundle branch block right and bundle branch block left.
[3] VTE includes pulmonary embolism, deep vein thrombosis, embolism and venous thrombosis.

Description of selected adverse reactions

Pyrexia
Fever has been reported in clinical trials. 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. The onset of these serious non-infectious febrile events was typically within the first month of therapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care (see sections 4.2 and 4.4).

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. Approximately 70% of events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. Ninety-six percent of patients 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).

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).Cases of RAS-driven malignancies have been seen with TAFINLAR. Patients should be monitored as clinically appropriate.

Special populations

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

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

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: B-Raf serine-threonine kinase (BRAF) inhibitors. ATC Code: L01EC02

Mechanism of action

TAFINLAR monotherapy – Metastatic Melanoma

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. Dabrafenib also inhibits a small number of other kinases, including wild-type BRAF and CRAF with IC_{50} values of 3.2 and 5.0nM, respectively in biochemical assays. Oncologic amino acid variants in BRAF at valine 600 (V600) lead to constitutive activation of the RAS/RAF/MEK/ERK pathway and stimulation of tumour cell growth. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50 % of melanoma and 1-3 % of NSCLC. The most commonly observed BRAF mutation (V600E), and the next most common (V600K) account for 95 % of the BRAF mutations found in all patients with 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).

Dabrafenib inhibits BRAF V600 mutant melanoma, NSCLC, and ATC cell growth *in vitro* and melanoma xenograft models *in vivo*.

TAFINLAR in combination with trametinib

Trametinib is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. MEK proteins are components of the extracellular signal-related kinase (ERK) pathway. Dabrafenib and trametinib inhibit two critical kinases in this pathway, BRAF and MEK, and the combination provides concomitant inhibition of the pathway. The combination of dabrafenib with trametinib is synergistic in BRAF V600 mutation positive melanoma, NSCLC, and ATC cell lines *in vitro* and delays the emergence of resistance *in vivo* in BRAF V600 mutation positive melanoma xenografts.

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

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

Cardiac electrophysiology

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

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

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

- BRF113683 [BREAK-3]
- BRF113710 [BREAK-2] and
- BRF113929 [BREAK-MB].

Included in these studies were in total 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 3 months were excluded from the pivotal Phase III BREAK-3 study.

BREAK-3: Study in previously untreated patients with BRAF V600E mutation positive advanced (unresectable Stage III) or metastatic (Stage IV) melanoma
The efficacy and safety of dabrafenib were evaluated in a Phase III randomised, open-label study [BREAK-3] comparing dabrafenib to dacarbazine (DTIC) in previously untreated patients with BRAF V600E mutation positive advanced (unresectable Stage III) or metastatic (Stage IV) melanoma. Screening included central testing of BRAF mutation V600E using a BRAF mutation assay conducted on the most recent tumour sample available.

The trial enrolled 250 patients randomised 3:1 to receive either dabrafenib 150 mg twice daily or intravenous DTIC 1000 mg/m^2 every 3 weeks. The primary objective for this study was to evaluate the efficacy of dabrafenib compared to DTIC with respect to progression-free survival (PFS) per investigator assessment for patients with BRAF V600E mutation positive unresectable or metastatic melanoma. Patients on the DTIC arm were allowed to cross over and receive dabrafenib after independent radiographic confirmation of initial progression. Baseline characteristics were balanced between treatment groups. Sixty percent of patients were male and 99.6 % were Caucasian ; the median age was 52 years with 21 % of patients being ≥ 65 years, 98.4 % had 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 10.

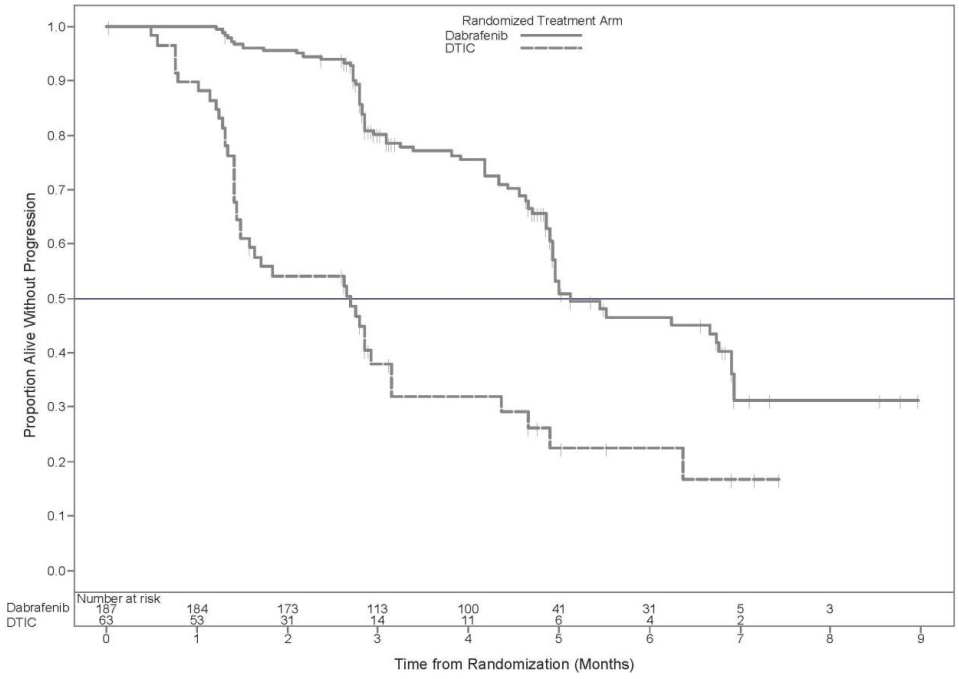
Table 10 Monotherapy efficacy data by Investigator Assessment in previously untreated patients (BREAK-3 study, 25 June 2012)

	Intention-to-Treat Population	
Endpoints/ Assessment	**TAFINLAR**	**DTIC**
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		
	N=110	N=15
Median, months (9 5% CI)	8.0 (6.6, 11.5)	7.6 (5.0, 9.7)

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

Confirmed response

Figure 1 Investigator Assessed Progression-Free Survival in previously untreated patients (BREAK 3 ITT population, 19 December 2011)



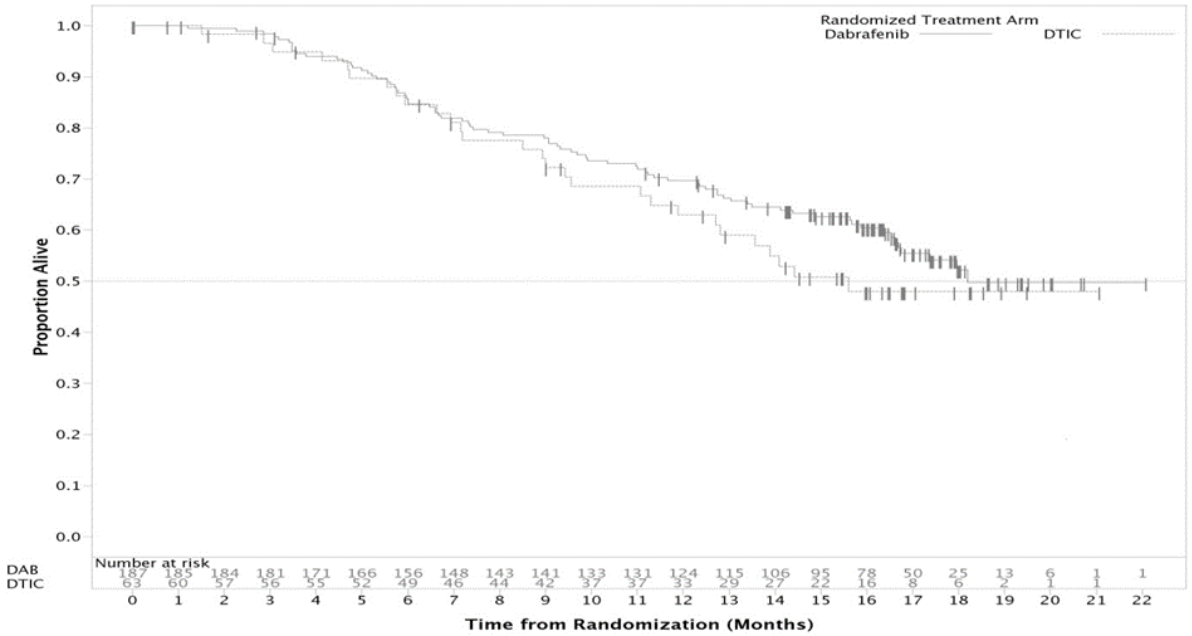
Overall survival data from a further post-hoc analysis based on an 18 December 2012 data cut is provided in Table 11 and shown in Figure 2.

Table 11 Survival data from a post-hoc analysis (18 December 2012)

Treatment	Number of deaths (%)	12-month OS rate	Hazard Ratio (95% CI)
DTIC	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 2 Kaplan-Meier curves of overall survival (BREAK-3) (18 December 2012)



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.

BREAK-MB: Patients with Stage IV BRAF-mutation positive (V600E or V600K) brain metastases

BREAK-MB was a multi-centre, open-label, two-cohort, Phase II study designed to evaluate the intracranial response of dabrafenib in patients with histologically confirmed (Stage IV) BRAF-mutation positive (V600E or V600K) melanoma metastatic to the brain. Patients were enrolled into two cohorts:

- Cohort A (patients with no prior local therapy for brain metastasis) or
- Cohort B (patients who received prior local therapy for brain metastasis).

Patients were given dabrafenib 150 mg twice daily until unacceptable adverse reactions, disease progression, or death. The primary endpoint of the study was overall intracranial response rate (OIRR), which is a measure of response (complete response [CR] + partial response [PR]) of intracranial lesions using modified RECIST criteria as assessed by investigators. The results are summarised in Table 12. 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 12 Efficacy Data in Patients with Brain Metastases (BREAK-MB study)

Endpoints/ Assessment	All Treated Patients Population			
	BRAF V600E (Primary)		BRAF V600K	
	Cohort A N=74	Cohort B N=65	Cohort A N=15	Cohort B N=18
Overall intracranial response rate				
OIRR **%** (95% CI) [a]	39 % (28.0, 51.2)	31 % (19.9, 43.4)	7 % (0.2, 31.9)	22 % (6.4, 47.6)
p-value	< 0.001	< 0.001 [b]		
Duration of intracranial response median months	N=29	N=20	N=1	N=4
Median, months (95% CI)	4.6 (2.8, NR)	6.5 (4.6, 6.5)	2.9 (NR, NR)	3.8 (NR, NR)
Overall response				
OR % (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	N=28	N=20	NA	N=5
Median, months (95% CI)	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.

BREAK-2: Study in Stage IV metastatic patients who were previously untreated or failed at least one prior systemic therapy (Results from the phase II study)

BRF113710 (BREAK-2) 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 dabrafenib 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 trametinib

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

MEK115306 (COMBI-d)

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

A total of 423 patients were randomised 1:1 to either the combination therapy arm (dabrafenib 150 mg twice daily and trametinib 2 mg once daily) (N = 211) or dabrafenib monotherapy arm (150 mg twice daily) (N = 212). Baseline characteristics were balanced between treatment groups. Males constituted 53 % of patients and the median age was 56 years; Majority of patients had an ECOG performance score of 0 (72 %) and had Stage IVM1c disease (66 %). Most patients had the BRAF V600E mutation (85 %); the remaining 15 % of patients had the BRAF V600K mutation. Patients with brain metastases were not included in the trial.

Median OS and estimated 1-year, 2-year, 3-year, 4 year and 5-year survival rates are presented in Table 13. An OS analysis at 5 years demonstrated continued benefit for the combination of dabrafenib and trametinib compared with dabrafenib monotherapy; the median OS for the combination arm was approximately 7 months longer than for dabrafenib monotherapy (25.8 months versus 18.7 months) with 5 year survival rates of 32% for the combination versus 27% for dabrafenib monotherapy (Table 13, Figure 3). The Kaplan-Meier OS curve appears to stabilise from 3 to 5 years (see Figure 3 arm versus 33% (95% CI: 25.0, 41.0) in the dabrafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 8.4, 26.0) in the combination arm versus 14% (95% CI: 6.8, 23.1) in the dabrafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline.

Table 13 Overall Survival results for Study MEK115306 (COMBI-d)

	OS analysis*		**3-year OS analysis***		**5-year OS analysis***	
	Dabrafenib + Trametinib (n=211)	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**
Number of Patients						
Died (event), n (%)	99 (47)	123 (58)	114 (54)	139 (66)	135 (64)	151 (71)

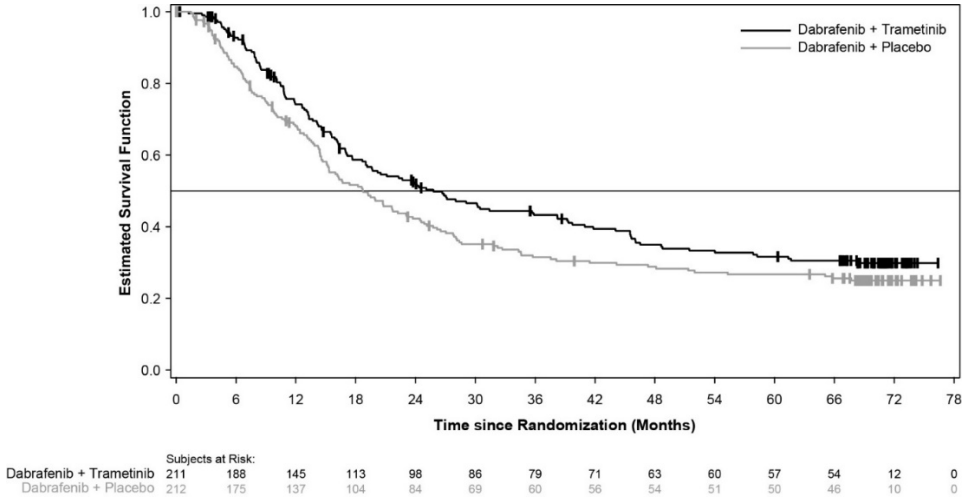
	OS analysis*		3-year OS analysis*		5-year OS analysis*	
	Dabrafenib + Trametinib (n=211)	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**
Estimates of OS (months)						
Median (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.7)	26.7 (19.0, 38.2)	18.7 (15.2, 23.1)	25.8 (19.2, 38.2)	18.7 (15.2, 23.1)
Hazard ratio (95% CI)	0.71 (0.55, 0.92)		0.75 (0.58, 0.96)		0.80 (0.63, 1.01)	
p-value	0.011		NA		NA	

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

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

NR = Not reached, NA = Not applicable

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



Clinically meaningful improvements for the primary endpoint of PFS were sustained over a 5 year timeframe in the combination arm compared to dabrafenib monotherapy. Clinically meaningful improvements were also observed for overall response rate (ORR) and a longer duration of response (DoR) was observed in the combination arm compared to dabrafenib monotherapy (Table 14).

Table 14 Investigator-assessed efficacy results for MEK115306 (COMBI-d) study

Endpoints	Primary Analysis*		Updated Analysis*		3 Year Analysis*		5 Year Analysis*	
	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)
Investigator Assessed PFS								
Progressive disease or death, n (%)	102 (48)	109 (51)	139 (66)	162 (76)	153 (73)	168[f] (79)	160 (76)	166[f] (78)
Median, months (95% CI[a])	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)	10.2 (8.0, 12.8)	7.6 (5.8, 9.3)	10.2 (8.1, 12.8)	8.8 (5.9, 9.3)
Hazard Ratio (95% CI)	0.75 (0.57, 0.99)		0.67 (0.53, 0.84)		0.71 (0.57, 0.88)		0.73 (0.59, 0.91)	

Endpoints	Primary Analysis*		Updated Analysis*		3 Year Analysis*		5 Year Analysis*	
	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)	Dabrafenib + Trametinib (n=211)	Dabrafenib + Placebo (n=212)
P value (log-rank test)	0.035		<0.001		NA		NA	
Overall Response Rate[b] (%) 95% CI	67 (59.9, 73.0)	51 (44.5,58.4)	69 (61.8, 74.8)	53 (46.3, 60.2)	68 (61.5, 74.5)	55 (47.8, 61.5)	69 (62.5, 75.4)	54 (46.8, 60.6)
Difference in response rate (CR[c] +PR[c]), % 95% CI for difference *P* value	15[d] 5.9, 24.5 0.0015		15[d] 6.0, 24.5 0.0014[g]		NA		NA	
Duration of Response (months)								
Median (95% CI)	9.2[e] (7.4, NR)	10.2[e] (7.5, NR)	12.9 (9.4,19.5)	10.6 (9.1,13.8)	12.0 (9.3, 17.1)	10.6 (8.3, 12.9)	12.9 (9.3, 18.4)	10.2 (8.3, 13.8)

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

a - Confidence interval

b - Overall Response Rate = Complete Response + Partial Response

c - CR: Complete Response, PR: Partial Response

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

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

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

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

NR = Not reached

NA=Not applicable

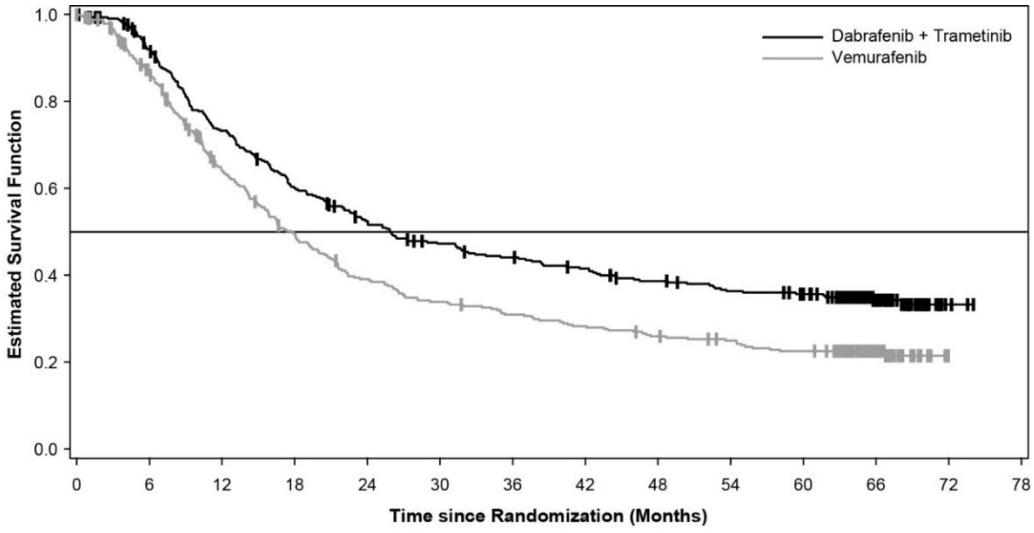
MEK116513 (COMBI-v)

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

A total of 704 patients were randomised 1:1 to either the combination therapy arm (dabrafenib 150 mg twice daily and trametinib 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 %).

An OS analysis at 5 years demonstrated continued benefit for the combination of dabrafenib and trametinib compared with vemurafenib monotherapy; the median OS for the combination arm was approximately 8 months longer than the median OS for vemurafenib monotherapy (26.0 months versus 17.8 months) with 5 year survival rates of 36% for the combination versus 23% for vemurafenib monotherapy (Table 15, Figure 4). The Kaplan-Meier OS curve appears to stabilise from 3 years to 5 years (see Figure 4). The 5-year overall survival rate was 46% (95% CI: 38.8, 52.0) in the combination arm versus 28% (95% CI: 22.5, 34.6) in the vemurafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 9.3, 23.3) in the combination arm versus 10% (95% CI: 5.1, 17.4) in the vemurafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline.

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



Subjects at Risk:													
Dabrafenib + Trametinib	352	311	246	201	171	151	140	130	118	109	104	49	4	0
Vemurafenib	352	287	201	154	120	104	94	86	78	72	65	30	1	0

Table 15 Overall Survival results for Study MEK116513 (COMBI-v)

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

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

NR = Not reached, NA = Not applicable

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

Clinically meaningful improvements for the secondary endpoint of PFS were sustained over a 5-year timeframe in the combination arm compared to vemurafenib monotherapy. Clinically meaningful improvements were also observed for overall response rate (ORR) and a longer duration of response (DoR) was observed in the combination arm compared to vemurafenib monotherapy (Table 16).

Table 16 Investigator-assessed efficacy results for MEK116513 (COMBI-v) study

Endpoint	**Primary Analysis***		**3-year analysis***		**5-year analysis***	
	Dabrafenib + Trametinib (n=352)	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
Investigator Assessed PFS						
Progressive disease or death, n (%)	166 (47)	217 (62)	250 (71)	257 (73)	257 (73)	259 (74)
Median, months (95% CI)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)	12.1 (9.7, 14.7)	7.3 (5.7, 7.8)	12.1 (9.7, 14.7)	7.3 (6.0, 8.1)
Hazard Ratio (95% CI)	0.56 (0.46, 0.69)		0.61 (0.51, 0.73)		0.62 (0.52, 0.74)	
P value	<0.001		NA		NA	

Endpoint	Primary Analysis*		3-year analysis*		5-year analysis*	
	Dabrafenib + Trametinib (n=352)	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
Overall Response Rate 95% CI	64 (59.1, 69.4)	51 (46.1, 56.8)	67 (61.9, 71.9)	53 (47.8, 58.4)	67 (62.2, 72.2)	53 (47.2, 57.9)
Difference in response rate (CR+PR), % 95% CI for difference	13 (5.7, 20.2)		NA		NA	
P value	0.0005		NA		NA	
Duration of Response (months)						
Median (95% CI)	13.8 (11.0, NR)	7.5 (7.3, 9.3)	13.8 (11.3, 17.7)	7.9 (7.4, 9.3)	13.8 (11.3, 18.6)	8.5 (7.4, 9.3)

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

PFS = Progression Free Survival; NR = Not reached

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

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

A total of 125 patients were enrolled into four cohorts:

- Cohort A: patients with BRAFV600E mutant melanoma with asymptomatic brain metastases without prior local brain-directed therapy and ECOG performance status of 0 or 1.
- Cohort B: patients with BRAFV600E mutant melanoma with asymptomatic brain metastases with prior local brain-directed therapy and ECOG performance status of 0 or1.
- Cohort C: patients with BRAFV600D/K/R mutant melanoma with asymptomatic brain metastases, with or without prior local brain-directed therapy and ECOG performance status of 0 or 1.
- Cohort D: patients with BRAFV600D/E/K/R mutant melanoma with symptomatic brain metastases, with or without prior local brain-directed therapy and ECOG performance status of 0 or 1 or 2.

The primary endpoint of the study was intracranial response in Cohort A, defined as the percentage of patients with a confirmed intracranial response assessed by the investigator using modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Efficacy results are summarised in Table 17. Secondary endpoints were duration of intracranial response, ORR, PFS and OS. Efficacy results are summarised in Table 17.

Table 17 COMBI-MB - Efficacy data by investigator assessment

	All treated patients population			
Endpoints/ assessment	**Cohort A N=76**	**Cohort B N=16**	**Cohort C N=16**	**Cohort D N=17**
Intracranial response rate, % (95 % CI)				
	59% (47.3, 70.4)	56% (29.9, 80.2)	44% (19.8, 70.1)	59% (32.9, 81.6)
Duration of intracranial response, median, months (95% CI)				
	6.5 (4.9, 8.6)	7.3 (3.6, 12.6)	8.3 (1.3, 15.0)	4.5 (2.8, 5.9)
ORR, % (95% CI)				
	59% (47.3, 70.4)	56% (29.9, 80.2)	44% (19.8, 70.1)	65% (38.3, 85.8)
PFS, median, months (95% CI)				
	5.7 (5.3, 7.3)	7.2 (4.7, 14.6)	3.7 (1.7, 6.5)	5.5 (3.7, 11.6)
OS, median, months (95% CI)				
Median, months	10.8 (8.7, 17.9)	24.3 (7.9, NR)	10.1 (4.6, 17.6)	11.5 (6.8, 22.4)
CI = Confidence Interval *NR = Not Reported*				

Study BRF115532 / CDRB436F2301 (COMBI-AD)

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

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

A total of 870 patients were randomised to the combination therapy (n=438) and placebo (n=432) arms. Most patients were Caucasian (99%) and male (55%), with a median age of 51 years (18% were ≥65 years). The study included patients with all sub-stages of Stage III disease prior to

resection; 18% of these patients had lymph node involvement only identifiable by microscope and no primary tumor ulceration. The majority of patients had a BRAF V600E mutation (91%).

Primary Analysis

At the time of the primary analysis, the median duration of follow-up (time from randomisation 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 Table 18. The study showed a statistically significant difference for the primary outcome of RFS between treatment arms, with an estimated 53% risk reduction in the dabrafenib and trametinib combination arm as compared to the placebo arm (HR=0.47; 95% CI: 0.39, 0.58; $p=1.53\times10^{-14}$). Results were consistent across subgroups, including stratification factors for disease stage and BRAF V600 mutation type. Median RFS was 16.6 months for the placebo arm, and was not reached for the combination arm at the time of the primary analysis.

Table 18 COMBI-AD Primary analysis – Relapse-free survival results

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

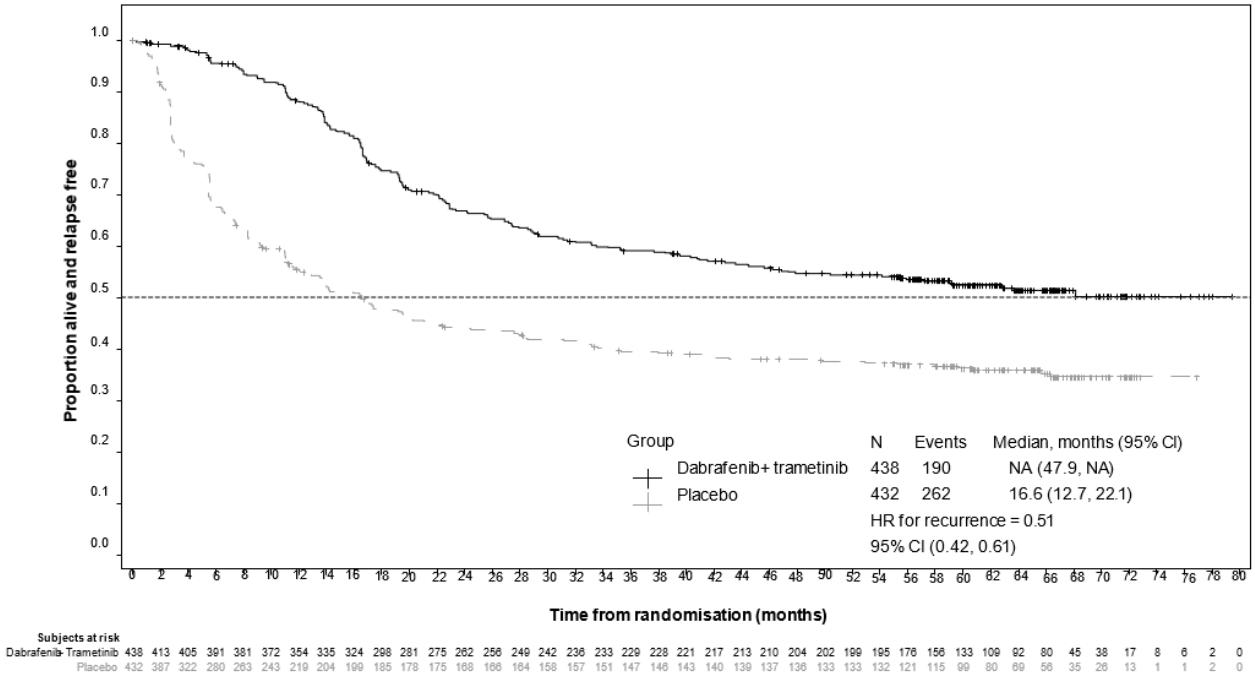
[1] Hazard ratio is obtained from the stratified Pike model.

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

NE = not estimable

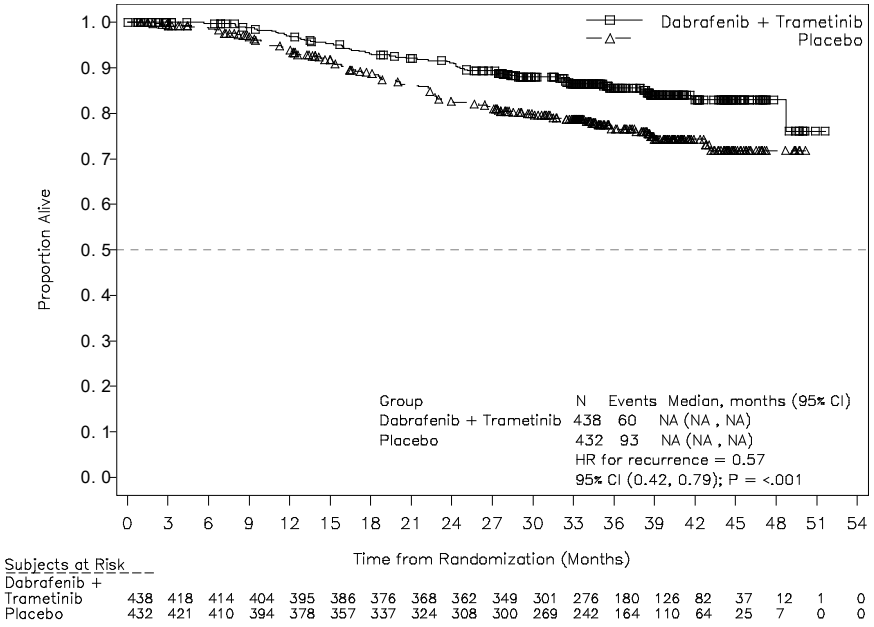
Based on updated data with an additional 29 months of follow-up compared to the primary analysis (minimum follow-up of 59 months), the RFS benefit was maintained with an estimated HR of 0.51 ([95% CI: (0.42, 0.61)] (Figure 4). The 5-year RFS rate was 52% (95% CI: 48, 58) in the combination arm compared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

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



Based on 153 events (60 (14%) in the combination arm and 93 (22%) in the placebo arm) corresponding to a 26% information fraction of the total target of 597 OS events, the estimated hazard ratio for OS was 0.57 (95% CI: 0.42, 0.79; p=0.0006). These results did not meet the pre-specified boundary to claim statistical significance at this first OS interim analysis (HR=0.50; p=0.000019). Survival estimates at 1 and 2 years from randomisation 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 6 COMBI-AD – Overall survival Kaplan-Meier curves (ITT Population)



Advanced NSCLC

Study E2201 (BRF113928)

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

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

Cohorts were enrolled sequentially:

- Cohort A: Monotherapy (TAFINLAR 150 mg twice daily): 84 patients enrolled. 78 patients had previous systemic treatment for their metastatic disease.
- Cohort B (n=57): Combination therapy (TAFINLAR 150 mg twice daily and MEKINIST 2 mg once daily): 59 patients enrolled. 57 patients had previously received one to three lines of systemic treatment for their metastatic disease. Two patients did not have any previous systemic treatment and were included in the analysis for patients enrolled in Cohort C.
- Cohort C (n=36): Combination therapy (TAFINLAR 150 mg twice daily and MEKINIST 2 mg once daily): 34 patients enrolled (note: the two patients from Cohort B that did not

have any previous systemic treatment were included in the analysis for patients enrolled in Cohort C a for total of 36 patients). All patients received study medication as first-line treatment for metastatic disease.

Among the total of 93 patients who were enrolled in the combination therapy in Cohorts B and C most patients were Caucasians (n = 79, 85%). There was a similar female to male ratio (54% vs 46%). The median age was 64 years in patients who had at least one prior therapy and 68 years in patients who were treatment naïve for their advanced disease. Most patients (n=87, 94%) enrolled in the combination therapy treated Cohorts had an ECOG performance status of 0 or 1. Twenty-six (26) patients (28%) had never smoked. Ninety-one (91) patients (97.8%) had a non-squamous histology. In the pre-treated population, 38 patients (67%) had one line of systemic anti-cancer therapy for metastatic disease.

Primary analysis

At the time of the primary analysis, the primary endpoint, the investigator-assessed ORR was 61.1 % (95 % CI, 43.5, 76.9) in the first-line population and 66.7 % (95 % CI, 52.9 %, 78.6 %) in the previously treated population. These results met the statistical significance to reject the null hypothesis that the ORR of MEKINIST in combination with TAFINLAR for both NSCLC populations was less than or equal to 30 %.

The efficacy of the combination with MEKINIST was superior when indirectly compared to TAFINLAR monotherapy in Cohort A.

The final analysis of efficacy performed 5 years after last subject first dose is presented in Table 19.

Table 19 Efficacy Results in Patients with BRAF V600E NSCLC

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

Endpoint	Analysis	Combination First Line	Combination Second Line Plus
Median OS, months (95 % CI)	-	17.3 (12.3, 40.2)	18.2 (14.3, 28.6)

TAFINLAR Monotherapy
At the time of the primary objective analysis for Cohort A, ORR as per investigator assessment was observed in 32.1 % of second-line plus all treated patients (95 % CI: 21.9, 43.6). Partial response was the best response among all these patients. At a subsequent data cut for mature DoR, the estimated median DoR was 9.6 months (95% CI: 5.4, 15.2). The estimated median PFS was 5.5 months (95 % CI: 3.4, 7.3). With an additional 18 months of follow-up from the primary objective analysis for Cohort A to determine a mature OS, the estimated median OS was 12.7 months (95 % CI: 7.3, 16.3).

Locally advanced or metastatic anaplastic thyroid cancer

Study BRF117019 / CDRB436X2201

The efficacy and safety of TAFINLAR in combination with MEKINIST was studied in a Phase II, nine-cohort, multicenter, non-randomised, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic anaplastic thyroid cancer (ATC).

The study had pre-specified interim analyses that were performed approximately every 12 weeks. Patients received Tafinlar 150 mg twice daily and Mekinist 2 mg once daily. The primary endpoint was the investigator-assessed overall response rate (ORR) using the 'Response Evaluation Criteria In Solid Tumors' (RECIST 1.1 assessed by the investigator). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. ORR, DoR, and PFS were also assessed by an Independent Review Committee (IRC).

Thirty-six patients were enrolled and were evaluable for response in the ATC cohort. The median age was 71 years (range: 47 to 85); 44% were male, 50% white, 44% Asian; and 94% had ECOG performance status of 0 or 1. Prior anti-cancer treatments included surgery (n=30, 83 %), external beam radiotherapy (n=30, 83 %), and systemic therapy (n=24, 67 %) for ATC. Central laboratory testing confirmed the BRAF V600E mutation in 33 patients (92 %).

For the primary endpoint, the investigator-assessed ORR was 56 % (95% CI: 38.1, 72.1) in the ATC cohort. The ORR results assessed by IRC and investigator-assessment were consistent (Table 20).

Responses were durable with a median DoR in the ATC cohort of 14.4 months (95 % CI: 7.4, 43.6) by investigator assessment, and a median PFS of 6.7 months (95 % CI: 4.7, 13.8).

For ATC patients, the median OS was 14.5 months (95% CI: 6.8, 23.2). Kaplan-Meier estimate of overall survival at 12 months for ATC patients was 51.7 % (95 % CI: 33.6, 67.1).

Table 20 Efficacy Results in Patients with BRAF V600E ATC

Endpoint	Analysis By Investigator[1] ATC Cohort N= 36	Analysis By IRC ATC Cohort N= 36
Overall confirmed response n (%) (95% CI)	20 (56%) (38.1, 72.1)	19 (53%) (35.5, 69.6)
Median DoR, months (95% CI)	14.4 (7.4, 43.6)	13.6 (3.8, NE[2])
Median PFS, months (95% CI)	6.7 (4.7,13.8)	5.5 (3.7, 12.9)
Median OS, months (95% CI)	14.5 (6.8, 23.2)	

[1] *Data cut-off:* 14-Sep-2020[2]
NE: Not Estimable

Other Studies

Pyrexia Management Analysis

Pyrexia is observed in patients treated with Tafinlar and Mekinist combination therapy. The initial registration studies for the combination therapy in the unresectable or metastatic melanoma setting (COMBI-d and COMBI-v; total N=559) and in the adjuvant melanoma setting (COMBI-AD, N=435) recommended to interrupt only Tafinlar in case of pyrexia. In two subsequent studies in unresectable or metastatic melanoma (COMBI-i control arm, N=264) and in the adjuvant melanoma setting (COMBI-Aplus, N=552), interruption of both Tafinlar and Mekinist when patient's temperature was ≥38ºC (100.4°F) (COMBI-Aplus) or at the first symptom of pyrexia (COMBI-i; COMBI-Aplus for recurrent pyrexia), resulted in improved pyrexia-related outcomes without impacting efficacy:

- Unresectable or metastatic melanoma setting (COMBI-d/v vs COMBI-i):
  - grade 3/4 pyrexia reduced from 6.6% to 3.4%
  - hospitalization due to pyrexia reduced from 12.3% to 6.1%
  - pyrexia with complications (dehydration, hypotension, renal dysfunction, syncope, severe chills) reduced from 6.4 % to 1.9%
  - treatment discontinuation rates due to pyrexia were comparable, 1.1% vs 1.9%
- Adjuvant melanoma setting (COMBI-AD vs COMBI-Aplus):
  - grade 3/4 pyrexia reduced from 5.7% to 4.3%
  - hospitalization due to pyrexia reduced from 11.0% to 5.1%
  - pyrexia with complications (dehydration, hypotension, renal dysfunction, syncope, severe chills) reduced from 6.0% to 2.2%
  - treatment discontinuation due to pyrexia reduced from 6.2% to 2.5%

5.2 Pharmacokinetic properties

The pharmacokinetics of dabrafenib 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

Dabrafenib is absorbed orally with median time to achieve peak plasma concentration of 2 hours post-dose. Mean absolute bioavailability of oral dabrafenib is 95 % (90 % CI: 81 %, 110 %). Dabrafenib exposure (C_{max} and AUC) increased in a dose proportional manner between 12 mg and 300 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 1478 ng/mL, 4341 ng*hour/mL and 26 ng/mL, respectively.

Effect of food

Administration of dabrafenib with food reduced the bioavailability (C_{max} and AUC decreased by 51 % and 31 % respectively) and delayed absorption of dabrafenib capsules when compared to the fasted state.

Distribution

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

Biotransformation/ metabolism

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidised via CYP3A4 to form carboxy-dabrafenib. Carboxy-dabrafenib can be decarboxylated via a non-enzymatic process to form desmethyl-dabrafenib. Carboxy-dabrafenib is excreted in bile and urine. Desmethyl-dabrafenib may also be formed in the gut and reabsorbed. Desmethyl-dabrafenib is metabolised by CYP3A4 to oxidative metabolites. Hydroxy-dabrafenib terminal half-life parallels that of parent with a half-life of 10 hours while the carboxy- and desmethyl-metabolites exhibited longer half-lives (21-22 hours). Mean metabolite to parent AUC ratios following repeat-dose administration were 0.9, 11 and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib; while the activity of carboxy-dabrafenib is not likely to be significant.

Elimination

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

Fecal excretion 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 populations

Hepatic Impairment

A population pharmacokinetic analysis in 65 patients with mild hepatic impairment indicates

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

Renal Impairment
The pharmacokinetics of TAFINLAR were characterised in 233 patients with mild renal impairment (GFR 60-89 mL/min/1.73 m^2) and 30 patients with moderate renal impairment (GFR 30-59 mL/min/1.73 m^2) enrolled in clinical trials, using a population analysis. The effect of mild to moderate renal impairment on TAFINLAR clearance was small (< 6 % for both categories) and was not clinically relevant. No data are available in patients with severe renal impairment (see section 4.2).

Paediatric patients (< 18 years of age)
No studies have been conducted to investigate the pharmacokinetics of TAFINLAR in pediatric patients.

Patients ≥ 65 years of age
Based on the population pharmacokinetic analysis, age had no significant effect on dabrafenib pharmacokinetics. Age greater than 75 years was a significant predictor of carboxy- and desmethyl-dabrafenib plasma concentrations with a 40% greater exposure in patients ≥ 75 years of age, relative to patients < 75 years old.

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

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

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

5.3 Preclinical safety data

Safety pharmacology
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 oestrous cycle, mating or fertility. Developmental toxicity including embryo-lethality and ventricular septal defects and variation in thymic shape were seen at 300 mg/kg/day, and delayed skeletal development and reduced foetal body weight at ≥ 20 mg/kg/day (≥ 0.5 times human clinical exposure based on AUC).

Male fertility studies with dabrafenib 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.

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

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

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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The hard capsules also contain:

- cellulose - microcrystalline
- magnesium stearate (vegetable source)
- silica - colloidal anhydrous
- iron oxide red
- titanium dioxide
- hypromellose
- iron oxide black (in the printing ink)
- shellac (in the printing ink)
- butan-1-ol (in the printing ink)
- isopropyl alcohol (in the printing ink)
- propylene glycol (in the printing ink)
- ammonium hydroxide (in the printing ink).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C. Protect from moisture and light. Store in the original container. Do not remove the desiccant.

6.5 Nature and contents of container

TAFINLAR capsules are supplied in high-density polyethylene (HDPE) bottles with child

resistant polypropylene closures containing 28 or 120 capsules*. The bottle contains a desiccant.

*Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Novartis New Zealand Limited
PO Box 99102 Newmarket Auckland 1149

Telephone: 0800 354 335
Fax number: (09) 361 8181
E-mail: medinfo.phauno@novartis.com

9. DATE OF FIRST APPROVAL

The date of consent to distribute these medicines were published in the New Zealand Gazette on: 19th June 2014

10. DATE OF REVISION OF THE TEXT

02 April 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Correction to "post-market adverse drug reaction" table: Atrioventricular block and Bundle Branch Block reported frequencies for TAFINLAR in combination with Mekinist. Editorial update to "post-market adverse drug reaction" table to remove specific reference to "Bundle Branch Block" from the preferred group term scope.

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