▼This medicinal product is subject to additional monitoring in Australia due to approval of an extension of indications. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION - TAFINLAR® (dabrafenib)

1. NAME OF THE MEDICINE

Dabrafenib.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

TAFINLAR 50 mg capsules

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

TAFINLAR 75 mg capsules

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

TAFINLAR 10 mg dispersible tablets

Each dispersible tablet contains dabrafenib mesilate equivalent to 10 mg of dabrafenib.

Note: dabrafenib capsules and dispersible tablets are not interchangeable

Excipients

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

3. PHARMACEUTICAL FORM

TAFINLAR 50 mg capsules

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

TAFINLAR 75 mg capsules

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

TAFINLAR 10 mg dispersible tablets

White to slightly-yellow, round biconvex 6 mm tablet debossed with “D” on one side and “NVR” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Unresectable or metastatic melanoma

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

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

Adjuvant treatment of melanoma

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

Anaplastic thyroid cancer (ATC)

TAFINLAR in combination with trametinib is indicated for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with a BRAF V600 mutation and with no satisfactory locoregional treatment options.

Non-small cell lung cancer (NSCLC)

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

Low-grade glioma

TAFINLAR in combination with trametinib is indicated for the treatment of paediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy (see Section 5.1 Pharmacodynamic properties - Clinical trials).

High-grade glioma

TAFINLAR in combination with trametinib is indicated for the treatment of paediatric patients 1 year of age and older with high-grade glioma (HGG) with a BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options (see Section 5.1 Pharmacodynamic properties - Clinical trials).

4.2. Dose and method of administration

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

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

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

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

Note: dabrafenib capsules and dispersible tablets are not fully bioequivalent/interchangeable; caution is advised when consideration is given to changing formulations due to any difficulty in swallowing solid forms, and frequent switching between formulations is discouraged.

Duration of treatment

The recommended duration of treatment for patients with unresectable or metastatic melanoma metastatic NSCLC, or locally advanced or metastatic anaplastic thyroid cancer is until disease progression or unacceptable toxicity.

In the adjuvant melanoma setting, the treatment duration is limited to a maximum of 1 year.

The recommended duration of treatment for paediatric patients with glioma is until disease progression or until unacceptable toxicity. There are limited data in patients older than 18 years of age with glioma. Therefore, continued treatment into adulthood should be based on benefits and risks to the individual patient as assessed by the physician.

Recommended Dosage

TAFINLAR is available in two dosage forms, capsules (for use in adult patients and in paediatric patients who weigh at least 26 kg) and dispersible tablets (for use in patients 1 year of age and older).

The recommended dose of TAFINLAR in adult patients is TAFINLAR 150 mg (two 75 mg capsules) taken twice daily (corresponding to a total daily dose of 300 mg), independent of body weight. Dose level reductions are shown in Table 1.

Table 1 Recommended dosing and dose level reductions for TAFINLAR capsules in adult patients

Dose Level	Dose/Schedule
Full starting dose	150 mg twice daily
First dose reduction	100 mg twice daily
Second dose reduction	75 mg twice daily
Third dose reduction	50 mg twice daily
Permanently discontinue if unable to tolerate Tafinlar 50 mg capsule orally twice daily	

The recommended dose and dose level reductions of TAFINLAR capsules in paediatric patients who weigh at least 26 kg, is based on body weight (Table 2). A recommended dose of TAFINLAR capsules for patients who weigh less than 26 kg has not been established.

Table 2 Recommended weight-based dosing and dose level reductions for TAFINLAR capsules in paediatric patients

Body weight	Recommended starting dosage	First dose reduction	Second dose reduction	Third dose reduction
26 to 37 kg	75 mg orally twice daily	50 mg orally twice daily	-	-
38 to 50 kg	100 mg orally twice daily	75 mg orally twice daily	50 mg orally twice daily	-
51 kg or greater	150 mg orally twice daily	100 mg orally twice daily	75 mg orally twice daily	50 mg orally twice daily
Permanently discontinue if unable to tolerate maximum of three dose reductions or a Tafinlar 50 mg capsule orally twice daily				

The recommended dosage and dose level reductions for TAFINLAR dispersible tablets are based on body weight (Table 3).

Table 3 Recommended weight-based dosing and dose level reductions for TAFINLAR dispersible tablets

	Recommended Starting Dosage		Dose Level Reductions		
Body weight (kg)	Daily Dose	# of 10 mg tablets twice daily	First Reduction	Second Reduction	Third Reduction
			# of 10 mg tablets twice daily		
8 to 9 kg	20 mg twice daily	2	1	-	-
10 to 13 kg	30 mg twice daily	3	2	1	-

14 to 17 kg	40 mg twice daily	4	3	2	1
18 to 21 kg	50 mg twice daily	5	3	2	1
22 to 25 kg	60 mg twice daily	6	4	3	2
26 to 29 kg	70 mg twice daily	7	5	4	2
30 to 33 kg	80 mg twice daily	8	5	4	3
34 to 37 kg	90 mg twice daily	9	6	5	3
38 to 41 kg	100 mg twice daily	10	7	5	3
42 to 45 kg	110 mg twice daily	11	7	6	4
46 to 50 kg	130 mg twice daily	13	9	7	4
≥51 kg	150 mg twice daily	15	10	8	5

Permanently discontinue if unable to tolerate a maximum of 3 dose reductions or a Tafinlar 10 mg dispersible tablet orally twice daily.

Dose modifications

Monotherapy and in combination with MEKINIST

The management of adverse reactions when TAFINLAR is used as monotherapy or in combination with MEKINIST (trametinib) may require treatment interruption, dose reduction, or treatment discontinuation (see Table 1, Table 2 and Table 3). Also refer to the full trametinib product information for dosing instructions and modifications.

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

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

The recommended dose modification schedule is provided in Table 4. When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The TAFINLAR dose should not exceed the recommended starting dose.

Table 4 Tafinlar dose modification schedule (excluding pyrexia)

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

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

Table 5 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.
CUTANEOUS	
• Intolerable Grade 2 skin toxicity • Grade 3 or 4 skin toxicity	Withhold TAFINLAR for up to 3 weeks. • If improved, resume at a lower dose level. • If not improved, permanently discontinue.
CARDIAC	
• Symptomatic congestive heart failure • Absolute decrease in LVEF of greater than 20 % from baseline that is below LLN	• Withhold TAFINLAR. If improved, resume at the same dose upon recovery of cardiac function
UVEITIS	
Uveitis including iritis and iridocyclitis	If mild or moderate uveitis does not respond to ocular therapy, or for severe uveitis, withhold TAFINLAR for up to 6 weeks. • If improved to Grade 0-1, then resume at the same or at a lower dose level. • If not improved, permanently discontinue.
OTHER	
Grade 2 (Intolerable) or Grade 3	Withhold TAFINLAR. • If improved to grade 0 – 1, resume at a lower dose level. • If not improved, permanently discontinue TAFINLAR.

Severity of adverse reaction[a]	TAFINLAR[b]
First occurrence of any Grade 4 adverse reaction	• Withhold TAFINLAR until adverse reaction improves to Grade 0-1. Then resume at a lower dose level. Or • Permanently discontinue TAFINLAR.

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

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

Detailed dosing modifications for selected adverse reactions

New Primary Cutaneous Malignancies

- No TAFINLAR dose modifications are required.

New Primary Non-Cutaneous Malignancies

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

Pyrexia Management

Follow the dose modifications in Table 5. 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 (preferred) or paracetamol. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection (see section 4.4 Special Warnings and Precautions for Use). 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 5). Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia.

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

Uveitis Management

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

Interstitial lung disease (ILD)/Pneumonitis

Do not modify the dose of TAFINLAR.

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

Serious Skin Toxicity

For dosing modifications in intolerable or severe skin toxicity see Table 5.

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

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

Special Populations

Paediatric use

The safety and efficacy of TAFINLAR in combination with trametinib have not been established in paediatric patients younger than 1 year of age with LGG/HGG with BRAF V600E mutation. Studies in juvenile animals have shown effects of TAFINLAR which had not been observed in adult animals (see Section 4.4 Special Warnings and Precautions for Use). The safety and effectiveness of TAFINLAR as a single agent in paediatric patients have not been established.

Use in the elderly

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

Renal impairment

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

Hepatic impairment

No dose adjustment is required for patients with mild hepatic impairment. Based on the population pharmacokinetic analysis, mild hepatic impairment had no significant effect on TAFINLAR oral clearance or on the concentrations of its metabolites (see section 5.2 Pharmacokinetic Properties). There are no clinical data in patients with moderate to severe hepatic impairment and the potential need for dose adjustment cannot be determined. Hepatic metabolism and biliary secretion are the primary routes of elimination of TAFINLAR and its metabolites and patients with moderate to severe hepatic impairment may have increased exposure. TAFINLAR should be used with caution in patients with moderate or severe hepatic impairment.

Administration

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

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

Hard capsules

TAFINLAR hard capsules should be swallowed whole with a glass of water. Do not open, crush, or break TAFINLAR capsules.

Dispersible tablets

TAFINLAR dispersible tablets are to be taken as a suspension only and should not be swallowed

whole, chewed, or crushed.

The oral suspension is prepared with approximately 5mL of water for 1 to 4 tablets, and approximately 10mL of water for 5 to 15 tablets in a provided dosing cup (refer to the Instruction for use for reconstitution instructions). TAFINLAR dispersible tablet suspension can be administered using three different methods: via drinking the suspension from the dosing cup; swallowing the suspension received from an oral syringe filled with the suspension withdrawn from the dosing cup or receiving the suspension via a feeding tube. Care should be taken to ensure the entire dose is administered. It may take 3 minutes (or more) to fully dissolve the tablets. Once they are dissolved, the suspension should be cloudy white.

Administer the suspension immediately after preparation from cup, oral dosing syringe or feeding tube. Discard suspension if not administered within 30 minutes after preparation in line with local regulations and restart from the beginning.

Combination therapy

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

Missed dose

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

BRAF V600 testing

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

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

Pyrexia and serious non-infectious febrile events

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

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

In 1 % of patients in clinical trials, serious non-infectious febrile events were identified defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency (see Section 4.4 Special Warnings and Precautions for Use and Section 4.8 Adverse Effects (Undesirable Effects)). The onset of these serious non-infectious febrile events was typically within the first month of therapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care.

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 antipyretics are insufficient.

For management of pyrexia also see Section 4.2 Dose and Method of Administration.

Renal failure

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

Cutaneous Squamous Cell Carcinoma (cuSCC)

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with TAFINLAR as monotherapy and in combination with MEKINIST (see Section 4.8 Adverse Effects (Undesirable Effects)). In a Phase III study in patients with unresectable or metastatic melanoma, 10 % (22/211) of patients receiving TAFINLAR as monotherapy developed cuSCC with a median time to onset of the first occurrence of approximately 8 weeks. In patients who received TAFINLAR with MEKINIST, 3

% (6/209) of patients developed cuSCC and, events occurred later, with the median time to onset of the first occurrence of 20 to 32 weeks. More than 90 % of patients on TAFINLAR who developed cuSCC, continued on treatment without dose modification. In a Phase III trial in the adjuvant treatment of melanoma, 1% (6/435) of patients receiving TAFINLAR in combination with MEKINIST as compared to 1% (5/432) of patients receiving placebo developed cuSCC. The median time to onset of the first occurrence of cuSCC in the combination arm was approximately 18 weeks.

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

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

New primary melanoma

New primary melanomas have been reported in patients treated with TAFINLAR. In clinical trials in unresectable or metastatic melanoma, these cases were identified within the first five months of therapy, were managed with excision, and did not require treatment modification. In the Phase III clinical trial in the adjuvant treatment of melanoma, new primary melanomas occurred in <1% (1/435) of patients receiving the combination of TAFINLAR and MEKINIST as opposed to 1% (6/432) of patients receiving placebo. Monitoring for skin lesions should occur as described for cuSCC.

Non-cutaneous 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. This may lead to an increased risk of non-cutaneous malignancies with TAFINLAR exposure, when RAS mutations are present. RAS-associated malignancies have been reported in clinical trials, both with another BRAF inhibitor (chronic myelomonocytic leukaemia and non-cutaneous SCC of the head and neck) as well as with TAFINLAR monotherapy (pancreatic adenocarcinoma, bile duct adenocarcinoma) and with TAFINLAR in combination with the MEK inhibitor MEKINIST (colorectal cancer, pancreatic cancer). In the Phase III trial in the adjuvant treatment of melanoma comparing combination of TAFINLAR and MEKINIST to placebo, non-cutaneous secondary malignancies or recurrent malignancies were observed in 1% (5/435) of patients receiving active therapy compared to 1% (3/432) of patients receiving placebo.

Prior to initiation of treatment, patients should undergo a head and neck examination with minimally visual inspection of oral mucosa and lymph node palpation, as well as chest/abdomen computerised tomography (CT) scan. During treatment, patients should be monitored as clinically appropriate which may include a head and neck examination every 3 months and a chest/abdomen CT scan every 6 months. Anal examinations and pelvic examinations (for women) are recommended before and at the end of treatment or when considered clinically indicated. Complete blood cell counts should be performed as clinically indicated. (See section 4.2 Dose and Method of Administration.)

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

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

Serious Skin Toxicity

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

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.

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 Adverse effects (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.

Visual impairment

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

Uveitis

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

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

Cases of biocular panuveitis or biocular iridocyclitis suggestive of Vogt-Koyanagi-Harada-like syndrome have been reported in patients treated with TAFINLAR in combination with MEKINIST. Systemic corticosteroid treatment can be considered in such cases.

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

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

Please refer to the MEKINIST Product Information.

Pancreatitis

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

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

Hyperglycaemia

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

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

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

TAFINLAR in combination with MEKINIST® (trametinib)

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

Haemorrhage

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

Six (6) out of 559 unresectable or metastatic melanoma patients (1.1 %) receiving dabrafenib in combination with trametinib in a phase III trial had fatal intracranial haemorrhagic events. Three cases were from study MEK115306 (COMBI-d) and three cases were from study MEK116513 (COMBI-v). No fatal haemorrhagic events occurred in the Phase III study in the adjuvant treatment of melanoma (0/438). Two out of 93 patients (2 %) receiving TAFINLAR in combination with MEKINIST 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.

In Study BRF113220, treatment with TAFINLAR in combination with trametinib resulted in an increased incidence and severity of any haemorrhagic event: 16 % (9/55) of patients treated with

trametinib in combination with TAFINLAR compared with 2 % (1/53) of patients treated with TAFINLAR as a single agent. The major haemorrhagic events of intracranial or gastric haemorrhage occurred in 5 % (3/55) of patients treated with MEKINIST in combination with TAFINLAR compared with none of the 53 patients treated with dabrafenib as a single agent. Intracranial haemorrhage was fatal in two (4 %) patients receiving the combination of MEKINIST and TAFINLAR.

Cardiac Effects

LVEF reduction/Left ventricular dysfunction

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

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

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

QT prolongation

Worst-case QTc prolongation of > 60 millisecond (ms) was observed in 3 % of TAFINLAR-treated patients (one > 500 ms in the integrated safety population). In the Phase III study MEK115306, no patients treated with trametinib in combination with dabrafenib had worst-case QTcB prolongation to > 500 ms; QTcB was increased more than 60 ms from baseline in 1% (3/209) of patients. In the Phase III study MEK116513 four patients (1 %) treated with MEKINIST in combination with TAFINLAR had a QTcB Grade 3 increase (> 500 ms). Two of these patients had a QTcB Grade 3 increase (>500 ms) that was also an increase > 60 ms from baseline. The potential effect of TAFINLAR on QT prolongation was assessed in a dedicated multiple dose QT study. A supra therapeutic dose of 300 mg TAFINLAR twice daily was administered in 32 patients with BRAF V600 mutation positive tumours. No clinically relevant effect of TAFINLAR or its metabolites on the QTc interval was observed.

Bradycardia

A dedicated cardiac study in solid tumour patients (n=30) confirmed early exploratory analyses in showing statistically significant changes in both PR interval (mean 21.68 ms increase, normal = 120 to 200) and heart rate (mean 8.12 bpm decrease) with MEKINIST versus placebo. The clinical

significance of this small increase in PR interval is unclear, however in a large ongoing trial (n=704), heart rate decrease to < 60 bpm has been recorded in 23 % of 348 patients on MEKINIST and TAFINLAR combined therapy compared to 12 % of patients in the vemurafenib monotherapy control arm.

Hepatic events

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

Hypertension

Elevations in blood pressure have been reported in association with dabrafenib in combination with trametinib, in patients with or without pre-existing hypertension (see section 4.8 Adverse Effects (Undesirable Effects)). Also refer to the MEKINIST Product Information for additional information.

Interstitial lung disease (ILD)/Pneumonitis

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

Rash

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

Rhabdomyolysis

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

Venous thromboembolism (VTE)

VTE, including pulmonary embolism or deep vein thrombosis (DVT) can occur when TAFINLAR is used in combination with MEKINIST. If patients develop symptoms of VTE, including PE or DVT such as shortness of breath, chest pain, or arm or leg swelling, they should immediately seek medical care. Permanently discontinue MEKINIST and TAFINLAR for life-threatening pulmonary embolism.

Use in hepatic impairment

See sections 4.2 Dose and Method of Administration, and 5.2 Pharmacokinetic Properties.

Use in renal impairment

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

Use in the elderly

See sections 4.2 Dose and Method of Administration, 4.8 Adverse Effects (Undesirable Effects), and 5.2 Pharmacokinetic Properties.

Paediatric use

The safety and efficacy of TAFINLAR in combination with trametinib have not been established in paediatric patients younger than 1 year of age with LGG/HGG with BRAF V600E mutation. For information of paediatric patients aged 1 to 18 years, refer to sections 4.1, 4.2, 4.8, 5.1 and 5.2. The safety and effectiveness of TAFINLAR as a single agent in paediatric patients have not been established.

Effects on laboratory tests

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

4.5 Interactions with other medicines and other forms of interactions

In vitro evaluation of drug interaction potential

Effect of other medicines on TAFINLAR

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

Ketoconazole

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

Gemfibrozil

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

Drugs that affect gastric pH

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

Effect of TAFINLAR on other medicines

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

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

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

Midazolam

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

Warfarin

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

Digoxin

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

Effects of dabrafenib on substance transport systems

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

Although TAFINLAR and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, were inhibitors of human organic anion transporter (OAT) 1 and OAT3 *in vitro*, the risk of a drug-drug interaction is minimal based on clinical exposure. TAFINLAR and desmethyl-dabrafenib were also shown to be moderate inhibitors of human breast cancer resistance protein (BCRP) and the human renal uptake transporter organic cation transporter 2 (OCT2); however, based on clinical exposure, the risk of a drug-drug interaction is minimal. Neither TAFINLAR nor its 3 metabolites were demonstrated to be inhibitors of P-gp *in vitro*.

Combination of TAFINLAR with MEKINIST

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

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

4.6 Fertility, pregnancy, and lactation

Effects on fertility

Infertility

There are no data in humans. TAFINLAR may impair male and female fertility as adverse effects on male and female reproductive organs have been seen in animals. Male patients should be informed of the potential risk for impaired spermatogenesis, which may be irreversible.

In combined female fertility, early embryonic and embryofetal development studies in rats numbers of ovarian corpora lutea were reduced in pregnant females at 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC), but there were no effects on estrous cycle, mating or fertility.

Males taking TAFINLAR in combination with MEKINIST

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

Use in Pregnancy (Category D)

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

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

Contraception

Females

Females of reproductive potential should be advised that animal studies have been performed showing TAFINLAR to be harmful to the developing fetus. Sexually active females of reproductive potential are recommended to use effective methods of contraception 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 alternate method of contraception (methods that result in less than 1 % pregnancy rates) should be used during treatment and for at least two weeks after stopping treatment with TAFINLAR (see section 4.5 Interactions with other medicines and other forms of interactions).

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

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 on the effect of TAFINLAR on milk production. Because many drugs are transferred into human milk and because of the potential for adverse reactions in nursing infants from TAFINLAR, a nursing woman should be advised on the potential risks to the child. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for TAFINLAR and any potential adverse effects on the breast-fed child from TAFINLAR or from the underlying maternal condition.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

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

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

Summary of the safety profile

Unresectable or metastatic melanoma

TAFINLAR Monotherapy

Safety data were 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 melanoma. Approximately 30 % of patients received treatment with TAFINLAR for more than 6 months.

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

Table 6 Unresectable or metastatic melanoma - adverse reactions with TAFINLAR monotherapy

Neoplasms benign and malignant (including cysts and polyps)	
Very common	Papilloma
Common	Acrochordon (skin tags), cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma, seborrhoeic 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 modification was required.

Table 7 lists the very common (≥ 10 % of patients) adverse events reported in the Phase III randomised, open-label study [BREAK-3].

Table 7 Adverse events reported ≥ 10 % of patients receiving TAFINLAR or dacarbazine in unresectable or metastatic melanoma - BREAK-3 (safety population) by maximum grade

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

	Number (%) of Patients					
	TAFINLAR (N=187)			dacarbazine (N=59)		
Preferred term	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Abdominal pain	7 (4)	1 (<1)	0	8 (14)	0	1 (2)
Anaemia	7 (4)	1 (<1)	0	7 (12)	1 (2)	1 (2)
Neutropenia	2 (1)	1 (<1)	0	10 (17)	4 (7)	4 (7)
Leukopenia	1 (<1)	0	0	6 (10)	2 (3)	0

Table 8 Incidence of Laboratory abnormalities increased from baseline occurring at a higher incidence in patients treated with TAFINLAR in BRF113683 [Between arm difference of ≥ 5 % (all Grades) or ≥ 2 % (Grades 3 or 4)]

	TAFINLAR (n=187)		dacarbazine (n=59)	
	All Grades (%)	**Grades 3 and 4 (%)**	**All Grades (%)**	**Grades 3 and 4 (%)**
Hyperglycemia	50	6	43	0
Hypophosphatemia	37	6*	14	2
Increased Alkaline phosphatase	19	0	14	2
Hyponatremia	8	2	3	0

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

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 trametinib. Because post-marketing adverse reactions 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. Adverse reactions 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 thrombo-embolism (VTE)[3]	Common	-
Skin and subcutaneous tissue disorders		
Acute febrile neutrophilic dermatosis (Sweet's syndrome)	Not known	-
Tattoo associated skin reaction	Not known	-
Immune system disorders		
Sarcoidosis	Uncommon	-
Haemophagocytic lymphohistiocytosis	Not known	-
Metabolism and nutrition disorders		
Tumour lysis syndrome	Not known	-
Nervous system disorders		
Peripheral neuropathy	Common	Common
Guillain-Barré syndrome	Uncommon	-

[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 with TAFINLAR as monotherapy and in combination with trametinib. The incidence and severity of pyrexia are increased with the combination therapy. In 1 % of patients in clinical trials, serious non-infectious febrile events were identified defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency

or pre-renal origin in patients with normal baseline renal function. The onset of these serious non-infectious febrile events was typically within the first month of therapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care (see section 4.2 Dose and method of administration).

Cutaneous squamous cell carcinoma

Cutaneous squamous cell carcinomas (including those classified as keratoacanthoma or mixed keratoacanthoma subtype) occurred in 9 % (52/578) of patients treated with TAFINLAR monotherapy in the integrated safety population and 3 % of patients treated with TAFINLAR in combination with MEKINIST in MEK115306. With TAFINLAR monotherapy, approximately 70 % of events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. In patients who received the combination dose of TAFINLAR in combination with MEKINIST, events occurred later with the median time to onset of 22 weeks. Ninety-six percent of patients on TAFINLAR monotherapy in the integrated safety population and all patients on combination therapy in the Phase III studies who developed cuSCC continued on treatment without dose modification.

New primary melanoma

New primary melanomas have been reported in clinical trials with TAFINLAR. Cases were managed with excision and did not require treatment modification (see section 4.4 Special warnings and precautions for use).

Non-cutaneous malignancy

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

TAFINLAR and trametinib combination therapy

In addition to adverse reactions observed with monotherapy treatments (Table 10 and Table 11, the safety of TAFINLAR and MEKINIST combination therapy has been evaluated in two randomised Phase III studies and one small phase II study of patients with BRAF mutant unresectable or metastatic melanoma treated with TAFINLAR 150 mg orally twice daily and MEKINIST 2 mg orally once daily (see section 5.1 Pharmacodynamic properties - Clinical trials). The following tables list adverse reactions which are specific to TAFINLAR in combination with MEKINIST.

In Table 13, there were 55 patients in the study and hence the frequencies of uncommon or rare events could not be calculated.

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

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

	TAFINLAR 150 mg BID + MEKINIST 2 mg QD combination (N = 209)		TAFINLAR 150 mg BID + placebo (N = 211)	
	All grades (%)	grades 3 and 4 (%)	All grades (%)	grades 3 and 4 (%)
Neoplasms benign and malignant (including cysts and polyps)				
Skin papilloma	1	0	21	0
Squamous cell carcinoma	<1	<1	4	2
Squamous cell carcinoma of skin	<1	<1	5	2
Metabolism and nutritional disorders				
Decreased appetite	11	<1	12	<1
Hyperglycaemia	3	2	<1	0
Hypophosphatemia	2	1	2	2
Nervous system disorders				
Headache	30	<1	29	1
Dizziness	10	0	6	0
Respiratory, thoracic, and mediastinal disorders				
Cough	16	0	17	0

	TAFINLAR 150 mg BID + MEKINIST 2 mg QD combination (N = 209)		TAFINLAR 150 mg BID + placebo (N = 211)	
	All grades (%)	grades 3 and 4 (%)	All grades (%)	grades 3 and 4 (%)
Dyspnea	6	<1	9	2
Gastrointestinal disorders				
Nausea	30	0	26	1
Diarrhoea	24	<1	14	<1
Vomiting	20	<1	14	<1
Constipation	11	<1	9	0
Abdominal pain	11	<1	7	1
Skin and subcutaneous tissue disorders				
Rash	23	0	22	<1
Dry skin	9	0	13	0
Hyperkeratosis	3	0	32	<1
Pruritus	8	0	12	0
Alopecia	7	0	26	0
PPE[a]	4	0	18	<1
Palmoplantar keratoderma	<1	0	11	0
Musculoskeletal, connective tissue and bone disorders				
Arthralgia	24	<1	27	0
Pain in extremity	14	1	16	<1
Myalgia	11	<1	11	0
General disorders and administrative site conditions				
Pyrexia	51	6	28	2

	TAFINLAR 150 mg BID + MEKINIST 2 mg QD combination (N = 209)		TAFINLAR 150 mg BID + placebo (N = 211)	
	All grades (%)	grades 3 and 4 (%)	All grades (%)	grades 3 and 4 (%)
Fatigue	35	2	35	<1
Chills	30	0	16	0
Asthenia	10	<1	13	<1
Edema peripheral	14	<1	5	<1
Infections and infestations				
Nasopharyngitis	10	0	7	0
Vascular disorders				
Hypertension	22	4	14	5
Hypotension	6	2	3	<1
Blood and Lymphatic System Disorders				
Neutropenia	9	3	<1	0
Anemia	6	2	7	3
Investigations				
ALT increased	11	2	5	<1
AST increased	11	3	3	<1
Lymphocyte count decrease	2	2	1	1

[a] PPE = Palmar-plantar erythrodysesthesia.

Table 11 **Study MEK115306 (COMBI-d) - Treatment emergent Liver function test abnormalities (worst case on therapy) occurring in patients treated with TAFINLAR in combination with MEKINIST or placebo**

Test	TAFINLAR 150 mg BID plus placebo (N = 211)			TAFINLAR 150 mg BID + MEKINIST 2 mg QD combination (N = 209)		
	All Grades[a]	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Increased ALP	20	<1	0	45	<1	0
Increased AST	17	<1	0	53	2	<1
Increased ALT	25	<1	0	38	24	<1
Hyperbilirubinemia	2	0	0	4	<1	<1

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

[a] No Grade 4 events were reported in the dabrafenib arm

Table 12 Adverse reactions for TAFINLAR in combination with MEKINIST in melanoma randomised Phase III studies MEK115306 (COMBI-d), and integrated safety data (ISD) from MEK115306 and MEK116513 (COMBI-v)

	Frequency category	
	COMBI-d n=209	COMBI-d & COMBI-v 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

	Frequency category	
	COMBI-d n=209	**COMBI-d & COMBI-v n=559**
Acrochordon (skin tags)	Common	Uncommon
New primary melanoma	Uncommon	Uncommon
Blood and lymphatic system disorders		
Neutropenia	Very common	Common
Anaemia	Common	Common
Thrombocytopenia	Common	Common
Leukopenia	Common	Common
Immune system disorders		
Hypersensitivity	Uncommon	Uncommon
Metabolic and nutrition disorders		
Decreased appetite	Very common	Very common
Dehydration	Common	Common
Hyperglycemia	Common	Common
Hyponatraemia	Common	Common
Hypophosphataemia	Common	Common
Nervous system disorders		
Headache	Very common	Very common
Dizziness	Very common	Very common
Eye disorders		
Vision blurred	Common	Common
Visual impairment	Common	Common
Chorioretinopathy	Uncommon	Uncommon
Uveitis	Uncommon	Uncommon
Retinal detachment	Uncommon	Uncommon
Periorbital oedema	Uncommon	Uncommon
Cardiac disorders		
Ejection fraction decreased	Common	Common
Left ventricular dysfunction	NR	Uncommon

	Frequency category	
	COMBI-d n=209	**COMBI-d & COMBI-v n=559**
Cardiac failure	NR	Uncommon
Bradycardia	Common	Common
Vascular disorders		
Hypertension	Very common	Very common
Haemorrhage[1]	Very common	Very common
Hypotension	Common	Common
Lymphoedema	Uncommon	Common
Respiratory, thoracic and mediastinal disorders		
Cough	Very common	Very common
Dyspnoea	Common	Common
Pneumonitis	Uncommon	Uncommon
Interstitial lung disease	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
Skin and subcutaneous tissue disorders		
Dry skin	Very common	Very common
Pruritus	Very common	Very common
Rash	Very common	Very common

	Frequency category	
	COMBI-d n=209	**COMBI-d & COMBI-v n=559**
Dermatitis acneiform	Very common	Common
Erythema	Common	Common
Actinic keratosis	Common	Common
Night sweats	Common	Common
Hyperkeratosis	Common	Common
Alopecia	Common	Common
Palmar-plantar erythrodysaesthesia syndrome	Common	Common
Skin lesion	Common	Common
Hyperhidrosis	Common	Common
Skin fissures	Common	Common
Panniculitis	Common	Common
Photosensitivity[2]	Common	Common
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Very common
Myalgia	Very common	Very common
Pain in extremity	Very common	Very common
Muscle spasms	Common	Common
Blood creatine phosphokinase increased	Common	Common
Rhabdomyolysis	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

	Frequency category	
	COMBI-d n=209	**COMBI-d & COMBI-v n=559**
Influenza-like illness	Common	Common
Face oedema	Common	Common
Investigations		
Alanine aminotransferase increased	Very common	Very common
Aspartate aminotransferase increased	Very common	Very common
Blood alkaline phosphatase increased	Common	Common
Gamma-glutamyltransferase increased	Common	Common

NR= Not reported;

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

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

Table 13 Adverse reactions specific for TAFINLAR in combination with MEKINIST in Part C of Phase II study BRF113220 (n=55) (data cut-off 31 May 2012)

Infections and infestations	
Very common	Urinary tract infection
Blood and lymphatic system disorders	
Very common	Neutropenia
Common	Thrombocytopenia
Metabolism and nutrition disorders	
Common	Hyponatraemia
Nervous system disorders	
Very common	Dizziness
Vascular disorders	
Very Common	Haemorrhage[a]
Common	Hypotension
Hepatobiliary disorders	

Common	Gamma-glutamyl transferase increased
Skin and subcutaneous tissue disorders	
Very common	Night sweats
Common	Hyperhidrosis
Musculoskeletal and connective tissue disorders	
Very Common	Muscle spasms
Common	Rhabdomyolysis

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

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 trials).

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 Pharmacodynamic properties).

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

Table 14 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 14 Adjuvant treatment of melanoma - Adverse drug reactions for TAFINLAR in combination with MEKINIST vs. placebo (Study BRF115532 [COMBI-AD])

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

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	
Diarrhoea	33	<1	15	<1	Very common
Vomiting	28	<1	10	NR	Very common
Abdominal pain[10)]	16	<1	11	<1	Very common
Constipation	12	NR	6	NR	Very common
Skin and subcutaneous tissue disorders					
Rash[11)]	37	<1	16	<1	Very common
Dry skin[12)]	14	NR	9	NR	Very common
Dermatitis acneiform	12	<1	2	NR	Very common
Erythema[13)]	12	NR	3	NR	Very common
Pruritus[14)]	11	<1	10	NR	Very common
Palmar-plantar erythrodysaesthesia syndrome	6	<1	1	<1	Common
Musculoskeletal and connective tissue disorders					
Arthralgia	28	<1	14	NR	Very common
Myalgia[15)]	20	<1	14	NR	Very common
Pain in extremity	14	<1	9	NR	Very common
Muscle spasms[16)]	11	NR	4	NR	Very common
Rhabdomyolysis	<1	<1	NR	NR	Uncommon

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	
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.

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	
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*					

Table 15 Treatment-emergent laboratory abnormalities (all grades) occurring with between arm difference ≥ 10 % (Study BRF115532 [COMBI-AD])

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

Locally advanced or metastatic anaplastic thyroid cancer (ATC)

TAFINLAR in combination with MEKINIST

The efficacy and safety of TAFINLAR in combination with MEKINIST was studied in a Phase II, nine- cohort, multicentre, 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 Pharmacodynamic properties - Clinical Trials).

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 16 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 16 Anaplastic Thyroid Cancer - Adverse drug reactions for TAFINLAR in combination with MEKINIST in the 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			

Adverse drug reactions	**TAFINLAR in combination with MEKINIST**		
	All grades n = 100 %	**Grades 3/4 n = 100 %**	**Frequency category**
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			
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

Adverse drug reactions	TAFINLAR in combination with MEKINIST		
	All grades n = 100 %	**Grades 3/4 n = 100 %**	**Frequency category**
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 – Pharmacodynamic properties - Clinical trials).

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 dyspnea.

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 – Pharmacodynamic properties - Clinical trials).

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 17 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 17 Advanced NSCLC - Adverse drug reactions for TAFINLAR in combination with MEKINIST

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

Adverse drug reactions	TAFINLAR in combination with MEKINIST		
	All grades n = 93 %	**Grades 3/4 n = 93 %**	**Frequency category**
Gastrointestinal disorders			
Nausea	46	NR	Very common
Vomiting	37	3	Very common
Diarrhoea	33	2	Very common
Decreased appetite	28	NR	Very common
Constipation	16	NR	Very common
Pancreatitis acute	1	NR	Common
Skin and subcutaneous tissue disorders			
Erythema	10	NR	Very common
Dry skin	32	1	Very common
Rash[3)]	31	3	Very common
Pruritus[4)]	15	2	Very common
Hyperkeratosis[5)]	13	1	Very common
Musculoskeletal and connective tissue disorders			
Muscle spasms	10	NR	Very common
Arthralgia	16	NR	Very common
Myalgia	13	NR	Very common
Renal and urinary disorders			
Renal failure	3	1	Common
Tubulointerstitial nephritis	2	2	Common
General disorders and administration site disorders			
Pyrexia	55	5	Very common
Asthenia[6)]	47	6	Very common
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

Adverse drug reactions	TAFINLAR in combination with MEKINIST		
	All grades n = 93 %	**Grades 3/4 n = 93 %**	**Frequency category**
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 alaise.

7) Oedema includes generalised oedema and peripheral oedema.

NR :Not Reported

Paediatric use

TAFINLAR in combination with Mekinist

The safety of TAFINLAR in combination with MEKINIST was studied in 171 paediatric patients across two studies (G2201 and X2101) with BRAF V600E mutation-positive advanced solid tumours, of which 4 (2.3%) patients were 1 to <2 years of age, 39 (22.8%) patients were 2 to <6 years of age, 54 (31.6%) patients were 6 to <12 years of age, and 74 (43.3%) patients were 12 to <18 years of age. The mean treatment duration was 2.3 years.

The overall safety profile in the paediatric population was similar to the safety profile observed in adults. The most frequently reported adverse drug reactions (≥20%) were pyrexia, rash, headache, vomiting, fatigue, dry skin, diarrhoea, haemorrhage, nausea, dermatitis acneiform, abdominal pain, neutropenia, cough, and transaminases increased.

An adverse drug reaction of weight increased was identified in the paediatric safety pool with a frequency of 16% (very common). Sixty-one out of 171 patients (36%) had an increase from baseline of ≥2 BMI-for-age- percentile categories.

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

Table 18 Most frequent Grade 3/4 Adverse drug reactions (≥2%) for TAFINLAR in combination with MEKINIST in paediatric patients

Adverse drug reactions	Tafinlar in combination with Mekinist N=171
	Grade 3/4 n (%)
Neutropenia[1]	25 (15)
Pyrexia	19 (11)
Transaminases increased[2]	11 (6)
Weight Increased	9 (5)
Headache	5 (3)
Vomiting	5 (3)
Hypotension	4 (2)
Rash[3]	4 (2)
Blood alkaline phosphatase increased	4 (2)

1. Neutropenia includes, neutrophil count decreased, neutropenia and febrile neutropenia.
2. Transaminases increased includes aspartate aminotransferase increased, alanine aminotransferase increased, hypertransaminasaemia, and transaminases increased.
3. Rash includes rash, rash maculo-papular, rash pustular, rash erythematous, rash papular, and rash macular.

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

Use in the elderly

No initial dose adjustment is required in patients over 65 years of age (see section 4.2 Dose and Method of Administration and section 5.2 Pharmacokinetic Properties).

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

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

Reporting suspected adverse effects

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

4.9 Overdose

Symptoms and Signs

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

Treatment

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

5. PHARMACOLOGICAL PROPERTIES

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

Anatomical Therapeutic Chemical (ATC Code): L01EC02

5.1 Pharmacodynamic properties

Mechanism of action

TAFINLAR monotherapy

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

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

TAFINLAR in combination with MEKINIST

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

Pharmacodynamic effects

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

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

Determination of BRAF mutation status

In the Phase II and III clinical trials for metastatic melanoma, 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.

In the Phase III clinical trial for adjuvant melanoma, screening for eligibility required central testing for BRAF V600 mutation with the bioMerieux THxID BRAF assay. Only patients with BRAF V600E or V600K mutation positive tumours were eligible for study participation.

In the Phase II clinical trial for NSCLC, patients determined to be BRAF V600E positive by the local laboratory tests were enrolled in the study and tumour tissue samples were required for central confirmation by the Oncomine Dx Target Test by Thermo Fisher Scientific.

In the Phase II trial for rare cancers, including anaplastic thyroid cancer, patients determined to be BRAF V600E positive by the local laboratory tests were enrolled in the study and tumour tissue samples were required for central confirmation by the bioMerieux THxID BRAF assay.

Clinical Trials

Unresectable or metastatic melanoma

TAFINLAR monotherapy - open label studies

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

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

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

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

Phase III study BREAK-3 in previously untreated melanoma patients

The efficacy and safety of TAFINLAR were evaluated in this Phase III randomised, open-label study [BREAK-3] comparing TAFINLAR 150 mg twice daily to IV dacarbazine (DTIC) 1000 mg/m2 every 3 weeks in previously untreated patients with BRAF V600E mutation positive unresectable or advanced (unresectable Stage III) or metastatic (Stage IV) melanoma. Screening included central testing of BRAF mutation V600E using a BRAF mutation assay conducted on the most recent tumour sample available. Two hundred and fifty patients were randomised 3:1 to receive either TAFINLAR or intravenous DTIC. The primary objective was to evaluate the efficacy of TAFINLAR compared to DTIC with respect to progression-free survival (PFS) per investigator assessment for patients with BRAF V600E mutation positive metastatic melanoma. Patients on the DTIC arm were allowed to cross over and receive TAFINLAR after independent radiographic confirmation of initial progression. Baseline characteristics were balanced between treatment

groups. Sixty percent of patients were male and 99.6 % were Caucasian; the median age was 52 years with 21 % of patients being ≥ 65 years, 98.4 % had an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1, and 97 % of patients had metastatic disease.

At the pre-specified analysis with a 19 December 2011 data cut, a significant improvement in the primary endpoint of PFS (HR = 0.30; 95 % CI 0.18, 0.51; p < 0.0001) was achieved. PFS from the primary analysis is shown in Figure 1. Efficacy results from a post-hoc analysis with 6-months additional follow-up are summarised in Table 19. Overall survival data from a further post-hoc analysis based on an 18 December 2012 data cut is provided in Table 20 and shown in Figure 2. As of 25 June 2012, thirty-five patients (55.6 %) of the 63 randomised to DTIC crossed over to TAFINLAR. Median PFS after cross-over was 4.4 months.

Table 19 Investigator assessed efficacy in previously untreated patients (BREAK-3 study, 25 June 2012)

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

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

Table 20 Survival data from a post-hoc analysis (18 December 2012)

Treatment	Number of deaths (%)	12-month OS rate	Hazard Ratio (95 % CI)
dacarbazine	28 (44 %)	63 %	0.76 (0.48, 1.21) [(a)]
TAFINLAR	78 (42 %)	70 %	

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

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

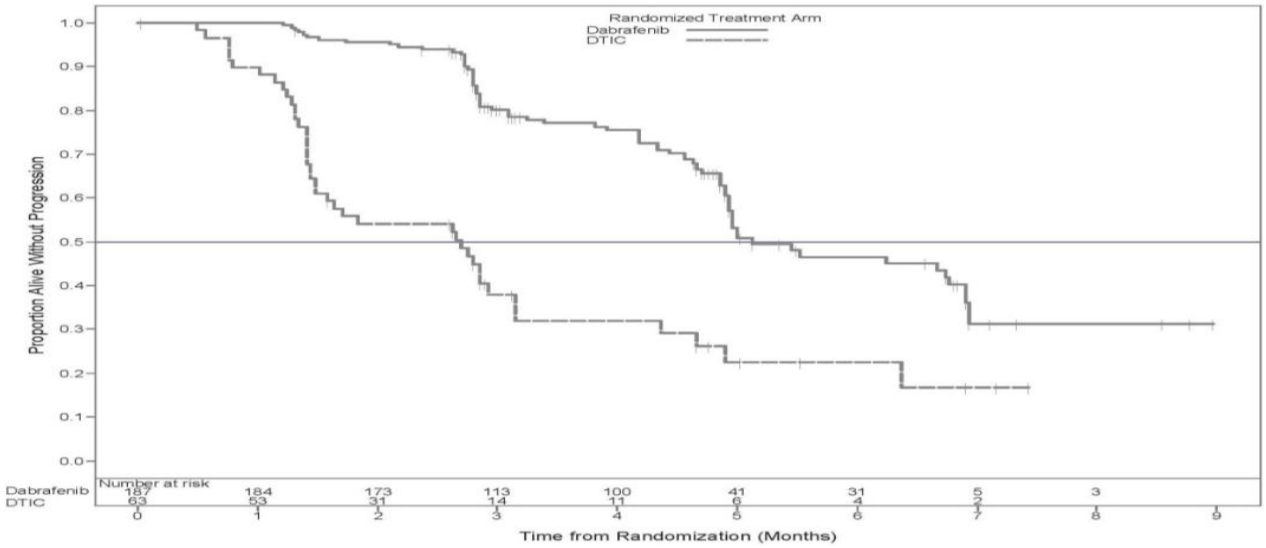
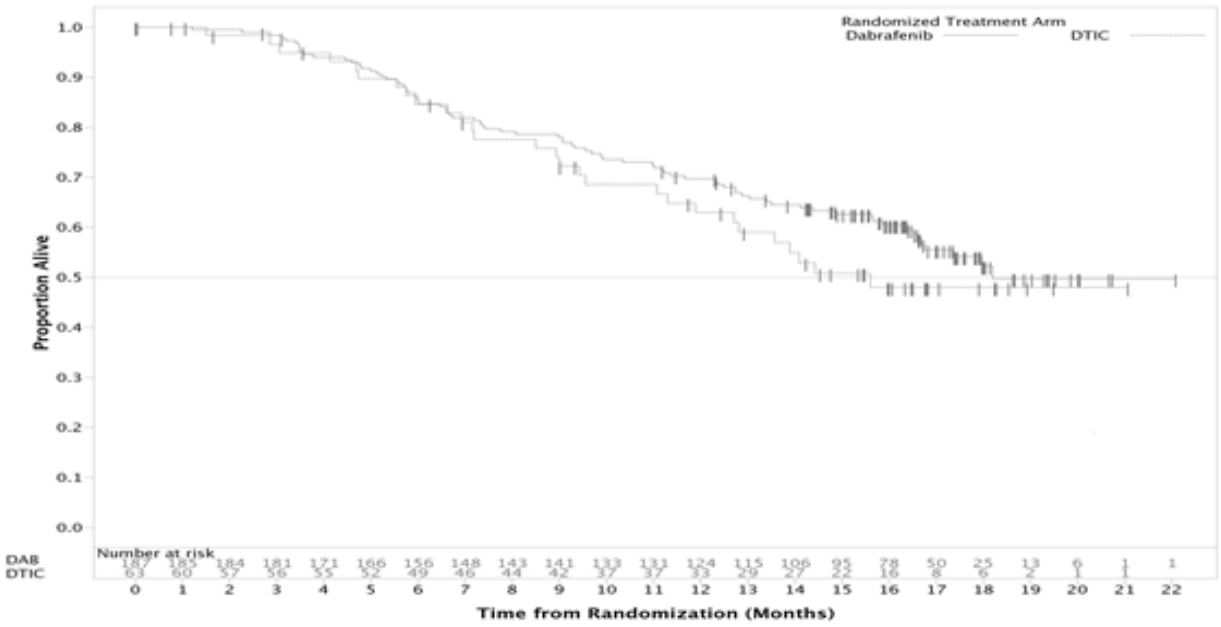


Figure 2 Investigator-assessed Kaplan-Meier curves of overall survival (BREAK-3) (18 December 2012)



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

This multi-centre, open-label, two-cohort, Phase II study was designed to evaluate the intracranial response of TAFINLAR in 172 patients with histologically confirmed (Stage IV) BRAF-mutation positive (V600E or V600K) melanoma metastatic to the brain. Patients were enrolled into Cohort A (patients with no prior local therapy for brain metastasis; n=89) or Cohort B (patients who received prior local therapy for brain metastasis; n= 83).

The major efficacy outcome measure was estimation of the overall intracranial response rate (OIRR) in each cohort. The intracranial response rate as determined by an independent radiology review committee for the BRAFV600E group, masked to investigator response assessments, was

18% (95% CI: 10%, 28%) in Cohort A (n=74) and 18% (95% CI: 10%, 30%) in Cohort B (n=65). The median duration of intracranial response was 4.6 months in both cohorts.

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 suggests that prior local treatment does not preclude subsequent benefit from BRAF inhibition.

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

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

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

TAFINLAR in combination with MEKINIST

The efficacy and safety of the recommended dose of TAFINLAR (150 mg twice daily) in combination with MEKINIST (2 mg once daily) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation was studied in Phase I/II study BRF113220 and two pivotal Phase III studies, MEK116513 and MEK115306.

Randomised open label studies

BRF113220 (Phase I/II Studies)

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

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

Prior BRAF inhibitor (BRAFi) therapy

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

Part B of open-label study BRF113220 included a cohort of 26 patients that had progressed on a BRAFi. The combination of 150 mg TAFINLAR with 2 mg MEKINIST demonstrated limited clinical activity in patients who had progressed on a BRAFi. The Investigator-assessed ORR was 15 % (95 % CI: 4.4, 34.9) and the median PFS was 3.6 months (95 % CI: 1.9, 5.2). Similar results were seen in the 43 patients who crossed over from TAFINLAR monotherapy to the combination of 150 mg TAFINLAR plus 2 mg MEKINIST in Part C of this study. In these patients a 9 % (95 % CI: 2.6, 22.1) ORR was observed with a median PFS of 3.6 months (95 % CI: 1.8, 3.9).

Part C

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

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

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

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

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

Randomised open label study in BRAFi-treatment-naïve patients

MEK116513 (COMBI-v, Phase III Study)

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

Seven hundred and four patients were randomised 1:1 to either the combination therapy arm (TAFINLAR 150 mg twice daily and MEKINIST 2 mg once daily) or the vemurafenib monotherapy arm (960 mg twice daily). Most patients were white (> 96 %) and male (55 %), with a median age of 55 years (24 % were ≥ 65 years). The majority of patients had Stage IV M1c disease (61 %). Most patients had LDH ≤ULN (67 %), ECOG performance status of 0 (70 %), and visceral disease (78 %) at baseline. Overall, 54 % of patients had < 3 disease sites at baseline. The majority of patients had a BRAF V600E mutation (89 %).

The final OS analysis 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% (95% CI: 30.5, 40.9) for the combination versus 23% (95% CI: 18.1, 27.4) for vemurafenib monotherapy (Table 18, Figure 3). The Kaplan-Meier OS curve appears to stabilise from 3 years to 5 years (see Figure 3).

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 18).

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

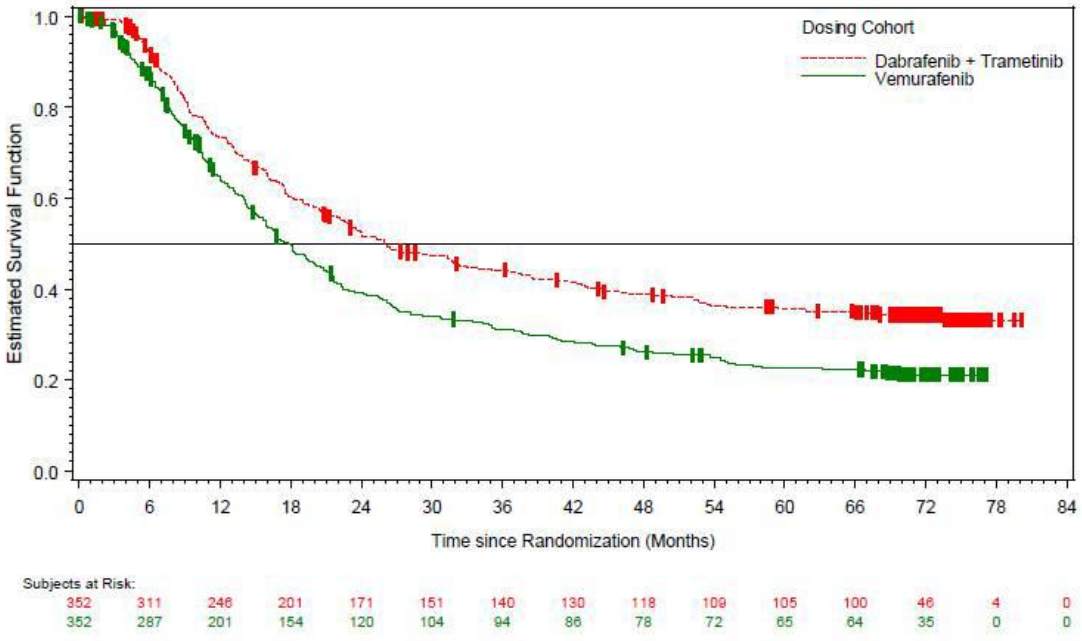


Table 21 Overall survival and Investigator-assessed efficacy results for MEK116513 (COMBI-v) study

	Primary analysis*		Final Analysis*	
	Dabrafenib + Trametinib (n=352)	**Vemurafenib (n=352)**	**Dabrafenib + Trametinib (n=352)**	**Vemurafenib (n=352)**
Number of Patients				
Died (event), n (%)	100 (28)	122 (35)	217 (62)	249 (71)
Estimates of OS				
Median, months (95% CI[a])	NR (18.3, NR)	17.2 (16.4, NR)	26.0 (22.1, 33.8)	17.8 (15.6, 20.7)
Hazard ratio (95% CI)	0.69 (0.53, 0.89)		0.70 (0.58, 0.83)	
p-value	0.005		NA	
Investigator-assessed PFS				
Progressive disease or death, n (%)	166 (47)	217 (62)	259 (74)	262 (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 (6.0, 8.1)
Hazard Ratio (95% CI)	0.56 (0.46, 0.69)		0.62 (0.52, 0.73)	
p-value	<0.001		NA	
Overall Response Rate (ORR)				
ORR[b] % (95% CI)	64 (59.1, 69.4)	51 (46.1, 56.8)	68 (62.3, 72.4)	53 (47.2, 57.9)
Difference in response rate (CR[c] +PR[c]), % 95% CI for difference (95% PI)	13[d] (5.7, 20.2)		NA	
p-value	0.0005		NA	
Duration of Response (DoR)				
Median, months (95% CI)	13.8 (11.0, NR)	7.5 (7.3, 9.3)	13.8 (11.3, 18.6)	8.5 (7.4, 9.3)

**Primary OS analysis data cut-off: 17-Apr-2014, Final OS analysis data cut-off: 25-Apr-2019*

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

NR = Not reached, NA = Not applicable

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

MEK115306 (COMBI-d, Phase III Study)

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

Four hundred and twenty-three patients were randomised 1:1 to either the combination therapy arm (TAFINLAR 150 mg twice daily and MEKINIST 2 mg once daily) (N = 211) or TAFINLAR monotherapy arm (150 mg twice daily) (N = 212). Baseline characteristics were balanced between treatment groups. Males constituted 53 % of patients and the median age was 56 years (28% were ≥65 years). The majority of patients had an ECOG performance score of 0 (72 %) and had Stage IVM1c disease (66 %). Most patients had the BRAF V600E mutation (85 %); the remaining 15 % of patients had the BRAF V600K mutation. Patients with brain metastases were not included in the trial.

The final OS analysis 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% (95% CI: 25.1, 38.3) for the combination versus 27% (95% CI: 20.7, 33.0) for dabrafenib monotherapy (Table 22, Figure 4). The Kaplan-Meier OS curve appears to stabilise from 3 to 5 years (see Figure 4).

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 21).

Figure 4 COMBI-d - Kaplan-Meier overall survival curves (ITT Population)

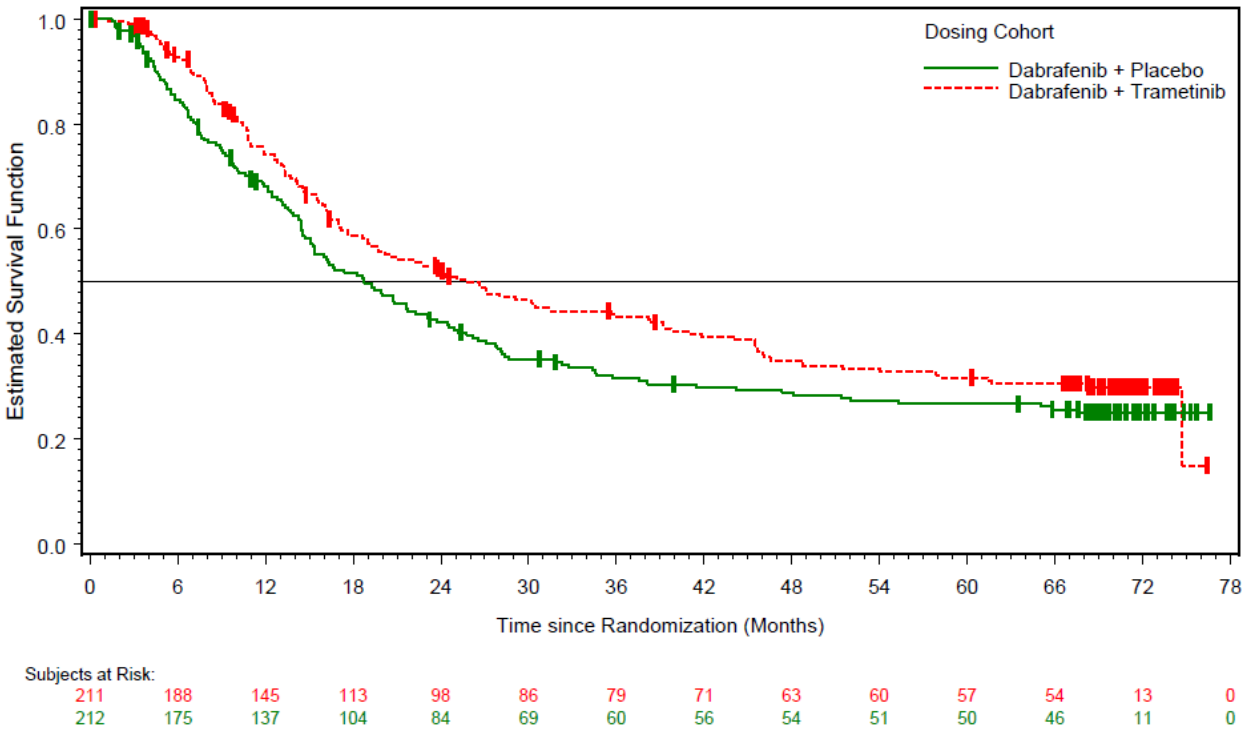


Table 22 Investigator-assessed efficacy results for MEK115306 (COMBI-d) study

	Primary OS analysis*		Final Analysis*	
	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)	136 (64)	151 (71)
Estimates of OS				
Median, months (95% CI[a])	25.1 (19.2, NR)	18.7 (15.2, 23.7)	25.8 (19.2, 38.2)	18.7 (15.2, 23.1)
Hazard ratio (95% CI)	0.71 (0.55, 0.92)		0.81 (0.64, 1.02)	
p-value	0.011		NA	
Investigator-assessed PFS				
Progressive disease or death, n (%)	139 (66)	162 (76)	160 (76)	166 (78)
Median, months (95% CI)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)	10.2 (8.1, 12.8)	8.8 (5.9, 9.3)
Hazard Ratio (95% CI)	0.67 (0.53, 0.84)		0.73 (0.59, 0.91)	
p-value	<0.001		NA	
Overall Response Rate (ORR)				
ORR[b] % (95% CI)	69	53	70	54

	Primary OS analysis*		Final Analysis*	
	Dabrafenib + Trametinib (n=211)	**Dabrafenib + Placebo (n=212)**	**Dabrafenib + Trametinib (n=211)**	**Dabrafenib + Placebo (n=212)**
	(61.8, 74.8)	(46.3, 60.2)	(62.8, 75.7)	(46.8, 60.7)
Difference in response rate (CR[c] +PR[c]), % 95% CI for difference (95% PI)	15[d] 6.0, 24.5		NA	
p-value	0.0014[e]		NA	
Duration of Response (DoR)				
Median, months (95% CI)	12.9 (9.4,19.5)	10.6 (9.1,13.8)	12.9 (9.3, 18.4)	10.2 (8.3, 13.8)

**Primary OS analysis data cut-off: 12-Jan-2015, Final analysis data cut-off: 28-Feb-2019*

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

NR = Not reached, NA = Not applicable

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-centre, 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 23. Secondary endpoints were duration of intracranial response, ORR, PFS and OS. Efficacy results are summarised in Table 23.

Table 23 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 / DRB436F2301 (COMBI-AD)

The efficacy and safety of TAFINLAR in combination with MEKINIST was studied in a Phase III, multicentre, 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. Enrolment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomisation. Any prior systemic anti-cancer treatment, including radiotherapy, was not allowed. Patients with a history of prior malignancy, if disease free for at least 5 years, were eligible. Patients presenting with malignancies with confirmed activating RAS mutations were not eligible. Patients were stratified by BRAF mutation status (V600E or V600K) and stage of disease prior to surgery (by Stage III sub-stage, indicating different levels of lymph node involvement and primary tumour size and ulceration). The primary endpoint was investigator-assessed relapse-free survival (RFS), defined as the time from randomisation to disease recurrence or death from any cause. Radiological tumour assessment was conducted every 3 months for the first two years and every 6 months thereafter, until first relapse was observed. Secondary endpoints include overall survival (OS; key secondary endpoint) and distant metastasis-free survival (DMFS).

A total of 870 patients were 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 tumour ulceration. The majority of patients had a BRAF V600E mutation (91%).

The median duration of follow-up at the time of the primary analysis 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 24. The study showed a statistically significant difference for the primary outcome of investigator-assessed RFS between treatment arms, with an estimated 53% risk reduction in the dabrafenib and trametinib combination arm as compared to the placebo arm (HR=0.47; 95% CI: 0.39, 0.58; p=1.53×10-14). Results were consistent across subgroups, including stratification factors for disease stage and BRAF V600 mutation type. Median RFS was 16.6 months for the placebo arm and was not reached for the combination arm at the time of the primary analysis.

Table 24 COMBI-AD – Primary analysis - Relapse-free survival results

	Dabrafenib + Trametinib		**Placebo**
RFS parameter	**N=438**		**N=432**
Number of events, n (%)			
Recurrence	166 (38%)		248 (57%)
Relapsed with distant metastasis	163 (37%)		247 (57%)
Death	103 (24%)		133 (31%)
	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)

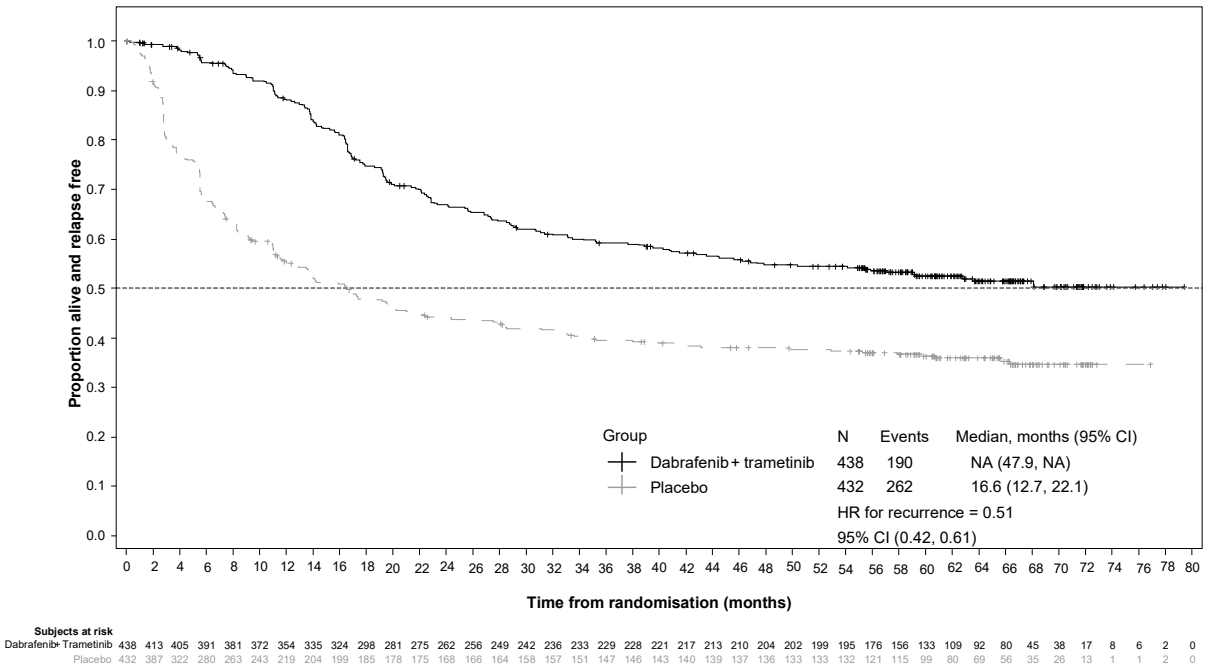
[1] Hazard ratio is obtained from the stratified Pike model.

[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

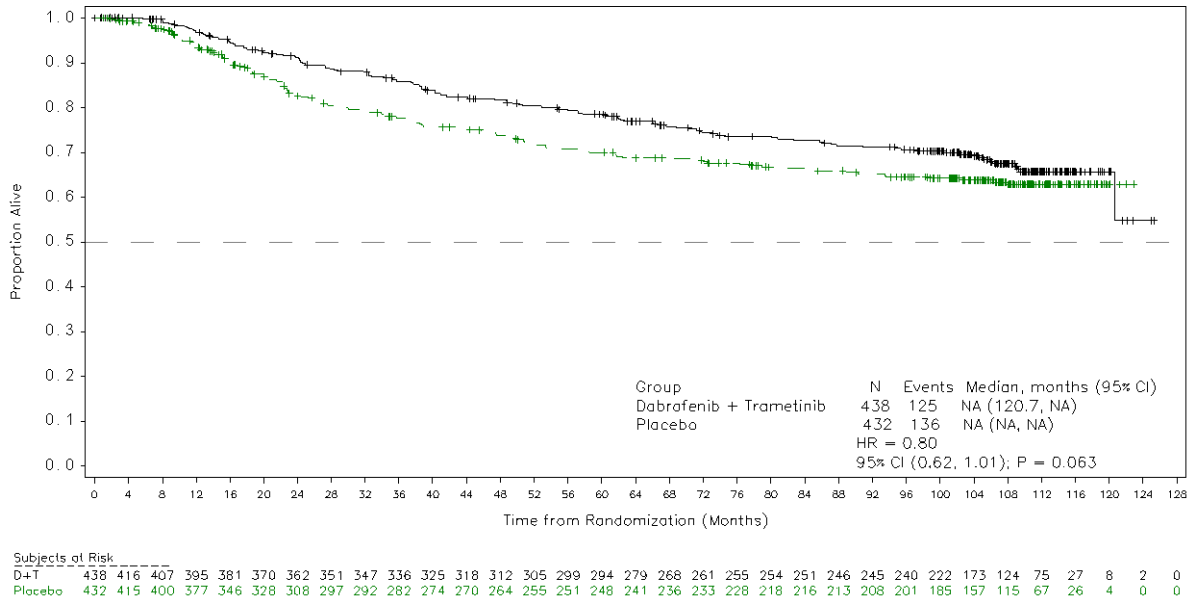
Based on updated data with an additional 29 months of follow-up compared to the primary analysis (minimum follow-up of 59 months), the RFS benefit was maintained with an estimated HR of 0.51 (95% CI: 0.42, 0.61) (Figure 5). The 5-year RFS rate was 52% (95% CI: 48, 58) in the combination arm compared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

Figure 5 **COMBI-AD – Investigator-assessed relapse-free survival Kaplan-Meier curves (ITT Population)**



The median duration of follow-up at the time of the final overall survival analysis was 8.3 years in the combination arm and 6.9 years in the placebo arm. The estimated hazard ratio for overall survival was 0.80 (95% CI: 0.62, 1.01; p=0.063) with 125 events (29%) in the combination arm and 136 events (31%) in the placebo arm. Estimated 5-year overall survival rates were 79% in the combination arm and 70% in the placebo arm, and estimated 10-year overall survival rates were 66% in the combination arm and 63% in the placebo arm. In patients who went on to receive subsequent anti-cancer therapies after study treatment, therapies included targeted therapy in 21% in the combination arm and 37% in the placebo arm, and immunotherapy in 29% in the combination arm and 29% in the placebo arm. The Kaplan-Meier curves for the final overall survival analysis are shown in Figure 6.

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



Locally advanced or metastatic anaplastic thyroid cancer (ATC)

Study BRF117019 / CDRB436X2201

The efficacy and safety of TAFINLAR in combination with MEKINIST was studied in a Phase II, nine-cohort, multicentre, 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 25).

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 25 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*

Advanced NSCLC

Study E2201 (BRF113928)

The efficacy and safety of TAFINLAR in combination with MEKINIST was studied in a Phase II, three-cohort, multicentre, 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), and 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 for a total of 36 patients). All patients received study medication as first-line treatment for metastatic disease.

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

In the pre-treated population, 38 patients (67%) had one line of systemic anti-cancer therapy for metastatic disease.

At the time of the primary analysis, the 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 26.

Table 26 Efficacy Results in Patients with BRAF V600E NSCLC

Endpoint	**Analysis**	**Tafinlar Monotherapy (Cohort A)**	**Combination First Line**	**Combination Second Line Plus**
		N=78	**N=36**	**N=57**
Overall confirmed response n (%) (95% CI)	By Investigator	27 (34.62%) (24.2, 46.2)	23 (63.9%) (46.2, 79.2)	39 (68.4%) (54.8, 80.1)
	By IRC	22 (28.2%) (18.6, 39.5)	23 (63.9%) (46.2, 79.2)	36 (63.2%) (49.3, 75.6)
Median DoR, months (95% CI)	By Investigator	11.8 (5.4, 23.5)	10.2 (8.3, 15.2)	9.8 (6.9, 18.3)
	By IRC	18.0 (5.5, 45.6)	15.2 (7.8, 23.5)	12.6 (5.8, 26.2)
Median PFS, months (95% CI)	By Investigator	5.4 (2.8, 6.9)	10.8 (7.0, 14.5)	10.2 (6.9, 16.7)

Endpoint	Analysis	Tafinlar Monotherapy (Cohort A)	Combination First Line	Combination Second Line Plus
		N=78	**N=36**	**N=57**
	By IRC	5.5 (2.8, 6.9)	14.6 (7.0, 22.1)	8.6 (5.2, 16.8)
Median OS, months (95% CI)	-	12.7 (7.3, 16.3)	17.3 (12.3, 40.2)	18.2 (14.3, 28.6)

Pyrexia Management Analysis

Other studies Study CPDR001F2301 (COMBI-i) and Study CDRB436F2410 (COMBI-Aplus)

Pyrexia is observed in patients treated with trametinib and dabrafenib combination therapy. The initial registration studies for the combination therapy in the unresectable or metastatic melanoma setting (COMBI-d and COMBI-v; total N=559) and in the adjuvant melanoma setting (COMBI-AD, N=435) recommended to interrupt only dabrafenib in case of pyrexia (fever ≥38.5°C). 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 medicinal products when patient's temperature is ≥38ºC (COMBI-Aplus) or at the first symptom of pyrexia (COMBI-i; COMBI-Aplus for recurrent pyrexia) was advised. In COMBI-i and COMBI-Aplus there was a lower incidence of grade 3/4 pyrexia, complicated pyrexia, hospitalisation due to serious pyrexia adverse events of special interest (AESIs), the time spent in pyrexia AESIs, and permanent discontinuations from both medicinal products due to pyrexia AESIs (the latter in the adjuvant setting only) compared to COMBI-d, COMBI-v and COMBI-AD. The COMBI-Aplus study met its primary endpoint with a composite rate of 8.0% (95% CI: 5.9, 10.6) for grade 3/4 pyrexia, hospitalisation due to pyrexia, or permanent treatment discontinuation due to pyrexia compared to 20.0% (95% CI: 16.3, 24.1) for the historical control (COMBI-AD).

Low-grade glioma (LGG) and High-grade glioma (HGG)

Study DRB436G2201

The clinical efficacy and safety of TAFINLAR plus MEKINIST combination therapy in paediatric patients aged 1 to <18 years of age with BRAF V600E mutation-positive glioma was evaluated in the multi-centre, open-label, Phase II clinical trial CDRB436G2201. Patients with low-grade glioma (WHO 2016 grades 1 and 2) who required first systemic therapy were randomised in a 2:1 ratio to dabrafenib plus trametinib (D+T) or carboplatin plus vincristine (C+V), and patients with relapsed or refractory high-grade glioma (WHO 2016 grades 3 and 4) were enrolled into a single arm dabrafenib plus trametinib cohort.

BRAF mutation status was identified prospectively via a local test, or a central laboratory real-time polymerase chain reaction (PCR) test when a local test was not available. In addition, retrospective testing of available tumour samples by the central laboratory was performed to confirm the BRAF

V600E mutation.

TAFINLAR and MEKINIST dosing was age and weight dependent, with TAFINLAR dosed orally at 2.625 mg/kg twice daily for ages <12 years and at 2.25 mg/kg twice daily for ages 12 years and older; MEKINIST was dosed orally at 0.032 mg/kg once daily for ages <6 years and at 0.025 mg/kg once daily for ages 6 years and older. TAFINLAR doses were capped at 150 mg twice daily and MEKINIST doses at 2 mg once daily. Carboplatin and vincristine were dosed based on age and body surface area at doses of 175 mg/m^2 and 1.5 mg/m^2, respectively as one 10-week induction course followed by eight 6-week cycles of maintenance therapy.

The primary efficacy endpoint in both cohorts was Overall Response Rate (ORR, sum of confirmed complete/CR and partial responses/PR) by independent review based on RANO criteria (RANO 2017 for LGG, and RANO 2010 for HGG). The primary analysis was performed when all patients in both cohorts had completed at least 32 weeks of therapy. The final analysis was performed 2 years after completion of enrolment in both cohorts.

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

In the low-grade glioma (LGG) cohort of study G2201, 110 patients were randomised to D+T (n=73) or C+V (n=37). Median age was 9.5 years, with 34 patients (30.9%) aged 12 months to <6 years, 36 patients (32.7%) aged 6 to <12 years and 40 patients (36.4%) aged 12 to <18 years; 60% were female.

At the time of the primary analysis, the ORR in the D+T arm (46.6%) showed a statistically significant improvement over C+V arm (10.8%), with an odds ratio of 7.19 and 1-sided p-value <0.001 (Table 28). The subsequent hierarchical testing also demonstrated improved progression-free survival (PFS) over chemotherapy, with an estimated 69% risk reduction in progression/death (HR 0.31; 1-sided log-rank p-value <0.001).

Table 28 Response and progression-free survival based on independent review in Study G2201 (LGG cohort, primary analysis)

	Dabrafenib + Trametinib N=73	Carboplatin plus Vincristine N=37
Best overall response		
Complete response (CR), n (%)	2 (2.7)	1 (2.7)
Partial response (PR), n (%)	32 (43.8)	3 (8.1)
Stable disease (SD), n (%)	30 (41.1)	15 (40.5)
Progressive disease (PD), n (%)	8 (11.0)	12 (32.4)
Unknown, n (%)	1 (1.4)	6 (16.2)[1]
Overall Response Rate		
ORR (CR+PR) (95% CI)[2], p-value	46.6% (34.8 - 58.6%), p<0.001	10.8% (3.0 - 25.4%)
Odds ratio[3] (95% CI)	7.19 (2.3 - 22.4)	
Clinical Benefit Rate		
CBR (CR+PR+SD), (95% CI)	86.3% (76.2 – 93.2%)	45.9% (29.5 – 63.1%)
Odds ratio (95% CI)	7.41 (2.9 – 18.8)	
Progression-Free Survival		
Median (months) (95% CI)[4]	20.1 (12.8, NE)	7.4 (3.6, 11.8)
Hazard ratio (95% CI)[5], p-value	0.31 (0.17-0.55), p<0.001	

CBR=clinical benefit rate; CI=confidence interval; CR=complete response; NE=not estimable; ORR=overall response rate; PD=progressive disease; PR=partial response; SD=stable disease.

[1] 4 patients randomised to C+V discontinued prior to receiving treatment.

[2] Based on Clopper-Pearson exact confidence interval.

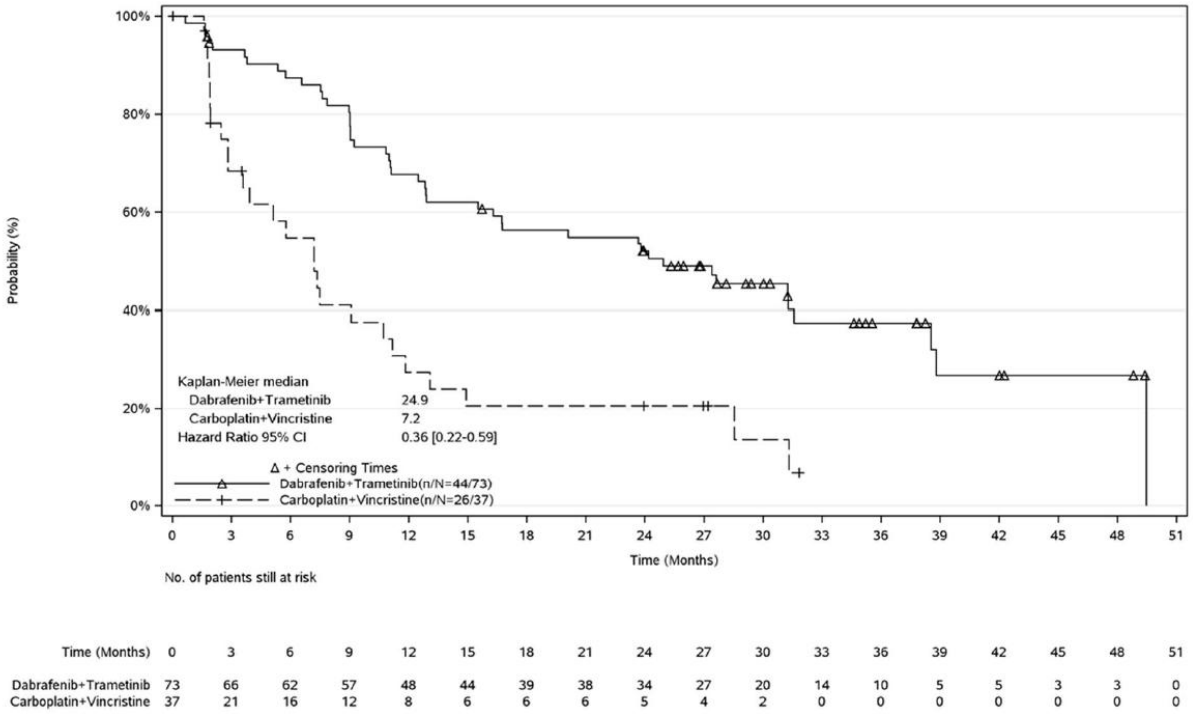
[3] Odds ratio (D+T vs C+V) and 95% CI are from a logistic regression with treatment as the only covariate, i.e. it is the odds of observing a response in the D+T arm compared to the odds of observing a response in the C+V arm. Odds ratio >1 favours D+T.

[4] Based on Kaplan-Meier method.

[5] Based on proportional hazards model.

At the time of the final analysis (median duration of follow-up: 39.0 months), the ORR based on independent review was 54.8% in the D+T arm and 16.2% in the C+V arm with an odds ratio of 6.26. The analysis also confirmed improved PFS over chemotherapy based on independent review with an estimated 64% risk reduction in progression/death (HR 0.36). The median PFS was 24.9 months in the D+T arm and 7.2 months in the C+V arm. No additional deaths were reported in either arm at the time of the final analysis.

Figure 7 Kaplan-Meier progression-free survival curves based on independent review for Study G2201 (LGG cohort, final analysis)



BRAF mutation-positive paediatric high-grade glioma (WHO grades 3 and 4)

In the single-arm high-grade glioma (HGG) cohort of Study G2201, 41 patients with relapsed or refractory HGG were enrolled and treated with Tafinlar plus Mekinist. Median age was 13.0 years, with 5 patients (12.2%) aged 12 months to <6 years, 10 patients (24.4%) aged 6 to <12 years and 26 patients (63.4%) aged 12 to <18 years; 56% were female.

At the time of the final analysis (median duration of follow-up: 45.2 months), the ORR based on independent review was 56.1% (23/41), (95% CI: 39.7, 71.5): CR in 14 patients (34.1%) and PR in 9 patients (22.0%). The median duration of response (DoR) was 27.4 months (95% CI: 9.2, NE). The Kaplan-Meier estimate of progression-free survival at 12 months was 45.5% (95% CI: 29.4, 60.3). The estimated 1-year, 2-year and 3-year survival rates were 77.0%, 61.0% and 55.1%, respectively.

5.2 Pharmacokinetic Properties

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

Absorption

TAFINLAR is absorbed orally with median time to achieve peak plasma concentration of 2 hours post-dose. Mean absolute bioavailability of oral TAFINLAR is 95 % (90 % CI: 81, 110 %). TAFINLAR exposure (C_{max} and AUC) increased in a dose proportional manner between 75 and 150 mg following single-dose administration, but the increase was slightly less than dose-proportional after repeat twice daily dosing. There was a decrease in exposure observed with repeat dosing, likely due to induction of its own metabolism. Mean accumulation AUC Day 18/Day 1 ratios averaged 0.73. Following administration of 150 mg twice daily, geometric mean C_{max}, $AUC_{(0-\tau)}$ and predose concentration ($C\tau$) at steady state were 1,478 ng/mL, 4,341 ng*hour/mL and

26 ng/mL, respectively.

Effect of food on TAFINLAR

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

Distribution

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

TAFINLAR is a substrate of human P-glycoprotein (Pgp) and murine BCRP *in vitro*. However, these transporters have minimal impact on TAFINLAR oral bioavailability and elimination and the risk for clinically relevant drug-drug interactions with inhibitors of Pgp or BCRP is low.

TAFINLAR is not an *in vitro* substrate of OATP1B1, OATP1B3, OATP2B1 OATP1A2 or OCT1 transporters.

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

Metabolism

The metabolism of TAFINLAR is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further 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 to 22 hours). Mean metabolite to parent AUC ratios following repeat-dose administration were 0.9, 11 and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of TAFINLAR; while the activity of carboxy-dabrafenib is not likely to be significant.

Excretion

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

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

<u>Special Patient Populations</u>

Hepatic Impairment

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

TAFINLAR should be undertaken with caution in patients with moderate to severe hepatic impairment (see section 4.2 Dose and Method of Administration).

Renal Impairment

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

Paediatric use

The pharmacokinetics of dabrafenib in glioma and other solid tumours were evaluated in 243 paediatric patients (1 to <18 years old) following single or repeat weight-adjusted dosing. Pharmacokinetic characteristics (drug absorption rate, metabolite ratios, drug clearance) of dabrafenib in paediatric patients are comparable to those of adults. Weight was found to influence dabrafenib oral clearance. The pharmacokinetic exposures of dabrafenib at the recommended weight-adjusted dosage in paediatric patients were within range of those observed in adults.

Use in the elderly

Based on the population pharmacokinetic analysis, age had no significant effect on TAFINLAR pharmacokinetics. Age greater than 75 years was a significant predictor of carboxy- and desmethyl-dabrafenib plasma concentrations with a 40 % greater exposure in 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 TAFINLAR oral clearance; weight also impacted oral volume of distribution and distributional clearance. These pharmacokinetic differences were not considered clinically relevant for adult patients.

Race/Ethnicity

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

5.3 Preclinical Safety Data

Genotoxicity

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

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard capsule

TAFINLAR capsules contain the following inactive ingredients: microcrystalline cellulose, magnesium stearate (vegetable source), colloidal anhydrous silica, iron oxide red, titanium dioxide,

hypromellose, iron oxide black, shellac, butan-1-ol, isopropyl alcohol, propylene glycol, and ammonium hydroxide.

Dispersible tablet

TAFINLAR dispersible tablets contain the following ingredients: Mannitol, microcrystalline cellulose, crospovidone, hypromellose, acesulfame potassium, magnesium stearate, artificial berry flavour 59454 AP0551 (Proprietary Ingredient No. 4614), colloidal anhydrous silica.

6.2 Incompatibilities

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

6.3 Shelf-life

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

6.4 Special precautions for storage

Hard capsule

Store TAFINLAR capsules below 30°C. Store in the original container in order to protect from light and moisture.

Dispersible tablet

Store TAFINLAR dispersible tablets below 25ºC. Store in original container in order to protect from moisture. Do not remove desiccant.

6.5 Nature and contents of the container

Hard capsule

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

Dispersible tablet

TAFINLAR dispersible tablets are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures. The bottles contain 210 dispersible tablets and a desiccant. There are either 1 or 2 bottles in a carton. * Two dosing cups are provided in the carton.

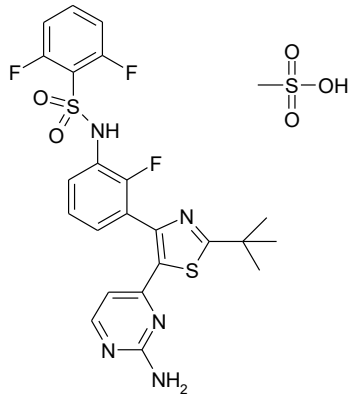
*Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

6.7 Physicochemical properties

Chemical structure



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

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

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

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
Macquarie Park NSW 2113

Telephone 1 800 671 203.

Web site: www.novartis.com.au

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9. DATE OF FIRST APPROVAL

21 August 2013

10. DATE OF REVISION

16 October 2025

Summary table of changes

Section changed	Summary of new information
4.8	Addition of "Tattoo associated skin reaction" as a post-marketing ADR for dabrafenib + trametinib combination therapy with a frequency of "Unknown"

Internal document code

taf161025i based on CDS dated 31 July 2025