Product Monograph

Including Patient Medication Information

PrTAFINLAR®

Dabrafenib capsules

Capsules, 50 mg and 75 mg dabrafenib (as dabrafenib mesylate), Oral

Dabrafenib tablets for oral suspension

Tablets for suspension, 10 mg dabrafenib (as dabrafenib mesylate), Oral

Antineoplastic agent

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Recent Major Label Changes

7 Warnings and Precautions, Endocrine and Metabolism	05/2024

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Part 1: Healthcare Professional Information

1 Indications

Unresectable or Metastatic Melanoma

TAFINLAR (dabrafenib mesylate) is indicated as a monotherapy, or in combination with trametinib, for:

- the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

TAFINLAR should not be used in patients with BRAF wild-type melanoma (see 7 General).

Effectiveness of TAFINLAR monotherapy is based on overall response rate (ORR) and progression-free survival (PFS) results. Prolongation of overall survival (OS) and improvement in quality-of-life has not been demonstrated (see 14 CLINICAL TRIALS).

Clinical data supporting the effectiveness of TAFINLAR monotherapy in patients with BRAF V600K mutations are limited, and clinical studies report fewer responses in BRAF V600K patients compared to BRAF V600E patients (see 14 CLINICAL TRIALS).

There are no clinical data for TAFINLAR in the treatment of patients with other less common BRAF V600 mutations.

TAFINLAR monotherapy has not been studied in patients previously treated with BRAF inhibitors.

TAFINLAR in combination with trametinib is not recommended in patients who have previously progressed on a BRAF inhibitor due to its limited efficacy in patients who progressed on TAFINLAR monotherapy (see 7 General).

Adjuvant Treatment of Melanoma

TAFINLAR (dabrafenib mesylate), in combination with trametinib, is indicated for:

- the adjuvant treatment of patients with melanoma with a BRAF V600 mutation and involvement of lymph node(s), following complete resection.

The indication is based on relapse-free survival (RFS) demonstrated in a randomized, placebo-controlled Phase III trial. Overall survival (OS) benefit has not been confirmed (see 14 CLINICAL TRIALS).

Clinical data supporting the effectiveness of TAFINLAR in combination with trametinib are limited to patients with BRAF V600E or BRAF V600K mutations. There are no clinical data for other less common BRAF V600 mutations.

Metastatic Non-Small Cell Lung Cancer (NSCLC)

TAFINLAR (dabrafenib mesylate) in combination with trametinib is indicated for:

- the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600 mutation.

TAFINLAR should not be used in patients with BRAF wild-type NSCLC (see 7 General).

Effectiveness is based on overall response rate (ORR). Prolongation of progression-free survival (PFS), overall survival (OS) and improvement in quality-of-life has not been demonstrated (see 14 CLINICAL TRIALS).

Clinical data supporting the effectiveness of TAFINLAR in combination with trametinib are limited to patients with a BRAF V600E mutation

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

TAFINLAR (dabrafenib mesylate) in combination with trametinib is indicated for:

- the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy (see 14 CLINICAL TRIALS).
- the treatment of pediatric patients 1 year of age and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment (see 14 CLINICAL TRIALS).

TAFINLAR should not be used in patients with wild-type BRAF tumours or in patients where the BRAF mutational status is not known (see 7 General).

A validated test is required to identify the BRAF V600 mutation status to select patients appropriate for treatment with TAFINLAR as monotherapy and in combination with trametinib.

When TAFINLAR is used in combination with trametinib, see also the trametinib Product Monograph.

1.1 Pediatrics

Pediatrics (< 1 age): The safety and efficacy of TAFINLAR in combination with trametinib in pediatric patients with glioma <1 year of age and/or < 8 kg have not been established. TAFINLAR is not recommended in this age group (see 7.1.3 Pediatrics).

TAFINLAR is not indicated for pediatric patients (<18 years old) with melanoma or NSCLC.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): In clinical studies in unresectable or metastatic melanoma, elderly patients (≥ 65 years) experienced more serious adverse events when taking TAFINLAR (see 7.1.4 Geriatrics).

2 Contraindications

TAFINLAR is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 Serious Warnings and Precautions Box

TAFINLAR (dabrafenib mesylate) should be prescribed by a physician experienced in the administration of anti-cancer agents.

TAFINLAR is teratogenic and embryotoxic in animals (see 7.1.1 Pregnant Women).

TAFINLAR may decrease the efficacy of oral contraceptives (see 7.1.1 Pregnant Women).

TAFINLAR has not been studied in patients with moderate or severe hepatic impairment (see 7 Hepatotoxicity).

The following are significant adverse drug reactions identified in clinical trials conducted with TAFINLAR:

- Secondary malignancies (see 7 Carcinogenesis and Mutagenesis)
- Non-infectious febrile events (see 7 General)

In addition to the above events, the following are significant adverse drug reactions identified in clinical trials conducted with TAFINLAR in combination with Trametinib:

- Venous Thromboembolism (see 7 Cardiovascular)
- Major hemorrhagic events (see 7 Hematologic)

4 Dosage and Administration

4.1 Dosing Considerations

TAFINLAR is available in two dosage forms: capsules, and tablets for suspension. Capsules can be used for adult and pediatric patients who weigh at least 26 kg. Tablets for suspension can be used for patients who weigh at least 8 kg. The two dosage forms of TAFINLAR are not bioequivalent. Use caution if switching patients from one dosage form to the other.

Concomitant Use with CYP3A4 Inhibitors or Inducers: Avoid administering strong CYP3A4 inhibitors or inducers as they will alter (increase or decrease) the levels of dabrafenib and may lead to increased toxicities or reduced efficacy (see 7 General and 9.4 Drug-Drug Interactions).

Concomitant Use with CYP3A4 Substrates: Dabrafenib is a moderate to potent inducer of CYP3A4 and concomitant use of sensitive CYP3A4 substrates can result in loss of efficacy. Substitute for these medications or monitor patients for loss of efficacy if use of these medications in unavoidable (see 7 General and 9.4 Drug-Drug Interactions).

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

When using TAFINLAR in combination with trametinib, please refer to the trametinib Product Monograph for full dosing instructions.

Capsules

Adult patients

The recommended dose regimens of TAFINLAR capsules in adult patients are:

Monotherapy: 150 mg (two 75 mg capsules) given orally twice daily (corresponding to a total daily dose of 300 mg).

Combination with trametinib: 150 mg (two 75 mg capsules) given orally twice daily (corresponding to a total daily dose of 300 mg) with 2 mg of trametinib given orally once daily.

Pediatric patients

The recommended dosage for TAFINLAR capsules in pediatric patients who weigh at least 26 kg is based on body weight (Table 1). A recommended dose of TAFINLAR capsules for patients who weigh less than 26 kg has not been established.

Table 1 Recommended Dosage for TAFINLAR Capsules in Pediatric Patients

Body weight (kg)	Recommended starting dosage
26 to 37 kg	75 mg orally twice daily
38 to 50 kg	100 mg orally twice daily
≥51 kg	150 mg orally twice daily

Tablets for suspension

The recommended dosage for TAFINLAR tablets for suspension is based on body weight (Table 2).

Table 2 Recommended Dosage for TAFINLAR Tablets for Suspension

	Recommended Starting Dosage	
Body weight (kg)	**Daily Dose**	**Number of 10 mg tablets twice daily**
8 to 9 kg	20 mg twice daily	2
10 to 13 kg	30 mg twice daily	3
14 to 17 kg	40 mg twice daily	4
18 to 21 kg	50 mg twice daily	5
22 to 25 kg	60 mg twice daily	6
26 to 29 kg	70 mg twice daily	7
30 to 33 kg	80 mg twice daily	8
34 to 37 kg	90 mg twice daily	9
38 to 41 kg	100 mg twice daily	10
42 to 45 kg	110 mg twice daily	11
46 to 50 kg	130 mg twice daily	13
≥51 kg	150 mg twice daily	15

Dose Modifications

The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation of TAFINLAR (see Table 3 to Table 6).

Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (see 7 Carcinogenesis and Mutagenesis).

Specific dose modifications and reductions for febrile related drug reactions and non-febrile

related events as graded by the Common Terminology Criteria for Adverse Events (CTC-AE) are provided in Table 3. Dose reductions are listed in Tables 4 to 6. Dosing adjustments resulting in a TAFINLAR dose lower than 50 mg twice daily are not recommended and TAFINLAR should be permanently discontinued in these instances. When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered.

Table 3 Recommended Dose Modifications for TAFINLAR Monotherapy and for TAFINLAR and Trametinib Combination Therapy

Adverse Reaction[a]	TAFINLAR
Cardiac	
• Symptomatic congestive heart failure	• Withhold TAFINLAR until adverse reaction resolves and resume TAFINLAR at the same dose or at a reduced dose
• Absolute decrease in LVEF of greater than 20% from baseline that is below LLN	• Withhold TAFINLAR until adverse reaction resolves and resume TAFINLAR at the same dose or at a reduced dose
Febrile Drug Reaction	
• Fever of 38– 40°C without complications	• Withhold TAFINLAR, then resume at the same or lower dose level if the patient is symptom free for at least 24 hours. • If pyrexia is recurrent, therapy can also be interrupted at the first symptom of pyrexia.
• Fever >40°C or any fever with complications due to rigors, hypotension, dehydration or renal failure	• Withhold TAFINLAR, then resume at lower dose if the patient is symptom free for at least 24 hours, Or Permanently discontinue • If pyrexia is recurrent, therapy can also be interrupted at the first symptom of pyrexia.
Cutaneous	
• Intolerable Grade 2 rash or ≥ Grade 3 rash	• Withhold TAFINLAR until adverse reaction resolves or improves to Grade 1 and reduce by one dose level when resuming therapy
• Intolerable Grade 2 or ≥ Grade 3 rash that does not improve within 3 weeks despite interruption of dosing	• Permanently discontinue TAFINLAR
Ocular	
• Uveitis that responds to local ocular therapy	• TAFINLAR may be continued at the same dose. Monitor as clinically indicated.
• Uveitis that does not improve despite ocular therapy	• Withhold TAFINLAR until adverse reaction resolves and reduce by one dose level when resuming therapy
Abnormal weight gain (pediatric patients)	
• Grade 1 or Grade 2	• Maintain TAFINLAR therapy.

Adverse Reaction[a]	TAFINLAR
• Grade 3	• Maintain TAFINLAR therapy if the patient is responding well in the absence of additional toxicities.
Other	
• Grade 1 or Grade 2 (tolerable)	• TAFINLAR may be continued at the same dose. Monitor as clinically indicated.
• Grade 2 (intolerable) OR Grade 3 adverse reaction	• Withhold TAFINLAR until adverse reaction resolves or improves to Grade 1 and reduce by one dose level when resuming therapy
• Grade 4 adverse reaction OR Grade 3 adverse reaction that does not improve to Grade 0-1	• Permanently discontinue TAFINLAR OR withhold therapy until adverse reaction resolves or improves to Grade 1 and reduce by one dose level when resuming therapy

[a] The intensity of clinical adverse events (with the exception of febrile drug reactions) graded by the Common Terminology Criteria for Adverse Events (CTC-AE) v4.0

Recommended dose reductions for TAFINLAR capsules in adult patients are provided in Table 4.

Table 4 Recommended Dose Reductions for TAFINLAR Capsules in Adult Patients

Dose Reductions for TAFINLAR	
First reduction	100 mg twice daily (2 x 50 mg twice daily)
Second reduction	75 mg twice daily (1 x 75 mg twice daily)
Third reduction	50 mg twice daily (1 x 50 mg twice daily)
If unable to tolerate 50 mg twice daily	Discontinue TAFINLAR

Recommended dose reductions for TAFINLAR capsules in pediatric patients are provided in Table 5.

Table 5 Recommended Dose Reductions for TAFINLAR Capsules in Pediatric Patients

Dose Reduction	Recommended starting dosage		
	75 mg orally twice daily	***100 mg orally twice daily***	***150 mg orally twice daily***
First dose reduction	50 mg orally twice daily	75 mg orally twice daily	100 mg orally twice daily
Second dose reduction	-	50 mg orally twice daily	75 mg orally twice daily
Third dose reduction	-	-	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 dose reductions for tablets for suspension are provided in Table 6.

Table 6 Recommended Dose Reductions for TAFINLAR Tablets for Suspension

	Recommended Starting Dosage		Dose Reductions		
Body weight (kg)	**Daily Dose**	**Number of 10 mg tablets twice daily**	**First Reduction**	**Second Reduction**	**Third Reduction**
			Number 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 TAFINLAR 10 mg tablet for suspension given orally twice daily.					

Duration of treatment

Unresectable or metastatic melanoma and metastatic NSCLC

Treatment should continue until disease progression or the development of unacceptable toxicity (see Table 3).

Adjuvant treatment of melanoma

Treatment should continue for a period of 12 months. Discontinue treatment upon disease recurrence or unacceptable toxicity (see Table 3).

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

Treatment should continue until disease progression or the development of unacceptable toxicity (see Table 3). 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 health professional.

Special Populations:

Pediatrics (< 1 year of age): TAFINLAR is not indicated in the pediatric population less than 1 year of age (see 7.1.3 Pediatrics).

Geriatrics: No dose adjustment is required in patients over 65 years of age (see 10 Geriatrics).

Renal Impairment: No dose adjustment is required in patients with mild or moderate renal impairment. Based on the population pharmacokinetic analysis, mild and moderate renal impairment had no significant effect on the oral clearance of dabrafenib or on the concentrations of its metabolites (see 10 Renal Insufficiency). There are no clinical data in patients with severe renal impairment and the potential need for dose adjustment has not been determined. TAFINLAR should be used with caution in patients with severe renal impairment.

Hepatic Impairment: No dose adjustment is required in patients with mild hepatic impairment. Based on the population pharmacokinetic analysis, mild hepatic impairment had no significant effect on the oral clearance of dabrafenib or on the concentrations of its metabolites (see 10 Hepatic Insufficiency). There are no clinical data in patients with moderate to severe hepatic impairment and the potential need for dose adjustment has not been determined. Hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites and patients with moderate to severe hepatic impairment may have increased exposure and increased toxicities.

4.4 Administration

TAFINLAR alone or in combination with trametinib should be taken without food at least one hour before, or at least two hours after a meal, leaving an interval of approximately 12 hours between doses (see 10.3 Pharmacokinetics). 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.

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

Health professionals should regularly monitor the weight of pediatric patients to ensure that they are receiving the appropriate dose and confirm that patients or caregiver(s) understand how to administer the correct daily dose.

Capsules

TAFINLAR capsules should be swallowed whole with a full glass of water. The capsules must not be chewed or crushed.

Tablets for Suspension

TAFINLAR tablets for suspension are to be taken as a suspension only and should not be swallowed whole, chewed, or crushed.

The oral suspension should be prepared in the provided dosing cup. TAFINLAR tablets for suspension can be administered via drinking the suspension from the dosing cup, swallowing the suspension from an oral syringe, or receiving the suspension via feeding tube.

Care should be taken to ensure the entire dose is administered. It may take 3 minutes (or more) to fully suspend the tablets. Once they are dispersed, the suspension should be cloudy white.

Administer the suspension no later than 30 minutes after the tablets have been dispersed.

A complete illustrated set of instructions for the tablets for suspension is in the Patient Medication Information section.

4.5 Missed Dose

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

5 Overdose

Symptoms and Signs

There is currently no experience with overdosage of TAFINLAR when used as either a monotherapy or in combination with trametinib.

Treatment

There is no specific antidote for overdosage of TAFINLAR. In case of suspected overdose, TAFINLAR should be withheld and supportive care instituted. Patients who develop adverse reactions should receive appropriate symptomatic treatment.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Table 7 Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Capsules 50 mg, 75 mg dabrafenib (as dabrafenib mesylate)	Colloidal silicon dioxide, magnesium stearate and microcrystalline cellulose. Capsule shells contain hypromellose, red iron oxide (E172) and titanium dioxide (E171). Monogramming ink contains black iron oxide, shellac and propylene glycol.
Oral	Tablets for suspension 10 mg dabrafenib (as dabrafenib mesylate)	Acesulfame potassium, artificial berry flavour, colloidal silicon dioxide (silica, colloidal anhydrous), crospovidone, hypromellose (hydroxypropyl methyl cellulose), magnesium stearate, mannitol, microcrystalline cellulose (cellulose, microcrystalline).

Description

TAFINLAR 50 mg hard capsules are opaque, dark red capsules, monogrammed with 'GS TEW' and '50 mg'. Bottles contain 120 capsules, and a silica gel desiccant.

TAFINLAR 75 mg hard capsules are opaque, dark pink capsules, monogrammed with 'GS LHF' and '75 mg'. Bottles contain 120 capsules, and a silica gel desiccant.

TAFINLAR 10 mg tablets for suspension are white to slightly-yellow, round biconvex 6 mm tablets debossed with "D" on one side and "NVR" on the other. Bottles contain 210 tablets, and two silica gel desiccant canisters.

7 Warning and Precautions

Please see 3 Serious Warnings and Precautions Box.

When TAFINLAR is used in combination with trametinib, **also consult the trametinib Product Monograph** for important warnings and precautions for trametinib in regard to left ventricular dysfunction, retinal pigment epithelial detachment and retinal vein occlusion, interstitial lung disease, skin toxicity including serious cases, PR interval prolongation, hypertension, rhabdomyolysis and use in females, pediatrics and geriatrics.

General

BRAF V600 Testing: Confirmation of BRAF V600 mutation in a tumour biopsy using a validated test is required for selection of patients appropriate for treatment with TAFINLAR.

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signalling in BRAF wild-type cells exposed to BRAF inhibitors. This may promote growth of wild-type BRAF melanomas or wild-type BRAF NSCLCs. New primary melanomas have been reported in patients taking TAFINLAR (see Carcinogenesis and Mutagenesis below). TAFINLAR should not be used in patients with wild-type BRAF tumours or in patients where the BRAF mutational status is not known.

Prior BRAF Inhibitory Therapy: TAFINLAR monotherapy has not been studied in patients previously treated with BRAF inhibitors.

The combination of TAFINLAR and trametinib demonstrated limited clinical activity in patients who had progressed on TAFINLAR monotherapy and is not recommended for patients who have progressed on a prior BRAF inhibitor. Of 43 patients in a phase I/II study who crossed over from TAFINLAR monotherapy to the combination of TAFINLAR plus trametinib following progression, only 9 % (95% CI: 2.6, 22.1) had an ORR and the median PFS was 3.6 months (95% CI: 1.8, 3.9).

Cytochrome P450 (CYP) Interactions: Dabrafenib is a moderate to strong in vivo inducer of CYP3A4, a weak in vivo inducer of CYP2C9 and may induce CYP2B6, CYP2C8, and CYP2C19. Medicinal products that are substrates for these CYPs, particularly those sensitive to induction, should be avoided, if possible. Dabrafenib is likely to increase their metabolism and in most cases decrease their clinical effectiveness. In cases where metabolites are the active agent, an increase in toxicities associated with these medicinal products may be observed.

Dabrafenib is primarily metabolized by CYP3A4 and CYP2C8. There is potential for a greater risk of drug-related reactions following co-administration of moderate to strong CYP3A4 and CYP2C8 inhibitors as they may increase the systemic exposure of dabrafenib and its active metabolites. There is potential for loss of efficacy following co-administration of strong CYP3A4 and CYP2C8 inducers as they may decrease the systemic exposure of dabrafenib and its active metabolites (see 9.4 Drug-Drug Interactions).

Pyrexia and Serious Non-Infectious Febrile Events: Pyrexia was reported in clinical trials with TAFINLAR, and typically first occurred within two months of initiating therapy. The incidence and severity of pyrexia are increased when TAFINLAR is used in combination with trametinib (see below and 8.2 Clinical Trial Adverse Reactions). Serious febrile drug reactions, which are defined as serious cases of fever including fever of any severity accompanied by severe rigors or chills, dehydration, hypotension or renal failure in the absence of another cause (e.g. infection), have occurred following treatment with TAFINLAR.

In the phase III study in unresectable or metastatic melanoma comparing TAFINLAR monotherapy to dacarbazine, serious febrile drug reactions occurred in 4.8% (9/187) of patients who received TAFINLAR monotherapy compared to no patients in the dacarbazine control arm. In this study, 12% (22/187) and 9% (17/187) of patients had their dose interrupted or reduced, respectively, due to febrile-related events. The median time to initial onset of febrile events was 3 weeks (range 0 to 54 weeks).

In the phase III study comparing TAFINLAR in combination with trametinib to TAFINLAR monotherapy in unresectable or metastatic melanoma, pyrexia occurred in 57% (119/209; 7% Grade 3) of patients who received combination therapy compared to 33% (69/211; 2% Grade 3) of patients treated with monotherapy. Serious febrile drug reactions occurred in 17% (35/209) of patients who received combination therapy compared to 7% (15/211) of patients

treated with the monotherapy. The median time to initial onset of any (non-serious and serious) febrile event was 38 days (range: 1 to 716 days) and 20 days (range: 1 to 698 days) in patients receiving combination therapy and monotherapy, respectively. Thirty-one percent (64/209) of patients treated with the combination had 3 or more occurrences of pyrexia (any grade) compared to 7% (14/211) of patients treated with monotherapy. Permanent discontinuation of therapy due to pyrexia events was reported in 2% (4/209) of patients receiving combination therapy and in < 1% (2/211) of patients treated with monotherapy. Pyrexia events resulted in hospitalization in 14% of patients treated with the combination and in 5% of patients treated with monotherapy. In this study, the majority of patients in the combination therapy group with pyrexia required TAFINLAR dose modification to manage pyrexia events (dose interruption, dose reduction or permanent discontinuation). Compared to trametinib, approximately twice as many patients required TAFINLAR dose interruption, and approximately 5 times as many patients required TAFINLAR dose reduction, to manage events of pyrexia in the combination therapy group.

A higher percentage of patients treated with the combination (41%, 86/209) received medication for treatment of pyrexia than patients treated with the monotherapy (24%, 51/211). More patients receiving combination therapy (22%, 46/209) were also administered medications for secondary prophylactic treatment of pyrexia than patients receiving the monotherapy (9%, 19/211). Corticosteroids were used to manage pyrexia in 29% (61/209) of patients treated with the combination and 22% (47/211) of patients treated with monotherapy TAFINLAR. The median duration of corticosteroid use was approximately twice as long in patients treated with the combination (29 vs. 12 days).

In a phase III trial in the adjuvant treatment of melanoma, the incidence and severity of pyrexia (including influenza like illness, body temperature increased, hyperpyrexia and systemic inflammatory response syndrome) were higher in the TAFINLAR in combination with trametinib arm (67% (292/435); 6% Grade 3/4) compared to the placebo arm (15% (66/432); <1% Grade 3). The median time to onset was 23 days with the combination, with a median duration of 3 days.

In the NSCLC phase II study, pyrexia occurred in 57% (53/93; 5% Grade 3) of patients. The median time to onset of first occurrence of fever was 22 days (range: 3 days to 416 days) and the median duration of fever was 3.5 days (range: 1 to 33 days).

In a pooled safety population of pediatric patients receiving TAFINLAR in combination with trametinib (n=171), pyrexia was reported in 67% of patients.

Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia. Interrupt therapy (TAFINLAR when used in monotherapy, or both TAFINLAR and trametinib when used in combination) if the patient's temperature is ≥ 38°C or for any serious febrile drug reaction. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Initiate treatment with anti-pyretics and evaluate patients for signs and symptoms of infection. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient.

Resume therapy (TAFINLAR monotherapy, or both TAFINLAR and trametinib when used in combination) at the recommended daily dose if patient is symptom free of grade 1 and grade 2 fevers (38-40°C) for at least 24 hours. Reduce the dose if recurrent pyrexia cannot be managed with interruption or corticosteroids.

If patient is symptom free for at least 24 hours of fevers > 40.0°C or fevers associated with other severe signs or symptoms and a decision is made to restart therapy (TAFINLAR when used in monotherapy or both TAFINLAR and trametinib when used in combination), the dose

should be reduced according to dose modification protocols (see 4.2 Recommended Dose and Dosage Adjustment).

Brain Metastases: The safety and efficacy of the combination of TAFINLAR and trametinib has not been evaluated in patients with a BRAF V600 mutation-positive melanoma or NSCLC which has metastasized to the brain. Three patients who developed brain metastases while on treatment with TAFINLAR in combination with trametinib in melanoma phase III trials experienced fatal cerebral hemorrhage (see 7 Hematologic).

Carcinogenesis and Mutagenesis

Cutaneous malignancies

Cutaneous Squamous Cell Carcinoma (CuSCC): Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with TAFINLAR (see 8.2 Clinical Trial Adverse Reactions).

CuSCC occurred in 11% (86/797) of patients in the overall[1] TAFINLAR adult monotherapy population. In a pivotal phase III monotherapy study in unresectable or metastatic melanoma, cuSCC occurred in 9% of patients treated with TAFINLAR, and in no patients treated with dacarbazine (see 8.2 Clinical Trial Adverse Reactions). In the phase III combination study in unresectable or metastatic melanoma, cuSCC occurred in 3% (6/209) of patients receiving combination treatment with trametinib, compared to 10% (22/211) of patients receiving TAFINLAR monotherapy. In the study, the median time to onset of the first occurrence of cuSCC was 223 days for patients receiving combination therapy, and 60 days for patients in the monotherapy arm. All patients treated with monotherapy or combination therapy with trametinib who developed cuSCC continued on treatment without dose modification. Amongst the patients with cuSCC, 67% (4/6) of patients receiving combination treatment with trametinib, and 32% (7/22) of patients receiving TAFINLAR monotherapy, developed subsequent lesions.

In a phase III trial in the adjuvant treatment of melanoma, 1% (6/435) of patients receiving TAFINLAR in combination with trametinib developed cuSCC compared to 1% (5/432) of patients receiving placebo. The median time to onset of the first occurrence of cuSCC in the combination arm was approximately 18 weeks.

In the NSCLC phase II study, 3% (3/93) of patients who received TAFINLAR in combination with trametinib developed cuSCC.

In clinical trials in adult patients receiving TAFINLAR in combination with trametinib, the incidence of cuSCC was 2% (15/737).
In a pooled safety population of pediatric patients receiving TAFINLAR in combination with trametinib, no cases of cuSCC were reported.
Skin examination should be performed prior to initiation of TAFINLAR and every 2 months during treatment with TAFINLAR. Monitoring should continue every 2 to 3 months for 6 months

[1] The overall monotherapy population includes integrated safety population of 586 patients with unresectable or metastatic melanoma and the monotherapy arm patients (N=211) of the phase III combination treatment study in unresectable or metastatic melanoma.

following discontinuation of TAFINLAR.

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

New Primary Melanoma: New primary melanomas were reported in 1% (11/797) of the overall TAFINLAR adult monotherapy population. In the phase III study comparing TAFINLAR to dacarbazine in unresectable or metastatic melanoma, new primary melanomas were reported in 2% (4/187) of patients treated with TAFINLAR monotherapy and in no patients treated with dacarbazine (see 8.2 Clinical Trial Adverse Reactions). In the phase III combination study in unresectable or metastatic melanoma, new primary melanomas were reported in < 1% (1/209) of patients treated with combination treatment with trametinib and in 2% (4/211) of patients receiving TAFINLAR monotherapy. 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 trametinib as opposed to 1% (6/432) of patients receiving placebo.

Across clinical trials in adult patients, new primary melanomas were reported in 1% (11/797) of patients receiving TAFINLAR monotherapy and in <1% (2/644) of patients receiving combination therapy.
In a pooled safety population of pediatric patients receiving TAFINLAR in combination with trametinib, new primary melanoma occurred in < 1% (1/171) of patients.
Perform dermatologic monitoring as recommended for cuSCC above.

Non-cutaneous malignancies

The paradoxical activation of MAP-kinase signalling in BRAF wild-type cells exposed to BRAF inhibitors may lead to increased risk of non-cutaneous malignancies, including those with RAS mutations, in patients treated with TAFINLAR. In clinical trials, cases of RAS-associated malignancies have been reported including colorectal adenocarcinoma, bile duct adenocarcinoma and pancreatic adenocarcinoma, which have resulted in discontinuation of TAFINLAR.

Across clinical trials in adult patients, the incidence of non-cutaneous malignancies was lower in patients receiving combination therapy (1%, 9/737) or placebo (<1%, 3/432) than in patients receiving TAFINLAR monotherapy **(**3%, 10/398).
In a pooled safety population of pediatric patients receiving TAFINLAR in combination with trametinib (n=171), no cases of non-cutaneous malignancies were reported.
Evaluate patients for symptoms or clinical signs of non-cutaneous malignancies before initiation of treatment, periodically during treatment, or as clinically indicated. Consider the benefits and risks before continuing treatment with TAFINLAR in patients with a non-cutaneous malignancy that has a RAS mutation. No dose modification of trametinib is required when taken in combination with TAFINLAR.

Following discontinuation of TAFINLAR, monitoring for non-cutaneous malignancies should continue for up to 6 months. Abnormal findings should be managed according to clinical practices.

Cardiovascular

Valve Abnormalities: Patients were excluded from clinical studies of TAFINLAR if they had abnormal valve morphology of ≥ grade 2. Right sided heart valve defects were reported in one of 10 dogs treated with 50 mg/kg/day dabrafenib at > 5 times human clinical exposure (see 16

General Toxicology).

Worsening of baseline valve disease resulting in permanent discontinuation was reported in < 1% of patients (1/797) in the overall TAFINLAR monotherapy population.

QTc Prolongation: Patients were excluded from clinical studies of TAFINLAR if they had a baseline QTc of ≥ 480 msec. Particular care should be exercised when administering TAFINLAR to patients who are suspected to be at an increased risk of experiencing torsade de pointes (see 10.2 Pharmacodynamics).

Venous Thromboembolism: Fatal venous thromboembolism (VTE) events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), have occurred when TAFINLAR was used in combination with trametinib.

Across clinical trials in adult patients, the incidence of DVT and/or PE was higher in patients receiving combination therapy (3%, 29/941) than in patients receiving TAFINLAR monotherapy (< 1%; 2/211).
In a pooled safety population of pediatric patients receiving TAFINLAR in combination with trametinib, one case of embolism was reported (1/171 patients; <1%).
If patients develop symptoms of PE or DVT such as shortness of breath, chest pain, or arm or leg swelling, they should immediately seek medical care.

Endocrine and Metabolism

Hyperglycaemia: Grade 3 elevations of hyperglycaemia based on laboratory values were reported in 5% (39/797) of adult patients treated with TAFINLAR monotherapy; in addition, 1 subject reported a Grade 4 elevation. In a phase III combination study in patients with unresectable or metastatic melanoma, a higher percentage of patients receiving TAFINLAR and trametinib combination therapy (7%, 15/209) had hyperglycaemia adverse events than patients receiving monotherapy (3%, 7/211). In this study, 2% (5/209) of patients in the combination arm reported Grade 3 events compared to < 1% (1/211) in the monotherapy arm. In addition, there was 1 subject with Grade 4 hyperglycaemia in the combination arm, compared to no Grade 4 cases in the monotherapy arm. All subjects with hyperglycaemia events in both treatment arms continued dosing. Four of 15 patients with a history of diabetes receiving TAFINLAR in combination with trametinib, and 2 of 16 patients with a history of diabetes receiving monotherapy, required more intensive hypoglycaemic therapy in this study.

In a pooled safety population of pediatric patients receiving TAFINLAR in combination with trametinib (n=171), Grade 3 and Grade 4 hyperglycemia events occurred in < 1% of patients.

Monitor glucose regularly in patients with diabetes or hyperglycaemia and adjust anti-diabetic treatments accordingly. Advise patients to report symptoms of severe hyperglycaemia such as excessive thirst or any increase in the volume or frequency of urination.

Tumour Lysis Syndrome (TLS): Post-marketing cases of TLS, including fatal cases, have been reported in patients treated with TAFINLAR (dabrafenib) in combination with trametinib. Risk factors for TLS include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. Patients with risk factors for TLS should be closely monitored and prophylactic hydration should be considered. TLS should be treated promptly, as clinically indicated.

Hematologic

Hemorrhage: An increase in bleeding events including major hemorrhagic events (defined as symptomatic bleeding in a critical site, and fatal intracranial hemorrhages), have been reported when TAFINLAR is used in combination with trametinib.

In a phase I/II study in unresectable or metastatic melanoma, bleeding events (any grade) were reported in 31% (17/55) of patients treated with combination therapy, compared to 6% (3/53) treated with single agent TAFINLAR. Intracranial hemorrhage occurred in 5% (3/55) of patients in the combination arm, and was fatal in two patients (4%). Gastrointestinal hemorrhage occurred in 7% (4/55) of patients in the combination arm; none of the events were fatal. No intracranial or gastrointestinal hemorrhage was reported in the monotherapy arm. In a phase III study in unresectable or metastatic melanoma, bleeding events (any grade) were reported in 19% (40/209) of patients treated with combination therapy compared to 15% (32/211) of patients receiving TAFINLAR monotherapy. Intracranial hemorrhage was fatal in 1% (3/209) of patients in the study treated with combination therapy. Gastrointestinal hemorrhage occurred in 6% (12/209) of patients in the combination arm; none of the events were fatal. Gastrointestinal hemorrhage occurred in 3% (6/211) of patients in the TAFINLAR monotherapy arm; none of the events were fatal. No intracranial hemorrhage was reported in the monotherapy arm.

In the melanoma phase III trial in unresectable or metastatic melanoma, 6 patients (1%) taking TAFINLAR in combination with trametinib experienced fatal cerebral hemorrhage, including 2 who were taking anticoagulants and 3 who had developed brain metastases. The risk for serious hemorrhagic events in patients with unstable and/or symptomatic brain metastases or low platelets (< 75,000) is not established, as patients with these conditions were excluded from clinical trials. The risk of hemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy or in patients who develop brain metastases while on treatment.

No fatal hemorrhagic events occurred in the phase III study in the adjuvant treatment of melanoma.

In the NSCLC phase II study, the incidence of hemorrhagic events in patients receiving TAFINLAR in combination with trametinib was 26% (24/93). Fatal hemorrhagic events occurred in 2% (2/93) of patients receiving TAFINLAR in combination with trametinib, one with retroperitoneal hemorrhage and one with subarachnoid hemorrhage.

In a pooled safety population of pediatric patients receiving TAFINLAR in combination with trametinib (n=171), hemorrhagic events occurred in 25% of patients; the most common type of bleeding was epistaxis (16%). Serious events of bleeding occurred in 3.6% of patients and included gastrointestinal hemorrhage (1.2%), cerebral hemorrhage (0.6%) uterine hemorrhage (0.6%), post-procedural hemorrhage (0.6%) and epistaxis (0.6%).

If hemorrhage occurs, patients should be treated as clinically indicated. Patients should be advised to seek immediate medical care if they develop symptoms of hemorrhage.

Cerebral hemorrhage (including fatal cases) associated with TAFINLAR in combination with trametinib were reported in clinical trials and during post-marketing use.

Neutropenia: Neutropenia as an adverse event, including Grade 3 or 4 occurrences, has been reported in association with the combination of TAFINLAR and trametinib in both adult and pediatric patients. Patients receiving the combination therapy should have their complete blood counts determined at baseline and periodically on treatment (see Monitoring and Laboratory Tests).

Hepatic/Biliary/Pancreatic

Hepatotoxicity: Hepatic adverse events have been reported when TAFINLAR is used in combination with trametinib (see 8.2 Clinical Trial Adverse Reactions).

Across several large trials in patients treated with the combination of TAFINLAR and trametinib, hepatic adverse events were reported in 20% (150/737) of adult patients and in 20% (35/171) of pediatric patients.

Pancreatitis: Cases of pancreatitis have been reported in the overall TAFINLAR adult monotherapy melanoma population (< 1%, 3/797 patients) and in the post-marketing setting, generally occurring soon after initiation of TAFINLAR. One of the events occurred on the first day of dosing of a patient and recurred following re-treatment at a reduced dose.

Across several large trials in patients treated with the combination of TAFINLAR and trametinib, pancreatitis was reported in 1% (12/941) of adult patients and in 1% (2/171) of pediatric patients.

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

Immune

Sarcoidosis: Cases of sarcoidosis have been reported in patients treated with TAFINLAR in combination with trametinib, mostly involving the skin, lung, eye and lymph nodes. In the majority of the cases, treatment with TAFINLAR and trametinib was maintained. In case of a diagnosis of sarcoidosis, relevant treatment should be considered. It is important not to misinterpret sarcoidosis as disease progression.

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

Monitoring and Laboratory Tests

Before taking TAFINLAR, confirmation of the existence of a BRAF V600 mutation in a tumour specimen is required, using a validated test.

Before taking TAFINLAR, at every 2 months during therapy and every 2 to 3 months for 6 months after discontinuation, patients should be monitored for cuSCC and new primary melanomas. Monitor for non-cutaneous malignancies as clinically appropriate.

A thorough ophthalmological evaluation should be performed at baseline, if clinically warranted.Patients should also be monitored for eye disorders including visual disturbances during therapy.

Electrolytes (including phosphate) and glucose determinations should be performed at baseline and periodically while on TAFINLAR therapy. Glucose should be monitored more often in patients with pre-existing diabetes or hyperglycaemia.

Blood pressure should be measured at baseline and periodically during treatment (see 10.2 Pharmacodynamics).

Monitor serum creatinine and other evidence of renal function routinely during treatment and in

events of severe pyrexia.

Monitor uric acid levels and electrolytes in patients receiving treatment with TAFINLAR in combination with trametinib, especially in those patients at high risk of Tumour Lysis Syndrome.

Monitor patients receiving TAFINLAR in combination with trametinib carefully for bleeding events and neurologic symptoms.

Patients receiving the combination therapy should have their complete blood counts determined at baseline and periodically on treatment.

Monitor liver function in patients receiving treatment with TAFINLAR in combination with trametinib approximately every 4 weeks for 6 months after treatment initiation of this combination therapy. Liver monitoring may be continued thereafter as clinically indicated during therapy.

Monitor body weight and growth of pediatric patients receiving TAFINLAR in combination with trametinib.

Ophthalmologic

Uveitis: Ophthalmologic reactions, most notable uveitis (including iritis), have been reported in patients treated with TAFINLAR. The severity of uveitis is increased when TAFINLAR is used in combination with trametinib (see below and 8.2 Clinical Trial Adverse Reactions). Uveitis was observed in 1% (11/797) of patients in the overall TAFINLAR adult monotherapy population. All cases reported were Grade 1 or 2. Uveitis was reported in 2% (9/559) of patients treated with the combination of TAFINLAR and trametinib in a large phase III clinical trial population in unresectable or metastatic melanoma. The 9 patients experienced 10 events; four events were Grade 3.

In a pooled safety population of pediatric patients receiving TAFINLAR in combination with trametinib (n=171), uveitis occurred in 5 patients (3%).

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 trametinib. Systemic corticosteroid treatment can be considered in such cases.

Monitor patients for visual signs and symptoms (such as change in vision, photophobia, and eye pain) during therapy and withhold TAFINLAR (and trametinib when used in combination therapy) in patients with uveitis whose symptoms do not improve despite local ocular therapy (see 4.2 Recommended Dose and Dosage Adjustment).

Renal

Renal Failure: Renal failure was reported in 1.5% of patients in the overall TAFINLAR adult monotherapy population (12/797). Renal failure was associated with pyrexia and/or dehydration in 4 of 12 cases. In clinical trials in adult patients receiving TAFINLAR in combination with trametinib, renal failure was reported in 13/357 (3.6%) of patients.

Renal failure was associated with pyrexia and/or dehydration in 5 of the 8 cases in one study (n=209). In this study, 2 patients in the combination therapy arm and no patients in the TAFINLAR monotherapy arm reported Grade 3 events of increased blood creatinine and nephritis (including 1 case (0.5%, 1/209) of granulomatous/interstitial nephritis). In the phase II

NSCLC study, Grade 3 renal failure was reported in one patient, Grade 3 increased blood creatinine was reported in one patient, and Grade 3 tubulointerstitial nephritis was reported in 2% (2/93) of patients. Granulomatous/tubulointerstitial nephritis been reported in one (< 1%) patient in a clinical study with TAFINLAR monotherapy. Granulomatous/tubulointerstitial nephritis has also been reported in the post-marketing setting with TAFINLAR monotherapy and TAFINLAR in combination with trametinib (see 8 ADVERSE REACTIONS).

In a pooled safety population of pediatric patients receiving TAFINLAR in combination with trametinib (n=171), no cases of pre-renal or intrinsic renal failure were reported.

Monitor serum creatinine and other evidence of renal function routinely during treatment and in events of severe pyrexia.

Reproductive Health

Reproduction: Male patients (including those who have had a vasectomy) with sexual partners who are pregnant, or are of childbearing potential should use condoms during sexual intercourse while taking TAFINLAR and for at least 2 weeks following discontinuation of treatment and at least 16 weeks following the last dose of trametinib when taken in combination with TAFINLAR.

Women of childbearing potential should use effective methods of contraception during therapy (methods that result in less than 1% pregnancy rates) and for 2 weeks following discontinuation of TAFINLAR and at least 16 weeks following the last dose of trametinib when taken in combination with TAFINLAR. Dabrafenib is likely to decrease the efficacy of oral or any systemic hormonal contraceptives and effective alternative methods of contraception should be used (see 9 Effect of Dabrafenib on Other Drugs).

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

Fertility: There are no fertility data in humans. Adverse effects of dabrafenib on male reproductive organs have been seen in animals (see 16 Reproductive and Developmental Toxicity). Male patients should be informed of the potential risk for impaired spermatogenesis, which may be irreversible.

Skin

Severe cutaneous adverse reactions: Cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) 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.

7.1 Special Populations

7.1.1 Pregnancy

TAFINLAR should not be administered to pregnant women. Dabrafenib may cause foetal harm by interfering with BRAF function, which is essential for the developing embryo. There are no adequate and well-controlled studies of TAFINLAR in pregnant women (see 7 Reproductive

Health: Female and Male Potential). Dabrafenib caused reproductive toxicity and teratogenicity in rats (see 16 Reproductive and Developmental Toxicity).

7.1.2 Breastfeeding

No studies have been conducted with TAFINLAR in nursing mothers. TAFINLAR should not be used by nursing women. It is not known whether dabrafenib is transferred into human milk. Because many drugs are transferred into human milk, and because of the potential for serious adverse reactions from dabrafenib in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

Pediatrics (< 1 year of age): The safety and efficacy of TAFINLAR in pediatric patients <1 year of age have not been established. TAFINLAR is not recommended in this age group.

Pediatrics (≥ 1 year to <18 years of age):

The safety and efficacy of TAFINLAR in combination with trametinib in pediatric patients 1 year of age and older with low-grade glioma are supported by evidence from the randomized LGG cohort of the G2201 study (N=73).

The safety and efficacy of TAFINLAR in combination with trametinib in pediatric patients 1 year of age and older with high-grade glioma are supported by evidence from the single-arm HGG cohort of the G2201 study (N=41).

The warnings applicable to adults are also relevant to pediatric use.

Adverse drug reactions occurring at a higher frequency category in a pooled safety population of pediatric patients (N=171) compared to adult patients were neutropenia, dermatitis acneiform, paronychia, anaemia, leukopenia (very common); bradycardia, dermatitis exfoliative generalised, hypersensitivity and pancreatitis (common).

Weight increase has only been reported in the pediatric population. It was reported as an adverse reaction in 16.4% of pediatric patients, including Grade 3 cases in 5.3% of patients, with a discontinuation rate of 0.6% of patients. The median time to onset of the first occurrence of the reported weight increase in pediatric patients receiving dabrafenib in combination with trametinib was 3.5 months. Weight increase from baseline of ≥2 BMI (body mass index)-for-age percentile categories was observed in 35.7% of patients.

Please refer to pediatric Adverse Events Tables 12 and 13

Studies in juvenile animals have shown adverse effects, including effects on growth and renal toxicity, which had not been observed in adult animals (see 16 Juvenile Toxicity).

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Of the total number of patients in clinical studies of TAFINLAR monotherapy (N = 797), 23% were 65 years of age and older, and 6% were 75 years of age and older. Compared with younger patients (< 65 years), more patients ≥ 65 years old had adverse events that led to dabrafenib dose reductions (23% versus 14%) or interruptions (46% versus 30%). In addition, older patients experienced more serious adverse events compared to

younger patients (46% versus 27%).

Of the number of patients in a phase III clinical study in unresectable or metastatic melanoma receiving TAFINLAR in combination with trametinib (N = 209), 56 patients (27%) were 65 years of age and older, and 11 patients (5%) were 75 years of age and older. Compared with younger patients (< 65 years), more patients ≥ 65 years old had adverse events that led to dose reductions (43% versus 23%) or interruptions (66% versus 53%) of therapy with TAFINLAR or trametinib. In addition, older patients experienced more serious adverse events compared to younger patients (59% versus 36%). The incidences of peripheral oedema in the combination (34% vs. 16%) and monotherapy arms (18% vs. 5%) and of decreased appetite in the combination (21% vs. 9%) and monotherapy arms (15% vs. 13%) were more frequent in patients ≥ 65 years than in patients < 65 years, respectively.

Of the 435 patients who received TAFINLAR plus trametinib in the combination phase III study in the adjuvant treatment of melanoma, 85 patients (20%) were aged 65 years and older and 12 patients (3%) were aged 75 years and older. No overall differences in the effectiveness or safety of TAFINLAR plus trametinib were observed in elderly patients compared to younger patients.

8 Adverse Reactions

8.1 Adverse Reaction Overview

Unresectable or Metastatic Melanoma - TAFINLAR Monotherapy

The safety of TAFINLAR monotherapy was evaluated in an integrated safety population of 586 patients with BRAF V600-mutant unresectable or metastatic melanoma, with a median duration of treatment of 5.5 months (range 0 to 23 months). Approximately 46% of patients received treatment with TAFINLAR for more than 6 months.

The most common adverse drug reactions (≥ 15%) of any grade for TAFINLAR in either the overall monotherapy safety population or the phase III pivotal study comparing TAFINLAR to dacarbazine in unresectable or metastatic melanoma, include hyperkeratosis, headache, pyrexia, palmar-plantar erythrodysaesthesia (PPE), arthralgia, fatigue, nausea, skin papilloma, alopecia, and rash.

Unresectable or Metastatic Melanoma - TAFINLAR in Combination with Trametinib

The safety of TAFINLAR in combination with trametinib was evaluated in a multicentre, randomized phase III study (MEK115306) in a safety population of 209 patients with unresectable or metastatic melanoma. In this study, approximately 71% of patients received treatment with TAFINLAR and trametinib for more than 6 months. The median durations of treatment in the combination and monotherapy arms were 11 and 8 months, respectively.

A higher percentage of patients had AEs leading to permanent discontinuation of study treatment in the combination therapy arm of the MEK115306 study (11%) than in the monotherapy arm (7%). The percentage of patients with AEs leading to dose interruptions and dose reductions was also higher in the combination therapy arm than with TAFINLAR monotherapy. Fifty six percent (56%) and 28% of patients receiving the combination therapy had dose interruptions and reductions, respectively, compared to 37% and 14% of patients treated with the monotherapy.

Adjuvant Treatment of Melanoma - TAFINLAR in Combination with Trametinib

The safety of TAFINLAR in combination with trametinib has been evaluated in a phase III, randomized, double-blind study of TAFINLAR in combination with trametinib versus two

placebos in the adjuvant treatment of Stage III BRAF V600 mutation-positive melanoma after surgical resection. The median duration of exposure was 11 months for dabrafenib and trametinib and 10 months for the placebo arm. The majority of patients had > 6 to 12 months of exposure to dabrafenib (71%) and trametinib (72%), respectively.

In the TAFINLAR 150 mg twice daily and trametinib 2 mg once daily arm, the most common adverse reactions (≥ 20%) were pyrexia, fatigue, nausea, headache, rash, chills, diarrhoea, vomiting, arthralgia and myalgia. The most common serious adverse reactions (≥ 1%) were pyrexia, chills, ejection fraction decreased, erysipelas, hypotension, cellulitis and chorioretinopathy.

Adverse reactions resulting in the permanent discontinuation of TAFINLAR in combination with trametinib occurred in 26% of patients. Adverse reactions leading to dose interruptions or reductions of TAFINLAR in combination with trametinib occurred in 66% and 38% of patients, respectively.

Female patients treated with combination therapy had higher incidences of treatment-related adverse events (95% vs. 88%) and treatment-related serious adverse events (31% vs. 24%), corresponding to more dose reductions (45% vs. 33%), dose interruptions (70% vs. 64%), and adverse events leading to discontinuation (32% vs. 22%) compared to male patients. No differences in the pattern of adverse events or the overall incidence of adverse events (females: 98% vs. males: 96%) were observed between genders.

Metastatic Non-Small Cell Lung Cancer - TAFINLAR in Combination with Trametinib

The safety of TAFINLAR in combination with trametinib was also evaluated in a phase II, multi-centre, multi-cohort, non-randomised, open-label study of patients with BRAF V600E mutation-positive metastatic NSCLC. Patients (N = 93) had a median exposure to TAFINLAR of 8.5 months (range: 0.3-31.6 months), with 62% of patients receiving treatment with TAFINLAR and trametinib for more than 6 months.

The most common adverse drug reactions (≥ 20%) reported in patients with NSCLC who received TAFINLAR in combination with trametinib were pyrexia, asthenia, nausea, vomiting, oedema peripheral, diarrhoea, dry skin, rash, decreased appetite, hemorrhage and chills.

The most common serious adverse drug reactions (≥2%) reported in patients with NSCLC who received TAFINLAR in combination with trametinib were pyrexia, ejection fraction decreased, alanine aminotransferase increased, aspartate aminotransferase increased, hypotension, vomiting, anaemia, nausea, abdominal pain, asthenia, back pain, blood alkaline phosphatase increased, chills, confusional state, decreased appetite, dehydration, diarrhoea, dyspnoea, haemoptysis, hypercalcaemia, lung infection, pulmonary embolism, renal failure, respiratory distress, squamous cell carcinoma of skin and tubulointerstitial nephritis.

Twenty percent (20%) of NSCLC patients treated with the TAFINLAR and trametinib combination had AEs leading to permanent discontinuation of study treatment. The percentage of patients with AEs leading to dose interruptions and dose reductions was 67% and 35%, respectively.

Low-grade Glioma and High-grade Glioma – TAFINLAR in combination with Trametinib

The safety of TAFINLAR in combination with trametinib was studied in 171 pediatric patients across two studies (G2201 and X2101) with BRAF V600E mutation-positive advanced solid tumours of which 118 patients had a BRAF mutation-positive low-grade glioma (WHO Grades 1 and 2), 41 patients had a BRAF mutation-positive high-grade glioma (WHO Grades 3 and 4) and 12 had Langerhans Cell Histiocytosis.

Of these 171 pediatric patients, 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 overall safety profile in the pediatric population was similar to the safety profile observed in adults. The most frequently reported adverse drug reactions (≥20%) were pyrexia, rash, headache, vomiting, musculoskeletal pain, dry skin, fatigue, diarrhoea, hemorrhage, neutropenia, nausea, dermatitis acneiform, abdominal pain, cough and transaminases increased.

An adverse drug reaction of weight increased was identified in the pediatric safety pool with a frequency of 16%. Sixty one out of 171 patients (36%) had an increase from baseline of ≥2 BMI-for-age percentile categories. In the pediatric G2201 study, 49.3% of patients in the LGG cohort and 40% of patients in the HGG cohort had a notably high weight gain velocity at Month 6.

Serious adverse reactions occurred in 29% of patients who received TAFINLAR in combination with trametinib. Serious adverse reactions occurring in > 3% of patients included pyrexia (15%), vomiting (4%) and hemorrhage (4%).

Permanent treatment discontinuation due to an adverse reaction occurred in 8% of patients. Adverse reactions which resulted in permanent discontinuation of TAFINLAR and trametinib in > 1% of patients included pyrexia (1%), rash (2%), ALT increased (1%), and AST increased (1%).

Dosage interruptions due to an adverse reaction occurred in 76% of patients. Adverse reactions which required dosage interruption in > 5% of patients included pyrexia (53%), vomiting (12%), neutropenia (8%) and rash (7%).

Dose reductions due to an adverse reaction occurred in 14% of patients. Adverse reactions which required dose reductions in > 2% of patients included pyrexia (5%) and rash (3%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

Unresectable or Metastatic Melanoma - TAFINLAR Monotherapy

Table 8 reports adverse drug reactions from the pivotal phase III study comparing TAFINLAR monotherapy to dacarbazine (DTIC) in previously untreated patients with unresectable or metastatic melanoma (BRF113683) and one phase II single-arm study in patients with melanoma metastatic to the brain (BRF113929) (see 14 CLINICAL TRIALS). The laboratory abnormalities presented in Table 14 were identified from the pivotal phase III study. In study BRF113683, patients were allocated to TAFINLAR 150 mg orally twice daily or to DTIC intravenously 1000 mg/m^2 every 3 weeks. In study BRF113929, TAFINLAR was administered as 150 mg orally twice daily in an open label fashion.

In the phase III study, 28% of patients treated with TAFINLAR and 24% of patients treated with dacarbazine experienced serious adverse events (SAEs). The most common treatment-related SAEs in patients treated with TAFINLAR were cuSCC and pyrexia. Serious cases of pyrexia occurred in 10 of 187 patients (5%). Serious cases of cuSCC occurred in 12 of 187 patients

(6%).

The incidence of adverse events resulting in permanent discontinuation of study medication in study BRF113683 was 3% for patients treated with TAFINLAR and 2% for patients treated with DTIC. In study BRF113929, the incidence of adverse events resulting in permanent discontinuation of study medication for TAFINLAR was 2%. The median duration of study treatment was 7.5 months for TAFINLAR and 2.8 months for DTIC in study BRF113683, and 3.9 months for TAFINLAR in study BRF113929. The incidence of adverse events leading to dose reductions was 20% for TAFINLAR and 17% for DTIC in study BRF113683 and was 14% for TAFINLAR in study BRF113929. The incidence of adverse events leading to dose interruptions was 32% for TAFINLAR and 27% for DTIC in study BRF113683 and was 32% for TAFINLAR in study BRF113929.

Table 8 Adverse Reactions Occurring in ≥ 10% (All grades) or ≥ 2% (Grades 3 or 4) of Patients in 2 Clinical Trials of TAFINLAR Monotherapy – Unresectable or Metastatic Melanoma Studies

	BRF113683: Treatment-Naïve Patients				BRF113929: Patients With Brain Metastases	
	TAFINLAR N = 187		DTIC N = 59		TAFINLAR N = 172	
	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)
Gastrointestinal disorders						
Nausea	27	<1	53	0	26	2
Vomiting	18	1	25	0	20	1
Diarrhoea	14	<1	12	0	13	<1
Constipation	13	2	15	0	8	0
General disorders and administration site conditions						
Pyrexia	31	3	14	0	26	<1
Fatigue	22	1	24	0	25	1
Asthenia	19	<1	15	2	5	0
Chills	12	0	2	0	11	<1
Infections and infestations						
Nasopharyngitis	16	0	7	0	6	0
Metabolism and nutritional disorders						
Decreased appetite	12	0	8	3	12	2
Hyperglycaemia	7	3	7	0	5	1
Hypophosphatemia	5	2	0	0	5	2
Musculoskeletal, connective tissue and bone disorders						
Arthralgia	32	2	2	0	17	0
Myalgia	13	0	0	0	15	0
Pain in extremity	13	<1	10	0	12	0
Neoplasms benign and malignant (including cysts and polyps)						

	BRF113683: Treatment-Naïve Patients				BRF113929: Patients With Brain Metastases	
	TAFINLAR N = 187		DTIC N = 59		TAFINLAR N = 172	
	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)
Skin papilloma	25	0	2	0	15	0
cuSCC[a, b]	9	7	0	0	6	4
Nervous system disorders						
Headache	34	0	8	0	28	2
Respiratory, thoracic and mediastinal disorders						
Cough	14	0	7	0	10	0
Skin and subcutaneous disorders						
Hyperkeratosis	39	2	2	0	26	<1
Alopecia	29	<1	3	0	15	0
PPE[c]	20	2	2	0	15	2
Rash	18	0	0	0	17	0
Dry Skin	10	0	0	0	8	0

[a] Includes squamous cell carcinoma of the skin, squamous cell carcinoma *in situ* (Bowen's disease) and keratoacanthoma
[b] Cases of cutaneous squamous cell carcinoma were required to be reported as Grade 3 per protocol
[c] PPE = Palmar-plantar erthyrodysesthesia syndrome (hand-foot syndrome)

Unresectable or Metastatic Melanoma - TAFINLAR in Combination with Trametinib

Table 9 and Table 15 present adverse drug reactions and laboratory abnormalities, respectively, from the phase III study of TAFINLAR 150 mg given twice daily in combination with trametinib 2 mg given once daily compared to TAFINLAR monotherapy (see 14 CLINICAL TRIALS). The common adverse reactions in Table 9 were reported in ≥ 10% of patients treated with the combination of TAFINLAR with trametinib, or were Grade 3 and 4 events reported in ≥ 2% of patients treated with the combination treatment.

Table 9 Adverse Reactions (%) Occurring in ≥ 10% (All Grades) or ≥ 2% (Grades 3 or 4) of Patients Treated with TAFINLAR in Combination with Trametinib in the Unresectable or Metastatic Melanoma Study MEK115306

	MEK115306			
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 209)		TAFINLAR 150 mg BID + Placebo (N = 211)	
	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)
Blood and lymphatic system disorders				
Neutropenia	10	3	2	<1
Anaemia	6	3	9	4

	MEK115306			
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 209)		TAFINLAR 150 mg BID + Placebo (N = 211)	
	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)
Cardiac disorders				
Ejection fraction decreased	6	1	3	2
Gastrointestinal disorders				
Nausea	34	<1	27	1
Diarrhoea	30	1	16	<1
Vomiting	25	<1	14	<1
Constipation	13	<1	10	0
Abdominal pain	13	<1	9	2
General disorders and administrative site conditions				
Pyrexia	57	7	33	2
Fatigue	39	2	37	1
Chills	31	0	17	<1
Oedema peripheral	21	<1	9	<1
Asthenia	12	1	14	<1
Hepatobiliary disorders				
ALT increased	13	2	6	<1
AST increased	13	3	4	<1
Infections and infestations				
Nasopharyngitis	12	0	10	0
Urinary tract infection	11	2	3	<1
Metabolism and nutritional disorders				
Decreased appetite	12	<1	13	<1
Hyperglycaemia[a]	7	3	3	<1
Musculoskeletal, connective tissue and bone disorders				
Arthralgia	26	<1	31	0
Pain in extremity	15	1	17	<1
Myalgia	13	<1	13	0
Neoplasms benign and malignant (including cysts and polyps)				
cuSCC[b,c]	3	3	10	10
Nervous system disorders				
Headache	33	<1	30	1
Dizziness	14	0	7	0
Respiratory, thoracic, and mediastinal disorders				
Cough	21	0	21	0
Skin and subcutaneous tissue disorders				
Rash	27	0	22	<1
Dry skin	12	0	16	0
Pruritus	12	0	14	0
Dermatitis acneiform	10	0	4	0
Vascular disorders				

	MEK115306			
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 209)		TAFINLAR 150 mg BID + Placebo (N = 211)	
	All Grades (%)	Grade 3 and Grade 4 (%)	All Grades (%)	Grade 3 and Grade 4 (%)
Hypertension	25	6	16	6
Hemorrhage[d]	19	2	15	2
Hypotension	6	2	3	<1

[a] Includes hyperglycaemia, type 2 diabetes, diabetes mellitus, and blood glucose increase
[b] Includes squamous cell carcinoma of skin, squamous cell carcinoma *in situ* (Bowen's disease) and keratoacanthoma
[c] Cases of cutaneous squamous cell carcinoma were required to be reported as Grade 3 per protocol
[d] Includes intracranial and gastric hemorrhage

Adjuvant Treatment of Melanoma - TAFINLAR in Combination with Trametinib

Table 10 and Table 16 present adverse drug reactions and laboratory abnormalities, respectively, from the adjuvant treatment of melanoma phase III study (BRF115532) of TAFINLAR 150 mg given twice daily in combination with trametinib 2 mg given once daily (see 14 CLINICAL TRIALS). The adverse drug reactions in Table 10 were reported in ≥ 10% of patients treated with the combination of TAFINLAR with trametinib, or were Grade 3 and 4 events reported in ≥ 2% of patients treated with the combination.

Table 10 Adverse Reactions (%) Occurring in ≥ 10% (All Grades) or ≥ 2% (Grades 3 and 4) of Patients Treated with TAFINLAR in Combination with Trametinib in the Adjuvant Treatment of Melanoma Study BRF115532

	Study BRF115532			
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 435)		Placebo (N = 432)	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Blood and lymphatic system disorders				
Neutropenia[1]	10	5	<1	NR
Gastrointestinal disorders				
Nausea	40	<1	20	NR
Diarrhoea	33	<1	15	<1
Vomiting	28	<1	10	NR
Abdominal pain[2]	16	<1	11	<1
Constipation	12	NR	6	NR
General disorders and administration site conditions				
Pyrexia[3]	63	5	11	<1
Fatigue[4]	59	5	37	<1
Chills	37	1	4	NR
Oedema peripheral[5]	16	<1	6	NR
Influenza-like illness	15	<1	7	NR
Infections and infestations				
Nasopharyngitis[6]	12	<1	12	NR
Investigations				

	Study BRF115532			
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 435)		Placebo (N = 432)	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Alanine aminotransferase increased[7]	17	4	2	<1
Aspartate aminotransferase increased[8]	16	4	2	<1
Metabolism and nutrition disorders				
Decreased appetite	11	<1	6	NR
Musculoskeletal and connective tissue disorders				
Arthralgia	28	<1	14	NR
Myalgia[9]	20	<1	14	NR
Pain in extremity	14	<1	9	NR
Muscle spasms[10]	11	NR	4	NR
Nervous system disorders				
Headache[11]	39	1	24	NR
Dizziness[12]	11	<1	10	NR
Respiratory, thoracic and mediastinal disorders				
Cough[13]	17	NR	8	NR
Skin and subcutaneous tissue disorders				
Rash[14]	37	<1	16	<1
Dry skin[15]	14	NR	9	NR
Dermatitis acneiform	12	<1	2	NR
Erythema[16]	12	NR	3	NR
Pruritus[17]	11	<1	10	NR
Vascular disorders				
Hemorrhage[18]	15	<1	4	<1
Hypertension[19]	11	6	8	2

[1] Neutropenia also includes febrile neutropenia and cases of neutrophil count decreased that met the criteria for neutropenia
[2] Abdominal pain also includes abdominal pain upper and abdominal pain lower
[3] Pyrexia also includes hyperpyrexia
[4] Fatigue also includes asthenia and malaise
[5] Oedema peripheral also includes peripheral swelling
[6] Nasopharyngitis also includes pharyngitis
[7] Alanine aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia
[8] Aspartate aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia
[9] Myalgia also includes musculoskeletal pain and musculoskeletal chest pain
[10] Muscle spasms also includes musculoskeletal stiffness
[11] Headache also includes tension headache
[12] Dizziness also includes vertigo
[13] Cough also includes productive cough
[14] Rash also includes rash maculo-papular, rash macular, rash generalized, rash erythematous, rash papular, rash pruritic, nodular rash, rash vesicular, and rash pustular
[15] Dry skin also includes xerosis and xeroderma
[16] Erythema also includes generalized erythema
[17] Pruritus also includes pruritus generalized and pruritus genital
[18] Hemorrhage includes a comprehensive list of hundreds of event terms that capture bleeding events.
[19] Hypertension also includes hypertensive crisis
NR: not reported

COMBI-APlus (Pyrexia Management Study)

Study COMBI-APlus evaluated the impact of pyrexia-related outcomes of a revised pyrexia management algorithm in patients who received TAFINLAR in combination with trametinib in the adjuvant treatment of BRAF V600 mutation-positive melanoma after complete resection. The pyrexia management guidance recommended to interrupt both TAFINLAR and trametinib when a patient's temperature was ≥ 38.0°C.

Grade 3-4 pyrexia occurred in 4.3% of patients, hospitalizations due to pyrexia occurred in 5.1% of patients, pyrexia with complications (dehydration, hypotension, renal dysfunction, syncope) occurred in 2.2% of patients, and treatment discontinuation due to pyrexia occurred in 2.5% of patients.

Metastatic Non-Small Cell Lung Cancer - TAFINLAR in Combination with Trametinib

Table 11 and Table 17 present adverse drug reactions and laboratory abnormalities, respectively, from the NSCLC phase II study of TAFINLAR 150 mg given twice daily in combination with trametinib 2 mg given once daily (see 14 CLINICAL TRIALS). The common adverse drug reactions in Table 11 were reported in ≥ 10% of patients treated with the combination of TAFINLAR with trametinib, or were Grade 3 and 4 events reported in ≥ 2% of patients treated with the combination.

Table 11 Adverse Reactions (%) Occurring in ≥ 10% (All Grades) or ≥ 2% (Grades 3 or 4) of Patients Treated with TAFINLAR in Combination with Trametinib in the NSCLC Study BRF113928

	Study BRF113928	
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 93)	
	All Grades (%)	Grades 3 and 4 (%)
Blood and lymphatic system disorders		
Anaemia	16	4
Neutropenia[1]	15	8
Leukopenia	6	2
Cardiac disorders		
Ejection fraction decreased	9	4
Gastrointestinal disorders		
Nausea	46	0
Vomiting	37	3
Diarrhoea	33	2
Decreased appetite	28	0
Constipation	16	0
General disorders and administration site disorders		
Pyrexia	55	5
Asthenia [2]	47	6
Oedema peripheral	34	0
Chills	24	1
Investigations		
Weight decreased	13	1
Blood alkaline phosphatase increased	12	0
Aspartate aminotransferase increased	11	2
Alanine aminotransferase increased	10	4

	Study BRF113928	
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 93)	
	All Grades (%)	Grades 3 and 4 (%)
Weight increased	10	3
Gamma-glutamyltransferase increased	2	2
Metabolism and nutrition disorders		
Hyponatraemia	14	9
Dehydration	8	3
Hypercalcaemia	3	2
Musculoskeletal and connective tissue disorders		
Arthralgia	16	0
Myalgia	13	0
Muscle spasms	10	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Squamous cell carcinoma of skin	3	2
Nervous system disorders		
Headache	16	0
Dizziness	14	0
Renal and urinary disorders		
Tubulointerstitial nephritis	2	2
Respiratory, thoracic and mediastinal disorders		
Cough	23	0
Dyspnoea	15	2
Skin and subcutaneous tissue disorders		
Dry skin	32	1
Rash[3]	31	3
Pruritus[4]	15	2
Hyperkeratosis[5]	13	1
Erythema	10	0
Vascular disorders		
Hemorrhage[6]	26	3
Hypotension	15	2
Hypertension	8	6
Pulmonary embolism	4	2

[1] Neutropenia includes neutropenia and neutrophil count decreased. Neutrophil count decreased qualified as a neutropenia event.
[2] Asthenia also includes fatigue and malaise
[3] Rash includes rash, rash generalized, rash papular, rash macular, rash maculo-papular and rash pustular
[4] Pruritus includes pruritus, pruritus generalized and eye pruritus
[5] Hyperkeratosis includes hyperkeratosis, actinic keratosis, seborrhoeic keratosis and keratosis pilaris
[6] Hemorrhage includes cases of haemoptysis, haematoma, epistaxis, purpura, haematuria, subarachnoid hemorrhage, gastric hemorrhage, urinary bladder hemorrhage, contusion, haematochezia, injection site hemorrhage, melaena, pulmonary and retroperitoneal hemorrhage

Low-grade Glioma and High-grade Glioma - TAFINLAR in Combination with Trametinib

A total of 151 patients were enrolled in the G2201 study; 110 in the LGG cohort and 41 in the HGG cohort.

The LGG cohort, consisting of pediatric patients with chemotherapy-naïve BRAF V600E mutation-positive LGG who required systemic therapy, was randomized 2:1 to receive TAFINLAR in combination with trametinib (n=73) or carboplatin in combination with vincristine

(n=37). The median age was 9.5 years (range 1-17) with approximately one third of patients in each of the three age ranges (12 months to < 6 years; ≥ 6 years to < 12 years; and 12 years to <18 years). The median follow-up was 39 months (range: 28-55.5), with a minimum study follow-up of approximately 28 months.

The HGG cohort, consisting of pediatric patients with BRAF V600E mutation-positive relapsed or refractory HGG tumours, was a single-arm clinical trial to evaluate the effect of TAFINLAR in combination with trametinib. The median age was 13.0 years (range: 2 to 17) with the majority of patients (63.4%) aged between 12 and < 18 years. The median follow-up was 45.2 months (range: 31.9-61.2), with a minimum study follow-up of approximately 31.9 months.

Dabrafenib and trametinib dosing was age- and weight-dependent, and carboplatin and vincristine were dosed based on age and body surface area (see 14.1 Clinical Trials by Indication).

LGG Cohort

Table 12 presents the adverse events that were reported in the LGG cohort of Study G2201.

The number of patients with serious adverse events (SAEs) was similar in both treatment arms. The most frequently reported SAEs (> 2% in either arm) by Preferred Term (PT) were: pyrexia (16.4% vs. 18.2%), tonsilitis and vomiting (4.1% vs. 0), apnea, hydrocephalus, procedural complication, seizure, urinary tract infection (2.7% vs. 0, each). All other SAEs were reported in 1 patient each in either of the treatment arms.

Notable serious adverse events in single patients were detachment of retinal pigment, embolism, hypernatremia, and toxic shock syndrome in the TAFINLAR in combination with trametinib arm and hemorrhage intracranial in the carboplatin in combination with vincristine arm.

Serious adverse events suspected to be study treatment-related were lower in the targeted therapy (TAFINLAR in combination with trametinib) arm compared to the chemotherapy (carboplatin in combination with vincristine) arm (15.1% vs. 27.3%). The most frequently reported SAEs suspected to be study treatment-related (difference of at least 2 patients) by Preferred Terms was pyrexia.

Serious adverse events were reported more frequently in patients aged 12 months to < 6 years of age (13/20; 65%) compared to patients aged 6 to < 12 years (10/25; 40%) and 12 to <18 years of age (11/28; 39%).

Table 12 Adverse Events (%) Occurring in ≥ 10% (All Grades) or ≥ 2% (Grades 3/4) of Pediatric LGG Patients Treated with TAFINLAR in Combination with Trametinib Study G2201

	Study G2201			
Adverse Events[a]	**TAFINLAR+ trametinib (N = 73)**		**Carboplatin + Vincristine (N = 33)**	
	All Grades (%)	**Grades 3 and 4 (%)**	**All Grades (%)**	**Grades 3 and 4 (%)**
Blood and lymphatic system disorders				
Anaemia	19	0	61	24

Neutropenia	14	10	30	30
Gastrointestinal disorders				
Vomiting	37	1	52	3
Diarrhoea	37	0	18	6
Nausea	29	0	52	0
Abdominal pain[b]	34	0	24	0
Constipation	14	0	36	0
General disorders and administration site disorders				
Pyrexia	75	14	18	3
Fatigue[c]	36	0	39	0
Investigations				
Transaminase increased[d]	20	7	30	9
Weight increased	16	8	0	0
Neutrophil count decreased	15	5	48	48
White blood cell count decreased	12	0	36	15
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain [e]	36	0	27	0
Nervous system disorders				
Headache	55	1	27	3
Dizziness	11	0	3	3
Respiratory, thoracic and mediastinal disorders				
Oropharyngeal pain	14	0	21	0
Cough	15	0	12	0
Vascular disorders				
Hemorrhage[f]	30	0	12	0
Infections and infestations				
Upper respiratory tract infection	22	0	6	0
Paronychial	23	0	0	0
Nasopharyngitis	12	0	6	0
Skin and subcutaneous tissue disorders				
Rash[g]	45	3	12	3
Dry skin	27	0	3	0
Eczema	18	0	0	0

Erythema	16	0	0	0
Acne	14	0	0	0
Dermatitis acneiform	14	0	0	0
Pruritus	12	0	6	0
Neoplasms, benign, malignant and unspecified (incl cysts and polyps)				
Skin papilloma	14	0	0	0

[a] NCI CTCAE version 4.03

[b] Includes abdominal pain and upper abdominal pain

[c] Includes fatigue and asthenia

[d] Transaminase increased Includes alanine aminotransferase increased, aspartate aminotransferase increased, hypertransaminasaemia, transaminases increased

[e] Includes pain in extremity, back pain, bone pain, musculoskeletal pain, neck pain, noncardiac chest pain, myalgia and arthralgia

[f] Includes epistaxis, post-procedural hemorrhage, hematuria, upper gastrointestinal hemorrhage and hemorrhage intracranial.

[g]Includes rash, rash macular, rash maculo-papular, rash pustular, rash papular, rash erythematous

HGG Cohort

Serious adverse events (SAEs) were reported in 28 patients (68.3%) of which 24 patients (58.5%) had grade ≥ 3 SAEs. The most frequently reported SAEs (occurring in ≥ 5% of patients) were headache and pyrexia (7.3% each). Except for the SAEs of hydrocephalus, intracranial pressure increased, and seizure that were reported in 2 patients, all other SAEs were reported in 1 patient each.

Serious AEs suspected to be related to study treatment were reported in 7 patients (17.1%); 6 patients (14.6%) had grade ≥ 3 SAEs. The SAEs suspected to be study treatment related were: pyrexia (2 patients), gastro-intestinal hemorrhage, pancreatitis, influenza-like illness, dysarthria, agitation, confusional state, uterine hemorrhage, erythema nodosum, rash, and hypotension (1 patient each).

Serious AEs with a fatal outcome were reported in 3 patients (7.3%); encephalomyelitis and increased intracranial pressure were each reported in 1 patient among patients who died due to 'other' reasons and apnea was reported in the patient who died due to disease progression.

Table 13 Adverse Events (%) Occurring in ≥ 10% (All Grades) or ≥ 2% (Grades 3/4) of Pediatric HGG Patients Treated with TAFINLAR in Combination with Trametinib Study G2201

	Study G2201	
Adverse Events[a]	**TAFINLAR + trametinib (N = 41)**	
	All Grades (%)	**Grades 3 and 4 (%)**

Blood and lymphatic system disorders		
Neutropenia	17	2
Gastrointestinal disorders		
Vomiting	29	5
Diarrhoea	24	2
Nausea	27	0
Abdominal pain[b]	17	0
Constipation	15	0
General disorders and administration site disorders		
Pyrexia	54	2
Fatigue[c]	17	0
Investigations		
White blood cell count decreased	12	2
Weight increased	15	2
Nervous system disorders		
Headache	46	10
Seizure	12	10
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[d]	27	2
Respiratory, thoracic and mediastinal disorders		
Hemorrhage[e]	29	5
Cough	17	0
Oropharyngeal pain	15	0
Infections and infestations		
Upper respiratory tract infection	24	0
Skin and subcutaneous tissue disorders		
Rash[f]	37	2
Dry skin	34	0
Acne	15	0
Erythema	12	0
Eczema	12	0
Urticaria	12	2

[a] NCI CTCAE version 4.03

[b] Includes abdominal pain and upper abdominal pain

[c] Includes fatigue and asthenia

[d] includes pain in extremity, back pain, bone pain, musculoskeletal pain, neck pain, non-cardiac chest pain, myalgia and arthralgia

[e] Includes epistaxis, hematuria, gastrointestinal hemorrhage, uterine hemorrhage, cerebral hemorrhage, anal hemorrhage, hematochezia and catheter site hemorrhage

[f] Includes rash, rash maculo-papular, rash pustular, rash erythematous

8.3 Less Common Clinical Trial Adverse Reactions

Unresectable or Metastatic Melanoma - TAFINLAR Monotherapy

Other clinically relevant adverse reactions reported in < 10% of patients or < 2% of patients with Grade 3 or 4 events treated with TAFINLAR monotherapy in the integrated safety population are presented below.

Cardiac disorders: Atrial fibrillation (2%), Hypotension (<1%)

Eye disorders: Uveitis (1%)

Gastrointestinal disorders: Pancreatitis (<1%)

Immune system disorders: Influenza-like illness (4%), Hypersensitivity (1%)

Metabolism and nutrition disorders: Hyponatremia (3%)

Renal and urinary disorders: Acute renal failure (1%), Renal failure (1%), Granulomatous/tubulointerstitial nephritis (<1%)

Skin and subcutaneous disorders: Actinic keratosis (9%), Seborrhoeic keratosis (8%), Erythema (6%), Acrochordon (5%), Skin lesion (5%), Pruritus (7%), Photosensitivity (3%), Panniculitis, including erythema nodosum (1%), New primary melanoma (1%)

Unresectable or Metastatic Melanoma - TAFINLAR in Combination with Trametinib

In addition to adverse reactions observed in the monotherapy studies, other clinically important adverse reactions reported in < 10% of patients or < 2% of patients with Grade 3 or 4 events treated with TAFINLAR 150 mg twice daily in combination with trametinib 2 mg once daily in the safety population from the phase III clinical trial include:

Blood and lymphatic system disorders: Thrombocytopenia (4%), Leukopenia (4%)

Cardiac disorders: Bradycardia (<1%)

Eye disorders: Vision blurred (3%), Visual impairment (2%), Periorbital oedema (<1%), Chorioretinopathy (<1%), Uveitis (<1%), Retinal detachment (<1%)

Gastrointestinal disorders: Dry mouth (8%), Stomatitis (1%), Pancreatitis (<1%), Colitis (<1%)

General disorders and administration site conditions: Mucosal inflammation (2%), Influenza-like illness (8%), Face oedema (2%)

Hepatobiliary disorders: Gamma-glutamyltransferase increased (2%), Blood alkaline phosphatase increased (8%)

Immune system disorders: Hypersensitivity (<1%)

Infections and infestations: Cellulitis (3%), Folliculitis (6%), Paronychia (2%), Rash pustular (3%)

Metabolism and nutrition disorders: Hyponatremia (2%), Dehydration (1%), Hypophosphatemia (4%)

Musculoskeletal and connective tissue disorders: Muscle spasm (9%), Blood creatine phosphokinase increased (3%)

Neoplasms benign, malignant and unspecified (including cysts and polyps): Seborrheic keratosis (4%), Skin papilloma (2%), Acrochordon (skin tags) (1%), New primary melanoma (<1%)

Renal and urinary disorders: Renal failure (<1%), Granulomatous/tubulointerstitial nephritis (<1%)

Respiratory, thoracic and mediastinal disorders: Dyspnoea (6%), Pneumonitis (<1%)

Skin and subcutaneous tissue disorders: Erythema (9%), Alopecia (9%), Night sweats (6%), Hyperhidrosis (7%), Hyperkeratosis (7%), Skin lesion (3%), Palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome) (5%), Actinic keratosis (5%), Urticaria (3%), Panniculitis, including erythema nodosum (3%), Skin fissures (2%), Photosensitivity (2%)

Vascular disorders: Deep vein thrombosis and pulmonary embolism (3%), Lymphedema (<1%)

Adjuvant Treatment of Melanoma - TAFINLAR in Combination with Trametinib

Other clinically important adverse reactions reported in < 10% of patients or < 2% of patients with Grade 3 or 4 events treated with TAFINLAR in combination with trametinib in the safety population from the adjuvant treatment of melanoma phase III clinical trial include:

Eye disorders: Blurred vision (6%), Uveitis (1%), Chorioretinopathy* (1%), Retinal detachment** (1%)

Investigations: Alkaline phosphatase increased (7%), Ejection fraction decreased (5%)

Musculoskeletal and connective tissue disorders: Rhabdomyolysis (<1%)

Renal and urinary disorders: Renal failure (<1%)

Skin and subcutaneous tissue disorders: Palmar-plantar erythrodysaesthesia syndrome (6%)

* Chorioretinopathy also includes chorioretinal disorder.
** Retinal detachment also includes detachment of macular retinal pigment epithelium and detachment of retinal pigment epithelium

Metastatic Non-Small Cell Lung Cancer (NSCLC) - TAFINLAR in Combination with Trametinib

Other clinically important adverse reactions reported in < 10% of patients or < 2% of patients with Grade 3 or 4 events treated with TAFINLAR in combination with trametinib in the safety population from the NSCLC phase II clinical trial include:

Eye disorders: Detachment of retina/retinal pigment epithelium (2%)

Gastrointestinal disorders: Pancreatitis acute (1%)

Renal and urinary disorders: Renal failure (3%)

Low-grade Glioma (LGG) - TAFINLAR in Combination with Trametinib

Other clinically important adverse reactions reported in < 10% of patients treated with TAFINLAR in combination with trametinib in the safety population from the study G2201 (LGG Cohort)

Blood and lymphatic system disorders: Leukopenia (4%), Thrombocytopenia (1%)

Cardiac disorders: Ejection fraction decreased (3%)

Eye disorders: Vision blurred (8%), Uveitis (5%), Detachment of retinal pigment epithelium (1%), Visual impairment (1%)

Gastrointestinal disorders: Stomatitis (8%), Colitis (1%), Pancreatitis (1%)

General disorders and administration site conditions: Chills (6%), Malaise (3%), Influenza like illness (1%), Oedema peripheral (3%), Face oedema (3%)

Infections and infestations: Skin infection (6%), Urinary tract infection (7%), Tonsilitis (4%)

Injury, poisoning and procedural complications: Contusion (4%), Procedural complications (3%)

Investigations: Blood alkaline phosphatase increased (10%), Blood creatine phosphokinase increased (4%), International normalised ratio increased (1%)

Metabolism and nutrition disorders: Decreased appetite (6%), Hyperglycaemia (3%), Hyponatraemia (3%), Dehydration (1%), Hypophosphataemia (1%)

Musculoskeletal and connective tissue disorders: Musculoskeletal stiffness (3%)

Nervous system disorders: Syncope (4%), Hydrocephalus (3%)

Respiratory, thoracic and mediastinal disorders: Apnoea (3%)

Skin and subcutaneous disorders: Panniculitis (8%), Dermatitis (6%), Skin lesion (6%), Skin exfoliation (3%), Alopecia (3%), Folliculitis (4%), Dermatitis exfoliative (1%), Night sweats (1%), Palmar-plantar erythrodysaesthesia syndrome (1%), Ecchymosis (1%)

Vascular disorders: Haematoma (3%)

High-grade Glioma (HGG) - TAFINLAR in Combination with Trametinib

Other clinically important adverse reactions reported in < 10% of patients treated with TAFINLAR in combination with trametinib in the safety population from the study G2201 (HGG Cohort)

Blood and lymphatic system disorders: Anaemia (10%), Leukopenia (7%), Thrombocytopenia (2%), Febrile neutropenia (2%)

Cardiac disorders: Ejection fraction decreased (10%), Bradycardia (2%)

Eye disorders: Vision blurred (2%), Blindness (5%), Papilloedema (5%), Exophthalmos (2%)

Gastrointestinal disorders: Stomatitis (7%), Pancreatitis (2%), Toothache (5%), Dysphagia (2%), Gastrointestinal haemorrhage (2%)

General disorders and administration site conditions: Oedema peripheral (10%), Influenza like illness (5%), Chills (2%), Face oedema (2%), Pain (2%)

Immune system disorders: Hypersensitivity (2%)

Infections and infestations: Paronychia (7%), Folliculitis (2%), Nasopharyngitis (5%), Urinary tract infection (7%), Brain abscess (2%), Encephalomyelitis (2%), Haematological infection (2%),Tooth abscess (2%), Viral infection (2%).

Injury, poisoning and procedural complications: Extradural hematoma (2%), Contusion (5%), Fracture (2%), Tooth avulsion (2%)

Investigations: Blood alkaline phosphatase increased (7%), Gamma-glutamyltransferase increased (5%), Transaminases increased (Includes alanine aminotransferase increased, aspartate aminotransferase increased, hypertransaminasaemia and transaminases increased) (10%), INR increased (2%), Ejection fraction decreased (10%), Neutrophil count decreased (5%), Amylase increased (2%), Body mass index increased (2%), C-reactive protein increased (2%), Lipase increased (2%), Platelet count decreased (2%), Protein urine present (2%).

Metabolism and nutrition disorders: Decreased appetite (7%), Dehydration (2%), Hyperglycaemia (2%), Hypernatraemia (7%), Hyponatraemia (2%), Hypophosphataemia (5%), Hypokalaemia (2%), Type 2 diabetes mellitus (2%)

Musculoskeletal and connective tissue disorders: Pain in extremity (10%), Muscle spasms (5%)

Nervous system disorders: Dizziness (10%), Ataxia (7%), Hydrocephalus (5%), Intracranial pressure increased (5%), Brain oedema (2%),Facial paralysis (2%), Hemiparesis (2%), Paresis (2%),Partial seizures (2%), Sciatica (2%), Syncope (2%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Skin papilloma (10%)

Renal and urinary disorders: Proteinuria (2%)

Reproductive system and breast disorders: Uterine haemorrhage (2%)

Psychiatric disorders: Anxiety (7%), Agitation (2%), Confusional state (2%), Mental status changes (2%)

Respiratory, thoracic and mediastinal disorders: Dyspnoea (5%), Atelectasis (2%)

Skin and subcutaneous disorders: Pruritus (10%), Dermatitis acneiform (10%), Skin lesion (5%), Alopecia (2%), Skin exfoliation (2%), Xeroderma (2%), Skin fissures (2%)

Vascular disorders: Hypertension (5%), Hypotension (5%)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Unresectable or Metastatic Melanoma - TAFINLAR Monotherapy

Table 14 Laboratory Abnormalities Increased from Baseline in the Unresectable or Metastatic Melanoma Phase III Study BRF113683*

Preferred Term	TAFINLAR	DTIC

	N = 187		N = 59	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hyperglycaemia	56	8	45	0
Hypophosphatemia	41	6	18	2
Hyponatremia	8	2	3	0
Increased Alkaline Phosphatase	23	0	16	2

*No grade 4 laboratory abnormalities in dabrafenib-treated or DTIC-treated patients were reported

Unresectable or Metastatic Melanoma - TAFINLAR in Combination with Trametinib

Table 15 Laboratory Abnormalities Changed from Baseline in the Phase III Unresectable or Metastatic Melanoma Study MEK115306

Preferred Term	MEK115306			
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 209)		TAFINLAR 150 mg BID + Placebo (N = 211)	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hyperglycaemia	65	6	57	4
Hypophosphatemia	38	4	35	7
Hyponatremia	24	6	14	3
Hypoalbuminemia	53	1	27	0
Creatinine	10	<1	7	<1
Increased Alkaline Phosphatase	50	<1	25	<1

Adjuvant Treatment of Melanoma - TAFINLAR in Combination with Trametinib

Table 16 Laboratory Abnormalities Changed from Baseline in the Phase III Adjuvant Treatment of Melanoma Study BRF115532

Test	TAFINLAR plus Trametinib N = 435		Placebo N = 432	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Haematology[a]				
Neutropenia	47	6	12	<1
Leukopenia	43	3	10	<1
Lymphopenia	26	5	6	<1
Anaemia	25	<1	6	<1
Liver Function Tests				
Increased AST[a]	57	6	11	<1
Increased ALT[a]	48	5	18	<1
Increased blood alkaline phosphatase[a]	38	1	6	<1
Chemistry				
Hyperglycaemia[a]	63	3	47	<1
Hypophosphatemia[a]	42	7	10	<1
Hypoalbuminemia[a]	25	<1	<1	0
Hyponatraemia [a]	16	3	3	<1

[a] For these laboratory tests the denominator varied from 429 to 431 for TAFINLAR plus trametinib and 426 to 428 for placebo

Metastatic Non-Small Cell Lung Cancer (NSCLC) - TAFINLAR in Combination with Trametinib

Table 17 Laboratory Abnormalities Changed from Baseline in the Phase II Study BRF113928

Preferred Term	Study BRF113928	
	TAFINLAR 150 mg BID + Trametinib 2 mg QD (N = 93)[1]	
	All Grades (%)	Grades 3 and 4[2] (%)
Hyperglycaemia	71	9
Hyponatraemia	57	17
Hypophosphataemia	36	7
Creatinine	21	1
Increased alkaline phosphatase	64	0
Increased AST	61	4
Anaemia	46	10
Leukocytopenia	48	8
Neutropenia	44	8
Lymphocytopenia	42	14
Thrombocytopenia	16	1

[1] For these laboratory tests the denominator is n = 90, except for leukocytopenia, neutropenia, lymphocytopenia and thrombocytopenia (n = 91)
[2] Grade 4 adverse reactions limited to AST increased (n =1), lymphocytopenia (n = 1), neutropenia (n = 1), hypophosphataemia (n = 1) and hyponatraemia (n = 1)

Low-grade Glioma and High-grade Glioma - TAFINLAR in Combination with Trametinib

Table 18 Laboratory Abnormalities (>20%) that Worsened from Baseline in Pediatric LGG Patients Treated with TAFINLAR in Combination with Trametinib in Study G2201

Laboratory Abnormality[b]	TAFINLAR plus Trametinib[a]		Carboplatin plus Vincristine	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hepatic				
Alkaline phosphatase increased	55	0	13	0
ALT increased	29	3	61	9
AST increased	37	1	55	0
Biochemistry				
Magnesium decreased	34	4	76	6
Magnesium increased	32	0	24	3
Hematology				
Hemoglobin decreased	46	0	94	36
Leukocytes decreased	59	0	91	18
Lymphocytes decreased	16	1	56	6
Lymphocytes increased	24	0	13	3
Neutrophils decreased	44	17	84	75
Platelets decreased	30	0	73	18

[a]The denominator used to calculate the rate varied from 70 to 73 in the D+T arm and 9 to 33 in the C+V arm based on the number of patients with a baseline value and at least one post-treatment value.

[b]Hyperglycemia has been previously reported during treatment with TAFINLAR in combination with trametinib. Accurate estimation of the frequency of hyperglycemia in pediatric LGG patients in Study G2201 could not be established due to limited data collection.

Table 19 Laboratory Abnormalities (>20%) that Worsened from Baseline in Pediatric HGG Patients Treated with TAFINLAR in Combination with Trametinib in Study G2201

Laboratory Abnormality[b]	TAFINLAR plus Trametinib[a]	
	All Grades (%)	Grade 3 or 4 (%)
Hepatic		
Alkaline phosphatase increased	46	0
ALT increased	25	0
AST increased	30	3
Biochemistry		
Calcium decreased	22	2
Magnesium decreased	34	0
Magnesium increased	27	0
Hematology		
Hemoglobin decreased	35	3
Leukocytes decreased	50	3
Lymphocytes decreased	28	5
Neutrophils decreased	46	15
Platelets decreased	23	3

[a]The denominator used to calculate the rate varied from 39 to 41 based on the number of patients with a baseline value and at least one post-treatment value.

[b]Hyperglycemia has been previously reported during treatment with TAFINLAR in combination with trametinib. Accurate estimation of the frequency of hyperglycemia in pediatric HGG patients in Study G2201 could not be established due to limited data collection.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been reported during post-approval use of TAFINLAR. These include spontaneous case reports as well as serious adverse events from registries, investigator sponsored studies, clinical pharmacology studies and exploratory studies in unapproved indications.

Cardiac disorders: There are post-marketing cases of Atrioventricular block (including atrioventricular block first degree, atrioventricular block second degree and atrioventricular block complete), Bundle branch block (including bundle branch block right and bundle branch block left) associated with the use of TAFINLAR when given in combination with trametinib.

Gastrointestinal: Gastrointestinal perforation

Immune system disorders: Sarcoidosis, Haemophagocytic lymphohistiocytosis

Metabolism and nutrition disorders: Tumour lysis syndrome

Musculoskeletal and connective tissue disorders: Rhabdomyolysis

Nervous system disorders: There are post-marketing cases of Peripheral neuropathy (including sensory and motor neuropathy) associated with the use of TAFINLAR when given as monotherapy or in combination with trametinib.

There are post-marketing cases of Guillain-Barré syndrome associated with the use of TAFINLAR when given in combination with trametinib.

Skin and subcutaneous tissue disorders:

Neutrophilic dermatoses (including acute febrile neutrophilic dermatosis [Sweet's syndrome], hidradenitis, dermatosis, pyoderma gangrenosum, and neutrophilic panniculitis), tattoo associated skin reaction.

Vascular disorders: Venous thromboembolism (VTE) (including pulmonary embolism, deep vein thrombosis, embolism and venous thrombosis)

9 Drug-Drug Interactions

9.1 Serious Drug Interactions

Dabrafenib is teratogenic and embryofoetal toxic in animals and is likely to reduce the effectiveness of oral contraceptives. Alternative means of contraception should be considered in women of childbearing potential taking TAFINLAR (see 9.4 Drug-Drug Interactions).

9.2 Drug Interactions Overview

Dabrafenib is a moderate to strong *in vivo* inducer of CYP3A4, a weak *in vivo* inducer of CYP2C9 and may induce other enyzmes or transporters including additional CYPs (CYP2B6, CYP2C8, CYP2C19), UDP glucuronosyltransferases (UGTs) and P-glycoprotein (P-gp). Dabrafenib is primarily metabolized by CYP2C8 and CYP3A4. Because dabrafenib induces CYPs involved in its own metabolism steady-state exposure to dabrafenib is lower than exposure following a single daily dose (see 10 CLINICAL PHARMACOLOGY).

Drug interactions have the potential to affect circulating concentrations of dabrafenib and its 3 predominant metabolites (hydroxy-, desmethyl- and carboxy-dabrafenib). The hydroxy and desmethyl metabolites have similar exposure and BRAF inhibitory activity compared to dabrafenib. The carboxy metabolite is less active but has >10-fold higher exposure compared to the parent drug and the other two metabolites (see 10.3 Pharmacokinetics).

The concomitant use of TAFINLAR with medicinal products known to prolong QTc interval or medicinal products able to induce torsades de pointes should be avoided if possible. Medicinal products that are generally accepted to carry the risk of QT prolongation and torsades de pointes include: Class IA (e.g. quinidine, disopyramide, procainamide), Class III (e.g. amiodarone, sotalol, ibutilide), or Class IC (e.g. flecainide), antiarrhythmic medicinal products, antipsychotics (e.g. chlorpromazine, haloperidol, pimozide), opioids (e.g. methadone), macrolide antibiotics (e.g. erythromycin), clarithromycin, quinolone antibiotics (e.g. moxifloxacin), antimalarials (e.g. chloroquine), GI stimulants or others (e.g. domperidone, droperidol).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 20 Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Midazolam	CT	Midazolam AUC ↓74%, C_{max} ↓61%	Dabrafenib is considered a moderate to strong inducer of CYP3A4.
Warfarin	CT	S-warfarin and of R-warfarin AUC ↓37% and ↓33%, C_{max} ↑18% and ↑19%	Dabrafenib is considered a weak inducer of CYP2C9. Potential loss of efficacy. Consider substitution. If co-administration of these medications is necessary, monitor patients for loss of efficacy.
Substrates of CYP2B6, CYP2C8, CYP2C19, and UGTs and P-gp	T	Decreased substrate concentration	Dabrafenib may induce other enzymes or transporters including CYP2B6, CYP2C8, CYP2C19, and UGTs and P-gp.
Hormonal contraceptives	T	Decreased substrate concentration	Potential loss of efficacy. Consider substitution. If co-administration of these medications is necessary, monitor patients for loss of efficacy (see 7.1 Special Populations).
Dexamethasone	T	Decreased substrate concentration	Potential loss of efficacy. Consider substitution. If co-administration of these medications is necessary, monitor patients for loss of efficacy.
OATP1B1 or OATP1B3 substrates such as statins	T	Transport inhibition	Caution is recommended.
Ketoconazole	CT	Dabrafenib AUC ↑71%, C_{max} ↑33%	Strong CYP3A4 inhibitors (e.g., ketoconazole, nefazodone, clarithromycin, ritonavir) should be avoided if possible and alternative agents should be considered during administration with TAFINLAR.
Gemfibrozil	CT	Dabrafenib AUC ↑47%	Strong CYP2C8 inhibitors (e.g. gemfibrozil) should be avoided if possible and alternative agents should be considered during administration with TAFINLAR.

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Rifampin	CT	Dabrafenib AUC ↓34%, C_{max} ↓27%	Co-administration with strong inducers of CYP3A4 and CYP2C8 (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St John's wort) should be avoided due to the possibility of sub-therapeutic exposure to dabrafenib. Monitor patients for loss of efficacy or consider substitutions of these medicinal products.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Effects of Dabrafenib on Other Drugs: In human hepatocytes, dabrafenib produced dose-dependent increases in CYP2B6 and CYP3A4 mRNA levels up to 32 times the control levels. In a clinical study of 12 patients, repeat-dose of dabrafenib lowered the C_{max} and AUC of a single-dose of midazolam, a CYP3A4 substrate, by 61 % and 74 %, respectively. In a separate trial in 14 subjects, repeat-dose dabrafenib decreased the single-dose AUC of S-warfarin (a substrate of CYP2C9) and of R-warfarin (a substrate of CYP3A4/CYP1A2) by 37 % and 33 %, respectively, with small increases in C_{max} (18 and 19 % respectively). Thus, dabrafenib is considered a moderate to strong inducer of CYP3A4 and a weak inducer of CYP2C9 at the recommended therapeutic dose and may induce other enzymes or transporters including CYP2B6, CYP2C8, CYP2C19, and UGTs and P-gp.

Co-administration of TAFINLAR with medications such as hormonal contraceptives (see 7 Reproductive Health: Female and Male Potential), warfarin, or dexamethasone may result in decreased concentrations and loss of their efficacy. Consider substitution of these medicinal products. If co-administration of these medications is necessary, monitor patients for loss of efficacy.

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

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

Effect of Other Drugs on Dabrafenib: Results of *in vitro* studies indicate that CYP2C8 and CYP3A4 are the primary CYP enzymes involved in the oxidative metabolism of dabrafenib while hydroxy-dabrafenib and desmethyl-dabrafenib are metabolized primarily by CYP3A4. Therefore, inhibitors or inducers of these enzymes have the potential to affect the PK of dabrafenib or its metabolites.

Patients experienced an increase in steady-state dabrafenib C_{max} (33%) and AUC (71%) with co-administration of the CYP3A4 inhibitor ketoconazole, and increases in the active

metabolites hydroxy- and desmethyl-dabrafenib (AUC increases of 82 and 68%, respectively). A decrease in exposure was noted for the less active carboxy-metabolite (AUC decrease of 16%). Co-administration of dabrafenib and gemfibrozil (a CYP2C8 inhibitor) resulted in an increase in steady-state dabrafenib AUC (47%) and no meaningful change in the concentrations of the metabolites. Strong CYP3A4 inhibitors (e.g., ketoconazole, nefazodone, clarithromycin, ritonavir) or CYP2C8 inhibitors (e.g. gemfibrozil) should be avoided if possible and alternative agents should be considered during administration with TAFINLAR.

Pharmacokinetic data showed a decrease in repeat-dose dabrafenib C_{max} (27%) and AUC (34%) upon co-administration with rifampin (CYP3A4/CYP2C8 inducer). There was an increase in C_{max} (85%) and AUC (73%) for carboxy-dabrafenib and a decrease in C_{max} (39%) and AUC (30%) for desmethyl-dabrafenib; no relevant change in AUC was noted for hydroxy-dabrafenib. Co-administration with strong inducers of CYP3A4 and CYP2C8 (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St John's wort) should be avoided due to the possibility of sub-therapeutic exposure to dabrafenib. Monitor patients for loss of efficacy or consider substitutions of these medicinal products.

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

Dabrafenib is a substrate of human P-glycoprotein (P-gp) and BCRP1 *in vitro*. However, these transporters have minimal impact on dabrafenib oral bioavailability and elimination, and the risk of a drug-drug interaction is minimal.

9.5 Drug-Food Interactions

High fat foods reduce the exposure to dabrafenib (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

TAFINLAR monotherapy: Dabrafenib is a selective, ATP-competitive small molecule inhibitor of RAF kinases, including BRAF.

Oncogenic amino acid variants in BRAF lead to constitutive activation of the mitogen-activated protein kinase (MAPK) pathway (including RAS/RAF/MEK/ERK) and may promote tumour cell growth. BRAF mutations have been identified in specific cancers, including approximately 50% of melanoma. The most commonly observed BRAF mutation, V600E, and the next most common, V600K, account for approximately 95% of BRAF mutations found in patients with melanoma. A number of less common substitutions include V600D, V600G and V600R.

Dabrafenib selectively inhibits BRAF V600E and other V600 mutations and with greater potency compared to wild-type BRAF in *in vitro* kinase inhibition assays. The concentration of dabrafenib required to inhibit 50% of enzyme activity (IC50) of each of the different BRAF proteins is shown in Table 21. The inhibitory activity of dabrafenib has not been determined for BRAF variants V600R, V600G and V600M.

Table 21 Inhibition of Different BRAF Variants by Dabrafenib

Kinase	IC_{50} (nM)
BRAF_wild-type	3.2
BRAF V600E	0.65
BRAF_V600D	1.84
BRAF_V600K	0.5

The results from the *in vitro* kinase assays were consistent with the inhibition of proliferation of melanoma cell lines. In addition, dabrafenib inhibited growth in a BRAF V600E positive NSCLC cell line with an IC_{50} value similar to those observed in BRAF mutation melanoma cell lines.

TAFINLAR in combination with trametinib: Trametinib is a small molecule inhibitor of mitogen-activated extracellular signal-regulated kinase 1 and 2 (MEK1 and MEK2). MEK1 and MEK2 are components of the MAPK pathway (including RAS/RAF/MEK/ERK). Dabrafenib and trametinib provide concomitant inhibition of the pathway at the level of the RAF and MEK kinases, respectively. The combination of dabrafenib with trametinib was synergistic in BRAF V600 mutation-positive melanoma and V600E mutated non-small cell lung carcinoma (NSCLC) cell lines and delayed the emergence of resistance in BRAF V600 mutation-positive melanoma xenografts.

10.2 Pharmacodynamics

Cardiac Electrophysiology: In a phase I, open-label, multiple-dose, dose escalation, first time-in-human study of dabrafenib in patients with solid tumours, serial ECG data were collected pre-dose and at 1, 2, 4, 6, and 8 h post-dosing on days 1, 8, and 15 of cycle 1 in temporal association with pharmacokinetic sampling. A statistically significant positive relationship was demonstrated between concentrations of the three major metabolites of dabrafenib and the QTc interval. At the 4 h time point, the mean increase in the QTc interval from baseline was 4.8 ms on day 1, 10.5 ms on day 8, and 6.6 ms on day 15 for all patients (N = 110). The mean increase in the QTc interval from baseline was 5.2 ms on day 1, 7.3 ms on day 8 and, 12.2 ms on day 15, in patients receiving a 150 mg twice daily dose (N = 20).

In a single-blind ECG assessment study in subjects with BRAF V600 mutation-positive tumours (N = 30), placebo was administered on Day -1 followed by a single dose of dabrafenib 300 mg on Day 1, dabrafenib 300 mg BID (twice the recommended dose) on Days 2 to 7, and a single dose of dabrafenib 300 mg on Day 8. ECG assessments performed on Days 1 and 8 showed an increase in heart rate, with statistically significant placebo-adjusted mean changes from baseline ranging from 3 to 12 bpm. No large changes in the mean QTc interval (i.e., > 20 ms) were detected.

Blood Pressure: TAFINLAR 150 mg BID was associated with decreases in systolic and diastolic blood pressure in the pivotal phase III study of patients with BRAF mutation-positive melanoma. During the first 18 weeks of treatment, the magnitude of the systolic blood pressure decrease averaged -4.0 to -7.5 mm Hg, while for diastolic blood pressure the decrease averaged -2.0 to -3.6 mm Hg.

10.3 Pharmacokinetics

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

Table 22 Pharmacokinetic Parameters of Dabrafenib Following a Single Dose and at Steady-State

	T_{max} (h) Median (Min, Max)	C_{max} (ng/mL) Geometric Mean (95% CI)	AUC[a] (ng*hr/mL) Geometric Mean (95% CI)	$t_{1/2}$ (hr) Geometric Mean (95% CI)
Single dose [b] (150 mg) N = 13 or 14	2.0 [d] (1.0, 4.0)	2160[d] (1601, 2914)	12120 [e] (9138, 16075)	8.4[e] (4.8, 14.5)
Repeat dose [c] (150 mg BID) Week 6, N = 17	1.9 (0.9, 6.0)	1478 (1229, 1777)	4341 (3599, 5235)	NA

CI = confidence interval; NA = not applicable

[a] AUC refers to AUC(0-∞) for single dose and AUC(0-τ) for repeat-dose

[b]. Data from phase I food effect study (fasting conditions)

[c] Data from steady-state phase III study (PK subset); d. N = 14; e. N = 13

Absorption: Dabrafenib is absorbed orally with a mean absolute bioavailability of 95% (with a lower 90% CI of 81%) and with a median time to achieve peak plasma concentration of 2 hours post-dose in the fasted state. Across a range of doses there was less than a dose-proportional increase after repeat twice daily dosing. There is a decrease in exposure observed with repeat dosing, due to induction of its own metabolism. The steady-state $AUC_{(0-\tau)}$ and C_{max} to single dose values were 0.73 and 1.0, respectively. Interpatient variability (CV%) in steady-state C_{max} and AUC for 14 patients in the phase III study was determined to be 37.1% and 37.7%, respectively. Single dose and steady-state PK parameters are shown in Table 22.

In a single dose study in healthy volunteers, the administration of dabrafenib as an oral suspension (10 x 10 mg tablets for suspension) resulted in a significantly lower exposure to dabrafenib than that observed following administration of dabrafenib capsules (2 x 50 mg). There was a decrease in the geometric means of AUC_{inf}, AUC_{τ}, and C_{max} by 20%, 21%, and 48.5%, respectively, with dabrafenib tablets for suspension relative to the dabrafenib capsules. A similar T_{max} was observed for dabrafenib following administration of both products. The difference in exposure is predicted to be smaller at steady state.

Administration of dabrafenib capsules with food reduced the bioavailability (C_{max} and AUC decreased by 51% and 31%, respectively) and delayed absorption of dabrafenib when compared to the fasted state (see 4 DOSAGE AND ADMINISTRATION).

Distribution: Dabrafenib and its metabolites hydroxy-, carboxy-, and desmethyl-dabrafenib, are highly bound to plasma proteins with percent bound of 99.7, 96.3, 99.5, and 99.9%, respectively. The apparent volume of distribution of dabrafenib (Vc/F) is 70.3 L.

Metabolism: The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidized via CYP3A4 to form carboxy-dabrafenib. Carboxy-dabrafenib can be decarboxylated via a non-enzymatic process to form desmethyl-dabrafenib. Carboxy-dabrafenib is excreted in bile and urine. Desmethyl-dabrafenib may also be formed in the gut and reabsorbed. Desmethyl-dabrafenib is metabolized by CYP3A4 to oxidative metabolites. Hydroxy-dabrafenib terminal half-life parallels that of parent with a half-life of 10 hours while the carboxy- and desmethyl-metabolites exhibited longer half-lives (21 to

22 hours). Mean metabolite to parent AUC ratios following repeat-dose administration were 0.9, 11 and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib.

Elimination: Dabrafenib terminal half-life is 8 hours after oral administration. Apparent clearance was estimated to be 34.6 L/h using the recommended 150 mg BID dosing regimen. Faecal excretion is the major route of elimination after oral dosing, accounting for 71% of a radioactive dose while urinary excretion accounted for 23% of radioactivity.

Combination with Trametinib: Co-administration of TAFINLAR 150 mg twice daily and trametinib 2 mg once daily resulted in a 16% increase in dabrafenib C_{max} and 25% increase in AUC at steady-state. A small decrease in trametinib bioavailability was also observed with the combination therapy, corresponding to a decrease in the trametinib AUC of 12% (estimated by Population PK analysis).

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of dabrafenib in glioma and other solid tumours were evaluated in 243 pediatric patients (1 to <18 years old) following single or repeat age- and weight-adjusted dosing. The pharmacokinetic exposures of dabrafenib in pediatric patients were within range of those previously observed in adults given the same dose based on weight. Weight was found to influence dabrafenib oral clearance.
- **Geriatrics:** Based on a population pharmacokinetic analysis, age had no relevant clinical effect on dabrafenib pharmacokinetics. Age greater than 75 years was a significant predictor of carboxy- and desmethyl-dabrafenib plasma concentrations with a 40% greater exposure in patients ≥ 75 years of age, relative to patients < 75 years' old.
- **Sex/Weight:** Based on the adult population pharmacokinetic analysis, gender and weight were found to influence dabrafenib oral clearance (<20%); weight also impacted oral volume of distribution and distributional clearance.
- **Ethnic Origin:** Based on the population pharmacokinetic analysis, oral dabrafenib clearance (CL/F) is similar in Asian and Caucasian cancer patients with similar liver function. There are insufficient data to evaluate the potential effect of other races/ethnicities on dabrafenib pharmacokinetics.
- **Hepatic Insufficiency:** The pharmacokinetics of dabrafenib were characterized in 65 patients with mild hepatic impairment (based on National Cancer Institute [NCI] classification) enrolled in clinical trials using a population analysis. Dabrafenib oral clearance was not significantly different between these patients and patients with normal hepatic function (4% difference). In addition, mild hepatic impairment did not have a significant effect on dabrafenib metabolite plasma concentrations. Administration of TAFINLAR in patients with moderate to severe hepatic impairment has not been studied and may lead to increased exposure to dabrafenib and its metabolites and the possibility of increased toxicities (see 4 DOSAGE AND ADMINISTRATION).
- **Renal Insufficiency:** The pharmacokinetics of dabrafenib were characterized in 233 patients with mild renal impairment (GFR 60 to 89 mL/min/1.73 m2) and 30 patients with moderate renal impairment (GFR 30 to 59 mL/min/1.73 m2) enrolled in clinical trials using a population analysis. The effect of mild or moderate renal impairment on

dabrafenib oral clearance was small (<6% for both categories) and not clinically relevant. In addition, mild and moderate renal impairment did not have a significant effect on hydroxy-, carboxy-, and desmethyl-dabrafenib plasma concentrations. No data are available in patients with severe renal impairment (see 4 DOSAGE AND ADMINISTRATION).

11 Storage, Stability, and Disposal

Capsules

Store between 15 - 30°C.

Tablets for Suspension

Store between 15 - 25°C.

Protect from moisture. Do not remove the desiccant.

After suspension (tablets dispersed in water) in the provided dosing cup, keep the suspension at 15-25°C. Discard suspension if not administered within 30 minutes after preparation.

12 Special Handling Instructions

Not applicable

Part 2: Scientific Information

13 Pharmaceutical Information

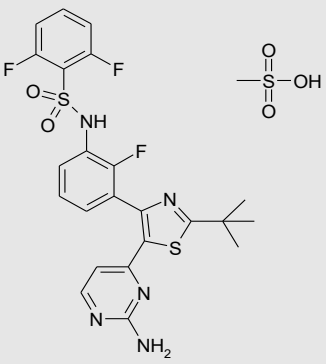
Drug Substance

Non-proprietary name of the drug substance(s): Dabrafenib mesylate

Chemical name: N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methanesulfonate salt

Molecular formula and molecular mass: $C_{23}H_{20}F_3N_5O_2S_2$. CH_4O_3S
519.57 g/mol (dabrafenib free base)
615.6 g/mol (dabrafenib mesylate)

Structural formula:



Physicochemical properties: Dabrafenib mesylate is a white to slightly coloured solid. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.

14 Clinical Trials

14.1 Clinical Trials by Indication

Unresectable or Metastatic Melanoma - TAFINLAR Monotherapy

Table 23 Summary of Patient Demographics for Clinical Trials in Unresectable or Metastatic Melanoma - TAFINLAR Monotherapy

Study #	***Study design***	***Dosage, route of administration and duration***	***Study subjects (n)***	***Mean age (Range)***	***Sex* n (%)**
BRF113683 *Treatment-Naïve Patients*	Phase III randomized (3:1, stratified by disease stage), open-label, efficacy and safety study comparing TAFINLAR to dacarbazine (DTIC) in previously untreated patients with BRAF V600E mutation-positive advanced (Stage III unresectable) or metastatic (Stage IV) cutaneous melanoma.	TAFINLAR 150 mg orally twice daily or intravenous DTIC 1000 mg/m2 every 3 weeks	**TAFINLAR** (N = 187)	**Age (years) Median (Min-Max)** 53.0 (22-93) **Age Group, n (%)** < 65: 146 (78) ≥ 65: 41 (22)	***Female*** 75 (40) ***Male*** 112 (60)
			DTIC (N = 63)	**Age (years) Median (Min-Max)** 50.0 (21-82) **Age Group, n (%)** < 65: 51 (81) ≥ 65: 12 (19)	***Female*** 26 (41) ***Male*** 37 (59)
BRF113929 *Patients with Brain Metastases with or without Prior Local Treatment*	Phase II open-label, efficacy and safety study of TAFINLAR in patients with histologically confirmed (Stage IV) BRAF V600E or BRAF V600K mutation, and melanoma metastatic to the brain. Cohort A: No prior local therapy for brain metastases. Cohort B: Prior local therapy for brain metastases.*	TAFINLAR 150 mg orally twice daily	**TAFINLAR** (N =172)	**Median age** 52.5 years	**Male** 70%
BRF113710 *Patients Who Were Previously Untreated or Failed at Least One Prior Systemic Therapy*	Phase II open-label, single-arm, efficacy and safety study of TAFINLAR in patients with BRAF V600E or BRAF V600K mutation-positive metastatic melanoma (Stage IV) who were previously-untreated or who had failed at least one prior systemic therapy.		**TAFINLAR** (N = 92)	**Median age** 55.5 years	**Male** 53%

* Prior treatment for patients in Cohort B included brain surgery, whole-brain radiation therapy and stereotactic radiosurgery.

Study BRF113683

The efficacy and safety of TAFINLAR in previously untreated patients with BRAF V600E mutation-positive advanced (Stage III unresectable) or metastatic (Stage IV) cutaneous melanoma were evaluated in study BRF113683 comparing TAFINLAR to dacarbazine (DTIC) (Table 23).

Patients were permitted to have prior IL-2 treatment, surgery and radiotherapy. The primary objective was to evaluate the efficacy of TAFINLAR compared to DTIC with respect to progression-free survival (PFS) per investigator assessment. Secondary efficacy endpoints included comparison of overall survival (OS), overall response rate (ORR), duration of response and health-related quality of life (HRQoL) status.

Patients were randomized (3:1) to receive either TAFINLAR 150 mg twice daily or intravenous DTIC 1000 mg/m^2 every 3 weeks. Randomization was stratified according to disease stage. Patients on the DTIC arm were permitted to cross over to TAFINLAR after initial progression

Study demographics and baseline characteristics were balanced between treatment groups (Table 24).

Table 24 Baseline Characteristics - Study BRF113683

	TAFINLAR (N = 187)	**DTIC (N = 63)**
ECOG PS at Baseline, n (%)		
ECOG PS = 0	124 (66)	44 (70)
ECOG PS ≥ 1	62 (33)	16 (25)
Unknown	1 (< 1)	3 (5)
Baseline LDH, n (%)		
≤ ULN	119 (64)	43 (68)
> ULN	67 (36)	19 (30)
Unknown	1 (< 1)	1 (2)
TNM staging at Screening: distant metastasis, n (%)		
M0	6 (3)	1 (2)
M1a	23 (12)	10 (16)
M1b	34 (18)	12 (19)
M1c	124 (66)	40 (63)

ECOG = Eastern Cooperative Oncology Group; PS = performance status

Efficacy results are presented in Table 25 and Figure 1.

Table 25 Results of Study BRF113683 in Unresectable or Metastatic Melanoma - TAFINLAR Monotherapy

Primary Endpoints	**Associated value and statistical significance for TAFINLAR (N = 187)**	**Associated value and statistical significance for DTIC (N = 63)**
PFS	Median, months (95% CI) 5.1 (4.9, 6.9)	Median, months (95% CI) 2.7 (1.5, 3.2)
	HR (95% CI) 0.30 (0.18, 0.51) p <0.0001	

OS[a]	% at 6 months (95% CI) 87 (79.2, 91.9)		% at 6 months (95% CI) 79 (59.7, 89.5)	
	HR (95% CI) 0.61 (0.25, 1.48)			
ORR	CR, n (%) PR, n (%) ORR (CR+PR), n (%) (95% CI)	6 (3) 93 (50) 99 (53) (45.5, 60.3)	CR, n (%) PR, n (%) ORR (CR+PR), n (%) (95% CI)	0 12 (19) 12 (19) (10.2, 30.9)
Duration of Response	N = 99 Median, months (95% CI) 5.6 (4.8, NR)		N = 12 Median, months (95% CI) NR (5.0, NR)	

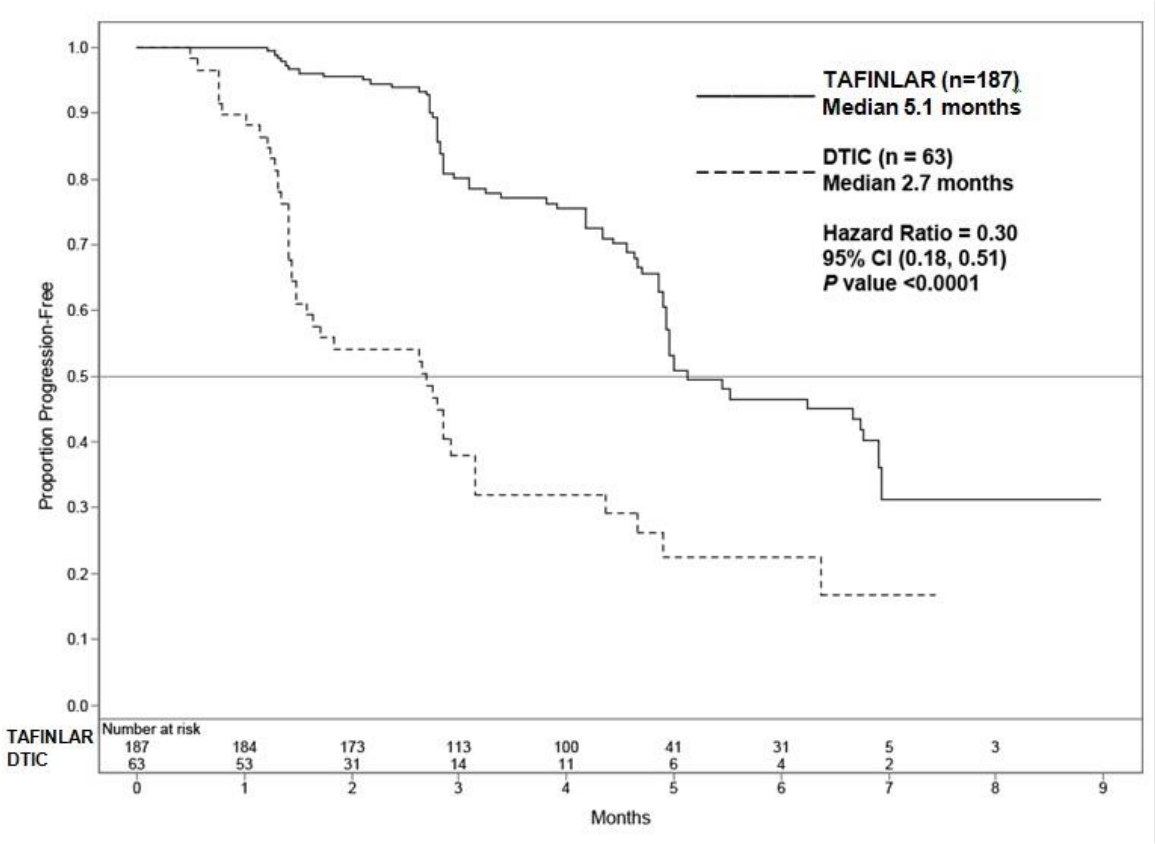
DTIC = dacarbazine, PFS = Progression-free Survival; CI: confidence interval; HR = Hazard Ratio; ORR = Overall Response Rate; CR = Complete Response; PR = Partial Response, NR = not reached
[a] Includes patients from DTIC arm (44%) who crossed over to TAFINLAR post-progression

Treatment with TAFINLAR monotherapy was associated with a statistically significant improvement on the primary endpoint, investigator-assessed PFS, compared to treatment with DTIC (HR 0.30, 95% CI: 0.18, 0.51; p <0.0001). This represents a relative reduction of 70% in the risk of disease progression or death compared with DTIC. Across subgroups, a consistent PFS benefit of the same magnitude as the overall study population was seen. Independent reviewer-assessed PFS results were consistent with investigator-assessed results.

The secondary endpoint of investigator assessed best confirmed ORR favoured dabrafenib over DTIC (see Table 25). Overall survival data were not mature at the time of the study's primary analysis.

There was no statistically significant difference in health-related quality of life (HRQOL), as measured by the EORTC QLQ C-30 questionnaire, between patients treated with TAFINLAR vs. DTIC.

Figure 1 Kaplan-Meier Curves for PFS - Study BRF113683



Study BRF113929

The efficacy and safety of TAFINLAR 150 mg twice daily were evaluated in a two-cohort phase II study (BRF113929) in patients with histologically confirmed (Stage IV) BRAF mutation-positive (V600E or V600K) melanoma metastatic to the brain (Table 23). Patients enrolled had no prior local therapy for brain metastases (Cohort A) or had received prior local therapy for brain metastases (Cohort B). Prior treatment for patients in Cohort B included brain surgery, whole-brain radiation therapy and stereotactic radiosurgery. The study employed modified RECIST criteria. Smaller lesions were allowed (≥ 5 mm) and up to 5 target lesions in the brain could be used.

In both cohorts, the majority of patients were male (70%), all were Caucasian, and the median age was 52.5 years. All patients had ECOG status of 0 or 1, all patients had measurable intracranial disease at baseline (100% M1c), and 89% also had measurable extracranial disease.

Investigator and independent-radiologist assessed overall intracranial response rates (OIRR) for Cohorts A and B are presented by BRAF mutation status (V600E and V600K) in Table 26.

Table 26 Results of Study BRF113929 in Unresectable or Metastatic Melanoma – TAFINLAR Monotherapy

Primary Endpoints	Associated value and statistical significance of TAFINLAR				Associated value and statistical significance for Placebo or active control
Investigator-assessed OIRR		**All Treated Patients**			Not Applicable
		BRAF V600E		**BRAF V600K**	
		Cohort A N = 74	**Cohort B N = 65**	**Cohort A N = 15**	**Cohort B N = 18**
	%	39	31	7	22
	(95% CI)	(28.0, 51.2)[a]	(19.9, 43.4)[a]	(0.2, 31.9)	(6.4, 47.6)
	CR	3	0	0	0
	PR	36	31	7	22
Independent radiologist-assessed OIRR		**All Treated Patients**			
		BRAF V600E		**BRAF V600K**	
		Cohort A N = 74	**Cohort B N = 65**	**Cohort A N = 15**	**Cohort B N = 18**
	%	20	18	0	11
	(95% CI)	(11.8, 31.2)	(9.9, 30.0)	(0.0, 21.8)	(1.4, 34.7)
	CR	1	0	0	0
	PR	19	18	0	11

Cohort A: patients with no prior local therapy for brain metastasis
Cohort B: patients who received prior local therapy for brain metastasis
CR = Complete Response; PR = Partial Response
[a] p <0.001. This study was designed to support or reject the null hypothesis of OIRR ≤10% (based on historical results) in favour of the alternative hypothesis of OIRR ≥30% in BRAF V600E positive subjects

In both cohorts, patients with BRAF V600E mutation-positive melanoma had better overall intracranial responses than patients with BRAF V600K mutation-positive melanoma. Overall intracranial response rates were higher by investigator-assessments compared to independent-radiologist assessments.

Study BRF113710

The efficacy and safety of TAFINLAR were evaluated in a phase II study (BRF113710) of patients with BRAF (V600E or V600K) mutation-positive metastatic melanoma (Stage IV) (Table 23). The majority (80%) had received prior chemotherapy (cytotoxic/non cytotoxic) in the unresectable or metastatic setting, while the remainder were considered treatment naïve for systemic therapy (20%).

In this study, 53% of patients were male and 99% were Caucasian; the median age was 55.5 years. Patients were either ECOG status 0 (55%) or ECOG status 1 (45%); 63% had M1c disease stage; and 62% had baseline LDH equal to or below ULN.

Results of Study BRF113710 in Unresectable or Metastatic Melanoma - TAFINLAR Monotherapy

Confirmed ORR for patients with BRAF V600E metastatic melanoma (n = 76) and V600K (n = 16) metastatic melanoma were reported by both investigator and independent radiologist assessments. There were greater numbers of overall responses for V600E patients of 59% and 41% by investigator and independent-radiologist reviews, respectively compared to V600K patients (ORR of 13% and 25% by investigator and independent radiologist reviews, respectively). Complete responses (CR) were only reported for the V600E patient population (7% and 3% by investigator and independent radiologist assessments, respectively).

Unresectable or Metastatic Melanoma - TAFINLAR in Combination with Trametinib

Table 27 Summary of Patient Demographics for Clinical Trials in Unresectable or Metastatic Melanoma - TAFINLAR in Combination with Trametinib

Study #	***Study design***	***Dosage, route of administration and duration***	***Study subjects (n)***	***Mean age (Range)***	***Sex* n (%)**
MEK115306	Phase III, randomized, double-blind study comparing the combination of TAFINLAR and trametinib to TAFINLAR and placebo as first-line therapy for subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma.	TAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily	**TAFINLAR + Trametinib** (N = 211)	**Age (years) Median (Min-Max)** 55.1 (22, 89) **Age Group, n (%)** < 65: 154 (73) ≥ 65: 57 (27)	***Female*** 100 (47) ***Male*** 111 (53)
			TAFINLAR + Placebo (N = 212)	**Age (years) Median (Min-Max)** 56.5 (22, 86) **Age Group, n (%)** < 65: 151 (71) ≥ 65: 61 (29)	***Female*** 98 (46) ***Male*** 114 (54)

MEK115306 was a phase III, randomized, double-blind study comparing the combination of TAFINLAR and trametinib to TAFINLAR and placebo as first-line therapy for subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma (Table 27).

Screening for eligibility included central laboratory testing for BRAF V600 mutation using a BRAF mutation assay conducted on the most recent tumour sample available from either a primary tumour or a tumour from a metastatic site.

Patients were not allowed to have prior systemic anti-cancer treatment in the unresectable or metastatic setting, although prior systemic treatment in the adjuvant setting was allowed. The primary endpoint was investigator-assessed PFS, which was to be assessed after 193 events (progression or death) were observed (Primary PFS Analysis); upon formal declaration of a data cut based on the 193 known events, an additional 18 progressions were discovered during the data retrieval and cleaning process. Secondary endpoints ORR and duration of response were reported at the time of this primary PFS analysis.

The secondary endpoint OS analysis was to be performed when 220 events (death) had occurred (Final OS Analysis).

Patients were stratified by lactate dehydrogenase (LDH) level (above the upper limit of normal [ULN] versus ≤ ULN) and BRAF mutation (V600E versus V600K). Crossover was not allowed.

TAFINLAR and trametinib were administered at their recommended monotherapy doses of 150 mg twice daily and 2 mg once daily, respectively.

Study demographics were balanced between treatment arms. Baseline disease characteristics and prognostic factors were well balanced between the treatment arms, with the exception of the occurrence of visceral disease, which was higher in the combination therapy arm compared with the TAFINLAR monotherapy arm (Table 28).

Table 28 Baseline Characteristics - Study MEK115306

	TAFINLAR + Trametinib (N = 211)	**TAFINLAR + Placebo (N = 212)**
ECOG PS at Baseline, n (%)		
0	155 (73)	150 (71)
1	55 (26)	61 (29)
Baseline LDH, n (%)		
≤ ULN	133 (63)	140 (66)
> ULN	77 (36)	71 (33)
Visceral Disease at Baseline, n (%)		
Yes	165 (78)	145 (68)
No	46 (22)	66 (31)
BRAF Mutation Status, n (%)		
V600E	179 (85)	181 (85)
V600K[a]	32 (15)	30 (14)
(M stage) at Screening, n (%)		
M0	5 (2)	10 (5)
M1a	19 (9)	31 (15)
M1b	45 (21)	32 (15)
M1c	142 (67)	138 (65)

[a] One subject was both BRAF V600E and BRAF V600K mutation-positive and is included in the V600K subset in this display.
ECOG = Eastern Cooperative Oncology Group; PS = performance status

Efficacy results are presented in Table 29 and in Figure 2 and Figure 3.

Table 29 Results of Study MEK115306 in Unresectable or Metastatic Melanoma – TAFINLAR in Combination with Trametinib

	Associated value and statistical significance for TAFINLAR +	**Associated value and statistical significance for TAFINLAR +**

	Trametinib	Placebo
Primary Endpoints		
PFS	**(N = 211)**	**(N = 212)**
	Primary Analysis*	
	Median, months (95% CI) 9.3 (7.7, 11.1)	Median, months (95% CI) 8.8 (5.9, 10.9)
	HR (95% CI) and log-rank p-value[a] 0.75 (0.57, 0.99) p = 0.035	
	Updated Analysis*	
	Median, months (95% CI) 11.0 (8.0, 13.9)	Median, months (95% CI) 8.8 (5.9, 9.3)
	HR (95% CI) and log-rank p-value[a] 0.67 (0.53, 0.84) p < 0.001	
Secondary endpoints		
ORR[d]	**N = 210**	**N = 210**
	Primary Analysis*	
	CR, n (%) 22 (10) PR, n (%) 118 (56) ORR (CR+PR), n (%) 140 (67) (95% CI) (59.9, 73.0)	CR, n (%) 18 (9) PR, n (%) 90 (43) ORR (CR+PR), n (%) 108 (51) (95% CI) (44.5, 58.4)
	Updated Analysis*	
	CR, n (%) 33 (16) PR, n (%) 111 (53) ORR (CR+PR), n (%) 144 (69) (95% CI) (61.8, 74.8)	CR, n (%) 28 (13) PR, n (%) 84 (40) ORR (CR+PR), n (%) 112 (53) (95% CI) (46.3, 60.2)
Duration of Response	**Primary Analysis***	
	Median, months (95% CI) **N = 140** 9.2 (7.4, NR)	Median, months (95% CI) **N = 109** 10.2 (7.5, NR)
	Updated Analysis*	
	Median, months (95% CI) **N = 144** 12.9 (9.4, 19.5)	Median, months (95% CI) **N = 113** 10.6 (9.1, 13.8)
OS	**(N = 211)**	**(N = 212)**
	Interim Analysis	
	Died (%) 40 (19)	Died (%) 55 (26)
	HR (CI) and log-rank p-value[a] 0.63 (0.30, 1.32)[b]	
	Median, months (95% CI)	

	NR	
	Final Analysis	
	Died (%) 99 (47)	Died (%) 123 (58)
	HR (CI) and log-rank p-value[a] 0.71 (0.55, 0.92)[c] p = 0.011	
	Median, months (95% CI) 25.1 (19.2, NR)	Median, months (95% CI) 18.7 (15.2, 23.7)

***Primary analysis data cut: 26 August 2013, Final OS data cut: 12 January 2015**

PFS = Progression-Free Survival; CI = Confidence Interval; HR = Hazard Ratio; CR = Complete Response; ORR = Overall response rate; PR = Partial Response; NR = Not Reached

[a] Hazard ratio and log-rank p-value are adjusted for randomized strata: baseline LDH and BRAF mutation status

[b] The stopping boundary for overall survival (one-sided alpha) for this interim analysis is based on the available information (95 events), and is 0.00014. Confidence interval is based on the allocated alpha. The results were not statistically significant.

[c] 95% CI

[d] Includes only patients with measurable disease at baseline

Treatment with the combination therapy resulted in a statistically significant improvement in investigator-assessed PFS compared with TAFINLAR monotherapy treatment (HR 0.75; 95% CI: 0.57, 0.99; p = 0.035). This represents a 25% reduction in risk of tumour progression or death in the combination therapy arm compared with TAFINLAR monotherapy. Median PFS for the combination therapy arm was 9.3 months compared with 8.8 months for the TAFINLAR monotherapy arm. Independent reviewer assessed PFS results were not statistically significant (HR 0.78; 95% CI: 0.59, 1.04).

The secondary endpoint of investigator assessed best-confirmed ORR favoured the combination therapy over dabrafenib monotherapy.

Figure 2 Kaplan-Meier Curves for PFS Primary Analysis (ITT Population) – Study MEK115306

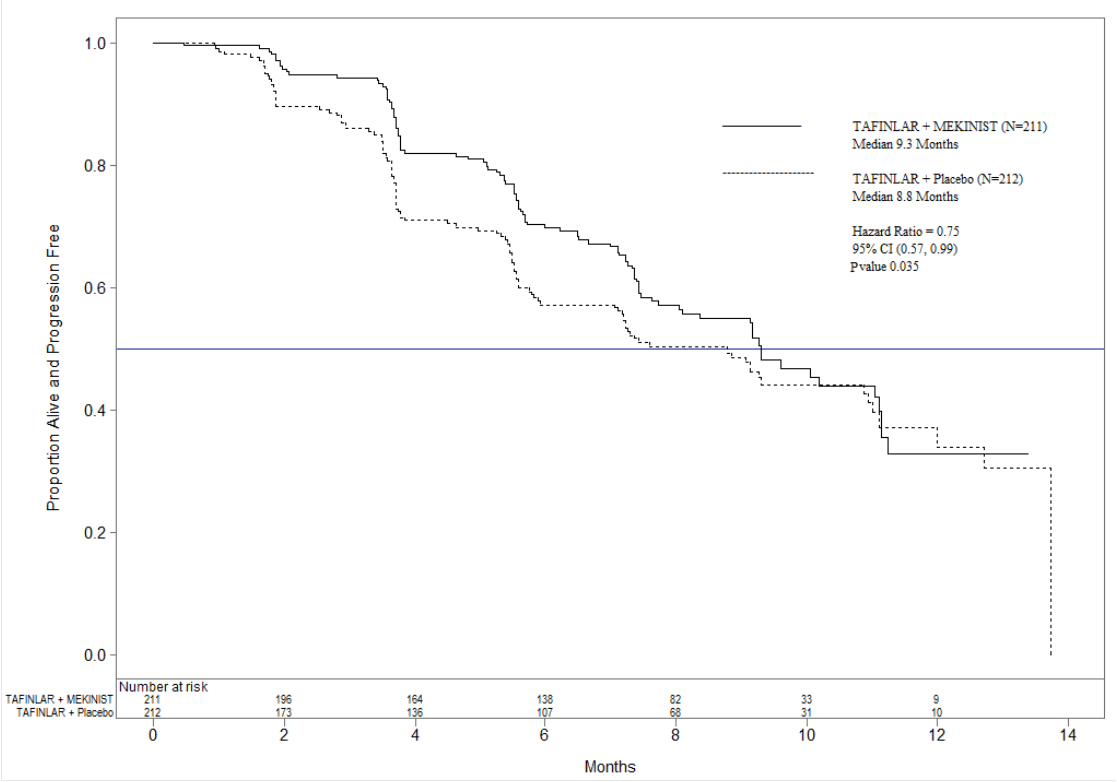
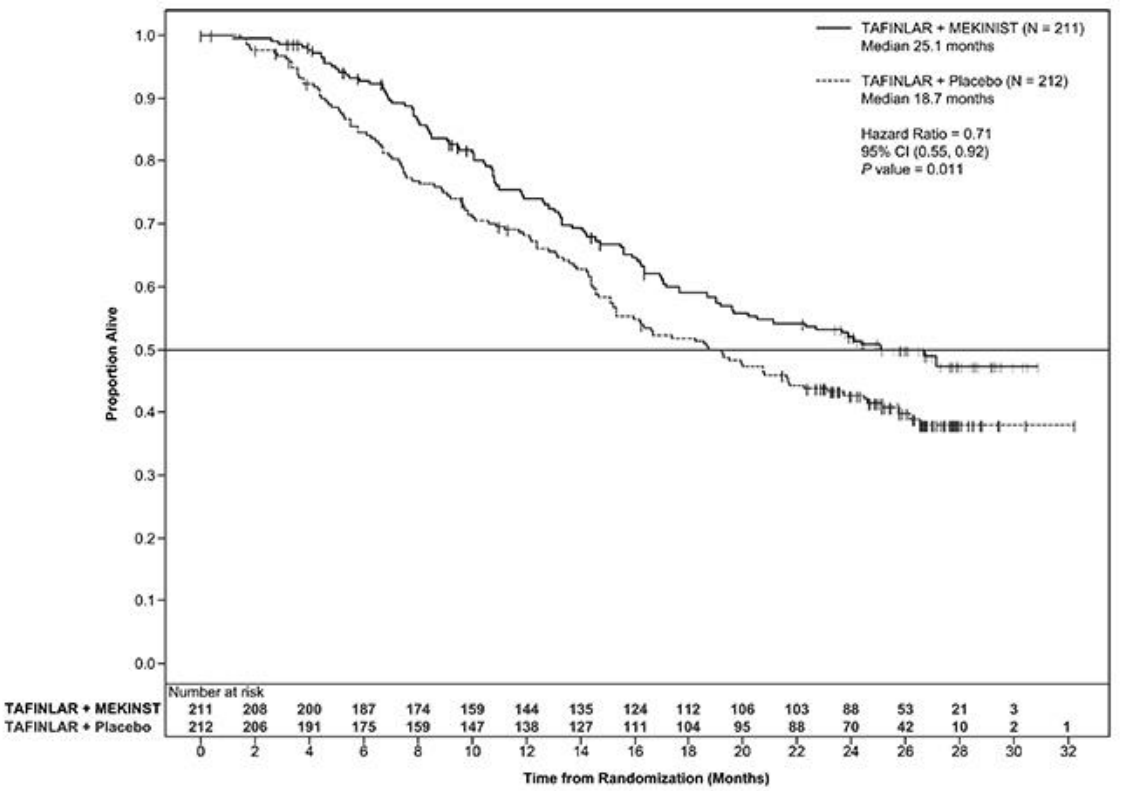

1.0
0.8
0.6
0.4
0.2
0.0
Proportion Alive and Progression Free
TAFINLAR + MEKINIST (N=211)
Median 9.3 Months
TAFINLAR + Placebo (N=212)
Median 8.8 Months
Hazard Ratio = 0.75
95% CI (0.57, 0.99)
Pvalue 0.035
Number at risk
TAFINLAR + MEKINIST 211 196 164 138 82 33 9
TAFINLAR + Placebo 212 173 136 107 68 31 10
0 2 4 6 8 10 12 14
Months

Figure 3 Kaplan-Meier Curves for Final OS (ITT population) – Study MEK115306



The OS analysis at 5 years shows an estimated survival rates of 32% for the combination of TAFINLAR and trametinib versus 27% for TAFINLAR monotherapy (HR 0.80, 95 % CI 0.63-1.01); the median OS for the combination arm was 25.8 months compared to 18.7 months for TAFINLAR monotherapy.

Adjuvant Treatment of Melanoma – TAFINLAR in Combination with Trametinib

Table 30 Summary of Patient Demographics for Clinical Trials in Adjuvant Treatment of Melanoma – TAFINLAR in Combination with Trametinib

Study #	***Study design***	***Dosage, route of administration and duration***	***Study subjects (n)***	***Mean age (Range)***	***Sex* n (%)**
BRF115532 *Phase III Pivotal Study*	Phase III, multi-centre, randomized (1:1), double-blind, placebo-controlled study of TAFINLAR in combination with trametinib in the adjuvant treatment of patients with Stage III melanoma with a BRAF V600 mutation, following resection.	TAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily or two placebos for 12 months.	**TAFINLAR + Trametinib** (N = 438)	**Age (years) Median (Min-Max)** 50.0 (18,89) **Age Group, n (%)** < 65: 353 (81%) ≥ 65: 85 (19%)	***Female*** 195 (45%) ***Male*** 243 (55%)
			Placebo (N = 432)	**Age (years) Median (Min-Max)** 51.0 (20,85)	***Female*** 193 (45%) ***Male***

				Age Group, n (%) < 65: 359 (83%) ≥ 65: 73 (17%)	239 (55%)

The efficacy and safety of TAFINLAR in combination with trametinib in the adjuvant treatment of patients with Stage III melanoma with a BRAF V600 mutation, following resection was evaluated in a phase III, multi-centre, randomized, double-blind, placebo-controlled study (BRF115532) (Table 30). Screening for the study included central laboratory testing of BRAF mutation (V600E or V600K) using a BRAF mutation assay conducted at baseline.

Patients were randomized 1:1 to receive either dabrafenib and trametinib combination therapy (TAFINLAR 150 mg twice daily and trametinib 2 mg once daily) or two placebos for a period of 12 months. Enrolment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomization. Any prior systemic anticancer treatment, including radiotherapy, was not allowed. Patients with a history of prior malignancy, if disease-free for at least 5 years, were eligible. Patients presenting with malignancies with confirmed activating RAS mutations were not eligible. Patients were stratified by BRAF mutation status (V600E or V600K) and stage of disease prior to surgery (by Stage III sub-stage, indicating different levels of lymph node involvement and primary tumour size and ulceration). The primary endpoint was investigator-assessed relapse-free survival (RFS), defined as the time from randomization to disease recurrence or death from any cause. Radiological tumour assessment was conducted every 3 months for the first two years and every 6 months thereafter, until first relapse was observed. The key secondary endpoint was overall survival (OS). The median duration of follow-up (time from randomization to last contact or death) was 2.83 years in the dabrafenib and trametinib combination arm and 2.75 years in the placebo arm.

The baseline characteristics of the patients were well balanced in the two groups. In both groups, 91% had a BRAF V600E mutation and 9% had a BRAF V600K mutation (Table 31).

Table 31 Baseline Characteristics – Study BRF115532

	TAFINLAR + Trametinib (N = 438)	Placebo (N = 432)
Race, n (%)		
White	432 (99%)	427 (99%)
Asian	6 (1%)	5 (1%)
Primary Tumour Type		
Melanoma	438 (100%)	432 (100%)
Time Since Initial Diagnosis (months)		
1st Quartile	4	4
Median	5.0	6.0
3rd Quartile	19	20
Min. – Max.	1 – 306	0 – 351
Stage at Screening*		
IIIA	83 (19%)	71 (16%)
IIIB	169 (39%)	187 (43%)
IIIC	181 (41%)	166 (38%)
Unknown	5 (1%)	8 (2%)
Primary Tumour Ulceration		
Yes	179 (41%)	177 (41%)
No	253 (58%)	249 (58%)
Missing	6 (1%)	6 (1%)
In-transit Disease		
Yes	51 (12%)	36 (8%)
No	387 (88%)	395 (91%)
Missing	0	1 (<1%)
BRAF Mutation Status, n (%)		
V600E	400 (91%)	395 (91%)
V600K	38 (9%)	37 (9%)

* Per the American Joint Committee on Cancer (AJCC) – Melanoma of the Skin Staging – 7th Edition

Results for the primary analysis of RFS are presented in Figure 4 and in Table 32.

Table 32 Results of Study BRF115532 in Adjuvant Treatment of Melanoma – TAFINLAR in Combination with Trametinib

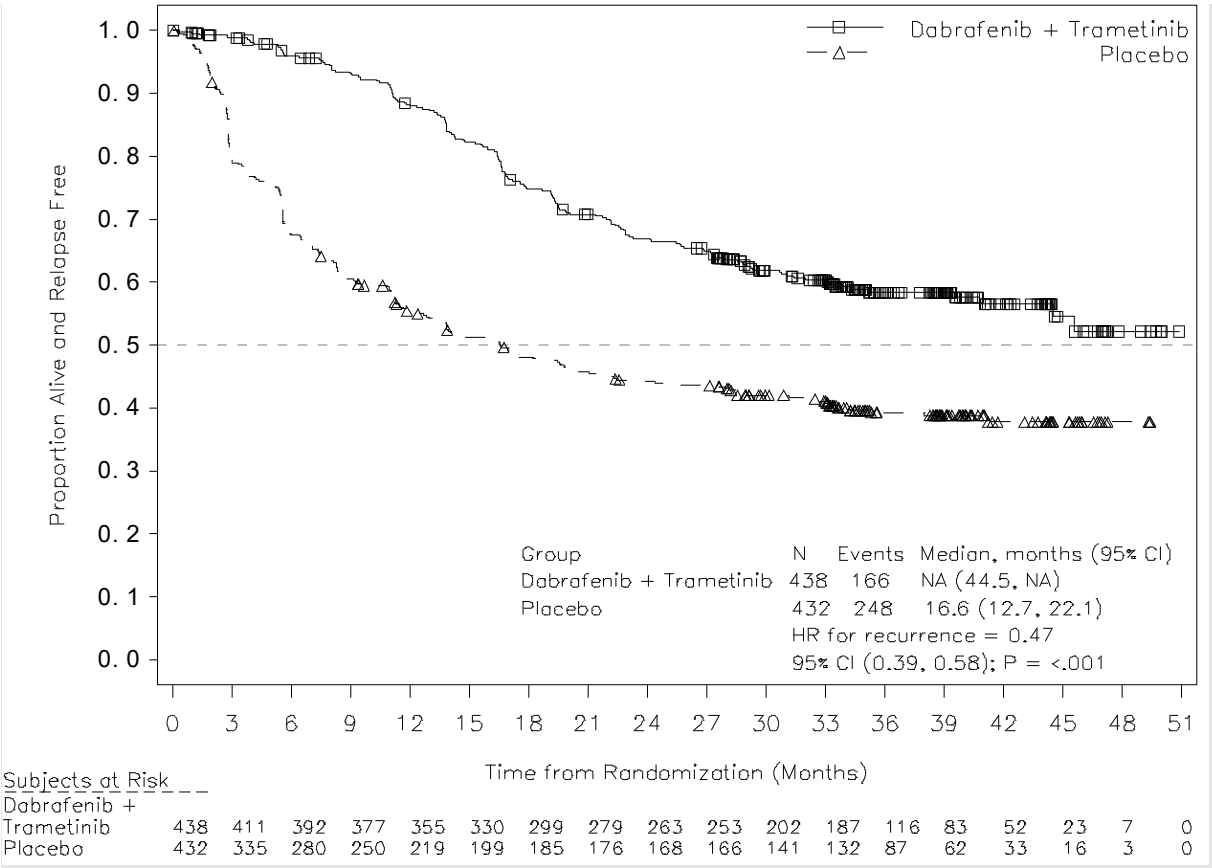
Primary Endpoints	Associated value and statistical significance for TAFINLAR + Trametinib (N = 438)		Associated value and statistical significance for Placebo (N = 432)	
PFS	Number of events, n (%)	166 (38%)	Number of events, n (%)	248 (57%)
	Recurrence	163 (37%)	Recurrence	247 (57%)
	Relapsed with distant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

	3-year rate (95% CI)	0.58 (0.54, 0.64)	3-year rate (95% CI)	0.39 (0.35, 0.44)
OS	Hazard ratio[1] 0.57			
	(95% CI) (0.42, 0.79)			

[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

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

Figure 4 Relapse-free survival Kaplan-Meier curves (ITT population) – Study BRF115532



Based on 153 events (60 (14%) in the combination arm and 93 (22%) in the placebo arm) corresponding to a 26% information fraction of the total target of 597 OS events, the estimated hazard ratio for OS was 0.57 (95% CI: 0.42, 0.79), which was not statistically significant. The overall survival data were not mature at the time of the study's primary efficacy analysis.

Metastatic Non-Small Cell Lung Cancer (NSCLC) – TAFINLAR in Combination with Trametinib

Table 33 Summary of Patient Demographics for Clinical Trials in Metastatic Non-Small Cell Lung Cancer (NSCLC) – TAFINLAR in Combination with Trametinib

Study #	***Study design***	***Dosage, route of administration and duration***	***Study subjects (n)***	***Mean age (Range)***	***Sex* n (%)**
BRF113928	Phase II, multi-centre, non-randomized, open-label study of TAFINLAR in combination with trametinib in patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation.	TAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily.	**Previously treated TAFINLAR + Trametinib** (N = 57)	**Age (years) Median (Min-Max)** 64 (41, 88) **Age Group, n (%)** < 65: 29 (51) ≥ 65: 28 (49)	***Female*** 28 (49) ***Male*** 29 (51)
			Treatment-naïve TAFINLAR + Trametinib (N = 36)	**Age (years) Median (Min-Max)** 67 (44, 91) **Age Group, n (%)** < 65: 14 (39) ≥ 65: 22 (61)	***Female*** 22 (61) ***Male*** 14 (39)

The efficacy and safety of TAFINLAR in combination with trametinib in the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation has been evaluated in the phase II multi-centre, international clinical study BRF113928. Screening for eligibility included local laboratory testing of BRAF V600E mutation conducted on tumour samples available mostly from the primary tumour.

The study enrolled 93 patients; 57 patients whose disease progressed following 1 to 3 previous systemic treatments and 36 patients who received the study medication as first-line treatment for metastatic disease. All patients received TAFINLAR 150 mg twice daily and trametinib 2 mg once daily.

The primary endpoint was the investigator-assessed ORR using the 'Response Evaluation Criteria In Solid Tumours' (RECIST), v1.1, and the secondary endpoint was Duration of Response (DoR); both were also assessed by an Independent Review Committee (IRC) as a sensitivity analysis. For those whose disease progressed following 1 to 3 previous systemic treatments, the null hypothesis was that the ORR is less than or equal to 30%. The alternative hypothesis was that the ORR is higher than or equal to 55%. For those who received the study medication as first line treatment for metastatic disease, the null hypothesis was that the ORR is less than or equal to 30%. The alternative hypothesis was that the ORR is higher than or equal to 60%.

Baseline characteristics are listed in Table 34.

Table 34 Demographic and Baseline Characteristics – Study BRF113928

	Previously treated TAFINLAR + Trametinib (N = 57)	Treatment-naïve TAFINLAR + Trametinib (N = 36)
Race, n (%)		
White	49 (86)	30 (83)
Asian	4 (7)	3 (8)
Black or African American	2 (4)	1 (3)
Other	2 (4)	2 (6)
ECOG PS at Baseline, n (%)		
0	17 (30)	13 (36)
1	35 (61)	22 (61)
2	5 (9)	1 (3)
Histology, n (%)		
Squamous	0	1 (3)*
Non-squamous	57 (100)	35 (37)
Smoking History, n (%)		
Never smoked	16 (28)	10 (28)
Current smoker	6 (11)	5 (14)
Former smoker	35 (61)	21 (58)
Prior anti-cancer therapy for metastatic disease, n (%)		
1	38 (67)	0 (0)
2	12 (21)	0 (0)
3	7 (12)	0 (0)

ECOG = Eastern Cooperative Oncology Group; PS = performance status
* 1 patient with adenosquamous carcinoma – predominately squamous histology. All histology was determined by local pathological report.

Efficacy results are presented in Table 35.

Table 35 Results of Study BRF113928 in Metastatic Non-Small Cell Lung Cancer (NSCLC) – TAFINLAR in Combination with Trametinib

	Associated value and statistical significance for Previously treated* TAFINLAR + Trametinib (N = 57)			Associated value and statistical significance for Treatment-naïve* TAFINLAR + Trametinib (N = 36)	
Primary Endpoints†					
Overall Response Rate (ORR)		**Investigator-Assessed**	**IRC-Assessed**	**Investigator-Assessed**	**IRC-Assessed**
	ORR, % (95% CI) CR, n (%) PR, n (%)	63.2 (49.3, 75.6) 2 (4) 34 (60)	63.2 (49.3, 75.6) 0 36 (63)	61.1 (43.5, 76.9) 2 (6) 20 (56)	61.1 (43.5, 76.9) 1 (3) 21 (58)
Secondary endpoints†					
Duration of response	Median, months (95% CI)	9.0 (6.9, 18.3)	9.0 (5.8, 17.6)	NE (8.3, NE)	NE (6.9, NE)

* Primary analysis data cut-off dates: 07 October 2015 (previously treated), 08 August 2016 (treatment-naïve)
† CI = Confidence interval; CR = Complete response; IRC = Independent review committee; NE = Not evaluable; PR = Partial response

The ORR in the previously treated combination therapy population was 63.2% (95% CI, 49.3, 75.6) by investigator assessment and median DoR was 9.0 months (95% CI: 6.9, 18.3). The median duration of treatment was 10.6 months. The ORR in the treatment-naïve population was 61.1% (95% CI, 43.5, 76.9) and median DoR was not reached. The median duration of treatment was 8.21 months. The IRC-assessed efficacy results were consistent with the investigator assessments (Table 35).

Low-grade Glioma (LGG) and High-grade Glioma (HGG) – TAFINLAR in Combination with Trametinib

The clinical efficacy and safety of TAFINLAR plus trametinib combination therapy in pediatric 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 (Study G2201). Study G2201 included a cohort of patients with low-grade glioma and a cohort of patients with high-grade glioma.

The study enrolled male and female patients with a Karnofsky/Lansky performance score of at least 50; adequate bone marrow, renal, liver and cardiac function; and without history or evidence of cardiovascular risk including LVEF below the institutional LLN. Patients with a history of retinal vein occlusion were excluded.

In both cohorts, TAFINLAR and trametinib dosing was age- and weight-dependent, with TAFINLAR (either as capsules or tablets for suspension) dosed orally at 2.625 mg/kg twice daily for ages <12 years and 2.25 mg/kg twice daily for ages 12 years and older. Trametinib (tablets or powder for oral solution) was dosed orally at 0.032 mg/kg once daily for ages <6 years and 0.025 mg/kg once daily for ages 6 years and older. TAFINLAR doses were capped at 150 mg twice daily and trametinib doses at 2 mg once daily until disease progression or intolerable toxicity. In the control arm of the LGG cohort, carboplatin and vincristine were dosed based on age and body surface area at doses 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 HGG cohort used a single-arm design.

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 evaluate BRAF V600E mutation status.

LGG Cohort

In Study G2201, patients with BRAF V600E mutation-positive low-grade glioma (WHO grades 1 and 2) who required first systemic therapy following prior surgery or who were not surgical candidates were randomized in a 2:1 ratio to TAFINLAR plus trametinib or carboplatin plus vincristine (Table 36). Participants in the carboplatin + vincristine arm could cross-over to receive the targeted TAFINLAR plus trametinib combination treatment upon centrally-confirmed disease progression.

Table 36 Summary of Patient Demographics for Clinical Trials in Pediatric Patients with LGG

Study #	*Study design*	*Dosage, route of administration and duration*	*Study subjects (n)*	*Median age (Range)*	*Sex* n (%)

DRB436G2201 **(Study G2201)** Phase II Pivotal Study, Low-grade Glioma (LGG) cohort	Phase II multi-centre, randomized, open-label study of TAFINLAR in combination with trametinib versus carboplatin in combination with vincristine in children and adolescent patients with BRAF V600E mutation-positive LGG following surgical excision or non-surgical candidates with necessity to begin first systemic therapy	TAFINLAR and trametinib dosing was age- and weight-dependent. Oral	**TAFINLAR + Trametinib** (N = 73)	**Median Age (years) (Min-Max)** 10.0 (1,17) **Age Group, n (%)** 12 months - < 6 years: 20 (27.4) 6 - <12 years: 25 (34.2) 12 - <18 years: 28 (38.4)	***Female*** 44 (60.3) ***Male*** 29 (39.7)
		Carboplatin and vincristine dosing was based on age and body surface area Intravenous	**Carboplatin + Vincristine** (N=37)	**Median Age (years) (Min-Max)** 8.0 (1,17) **Age Group, n (%)** 12 months - < 6 years: 14 (37.8) 6 - <12 years: 11 (29.7) 12 - <18 years: 12 (32.4)	***Female*** 22 (59.5) ***Male*** 15 (40.5)

Demographic and Baseline Characteristics - Study DRB436G2201 - LGG Cohort:

For patients enrolled in the LGG cohort of Study G2201, 73% were White, 9% were race unknown, 7% were Asian, 5% were Black or African American, and 3% were race not reported. The median time since initial diagnosis of primary site to study entry was 3.5 months. The predominant tumour histologies were pilocytic astrocytoma (31%), ganglioma (27%), and LGG not otherwise specified (NOS) (18%). The majority of patients (85% in D+T arm vs. 78% in C+V arm) had prior surgery, and only 2 patients (2%) did not have residual disease. None of the patients underwent prior radiotherapy.

The primary efficacy endpoint was Overall Response Rate (ORR, sum of confirmed complete/CR and partial responses/PR) by Independent review based on RANO 2017 criteria. The primary analysis was performed when all patients had completed at least 32 weeks of therapy. Progression-free survival (PFS) was evaluated as a key secondary endpoint. The final analysis was performed 2 years after completion of enrollment in both cohorts.

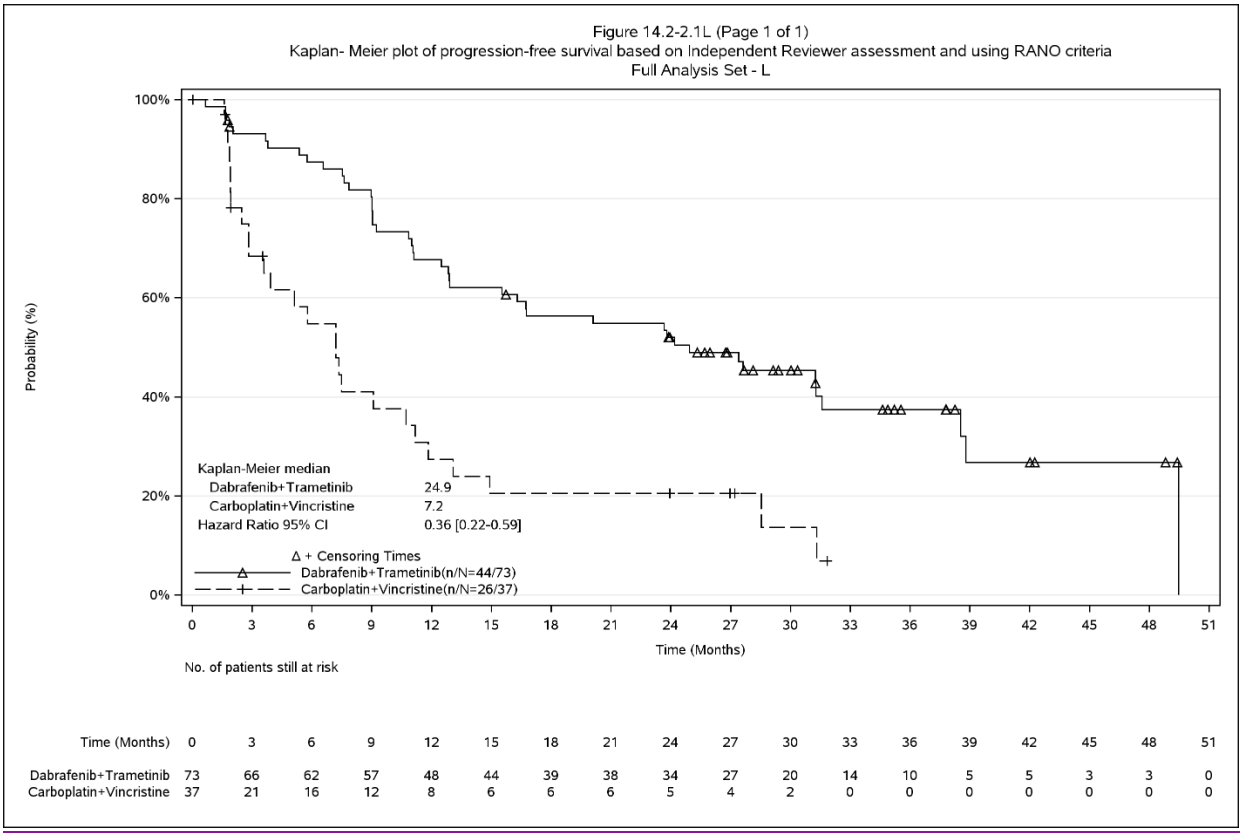
Efficacy results of the LGG cohort are presented in Table 37 and Figure 5. The ORR in the targeted therapy (TAFINLAR plus trametinib) arm (47%) showed a statistically significant improvement over the chemotherapy (carboplatin plus vincristine) arm (11%), with an odds ratio of 7.19 and 1-sided p-value <0.001 (Table 37).

Table 37 Results of Study G2201 in Pediatric Patients with LGG

	Dabrafenib + Trametinib N=73	**Carboplatin + Vincristine N=37**
	Primary Analysis	
Overall Response Rate		
ORR[a] (95% CI), p-value	47% (34.8, 58.6), p<0.001	11% (3.0, 25.4)
Odds ratio (95% CI)	7.19 (2.3, 22.4)	
Best overall response		
Complete response (CR), n (%)	2 (2.7)	1 (2.7)
Partial response (PR), n (%)	32 (43.8)	3 (8.1)
Progression-Free Survival		
Median (months)	20.1 (12.8, NE)	7.4 (3.6, 11.8)
Hazard ratio[b] (95% CI), p-value	0.31 (0.17, 0.55), p<0.001	
	Final Analysis	
Overall Response Rate		
ORR[a] (95% CI)	55% (42.7, 66.5)	16% (6.2, 32.0)
Odds ratio (95% CI)	6.26 (2.3, 16.8)	
Best overall response		
Complete response (CR), n (%)	2 (2.7)	1 (2.7)
Partial response (PR), n (%)	38 (52.1)	5 (13.5)
Progression-Free Survival		
Median (months)	24.9 (12.9, 31.6)	7.2 (2.8, 11.2)
Hazard ratio[b] (95% CI)	0.36 (0.22, 0.59)	

[a] Consisting of complete and partial responses; [b] Estimated using a Cox proportional hazards model

Figure 5 Kaplan-Meier PFS curves for Study G2201 (LGG cohort, final analysis)



At the time of the interim analysis of overall survival (OS), conducted when all patients had completed at least 32 weeks of treatment or had discontinued earlier, there was one death in the C+V arm. The OS results at primary analysis did not reach statistical significance (p=0.065).

For the nine patients who crossed over to targeted TAFINLAR plus trametinib therapy following centrally-confirmed disease progression on chemotherapy (carboplatin plus vincristine), the ORR was 33.3% (95% CI: 7.5, 70.1) as assessed by Independent review.

HGG Cohort

The single-arm high-grade glioma cohort of study G2201 included 41 patients who relapsed, progressed, or failed to respond to front-line therapy (optimal surgical approach with radiation or chemotherapy) (Table 38).

Table 38 Summary of Patient Demographics for Clinical Trials in Pediatric Patients with HGG

Study #	***Study design***	***Dosage, route of administration and duration***	***Study subjects (n)***	***Median age (Range)***	***Sex* n (%)**

DRB436G2201 **(Study G2201)** Phase II Pivotal Study, High-grade Glioma (HGG) cohort	Phase II multi-centre, open-label, single-arm study of TAFINLAR in combination with trametinib in children and adolescent patients with BRAF V600E mutation-positive HGG who had relapsed, progressed, or failed to respond to front-line therapy	TAFINLAR and trametinib dosing was age- and weight-dependent. Oral	**TAFINLAR +** **Trametinib** (N = 41)	**Median Age (years)** **(Min-Max)** 13.0 (2,17) **Age Group, n (%)** 12 months - < 6 years: 5 (12.2) 6 - <12 years: 10 (24.4) 12 - <18 years: 26 (63.4)	***Female*** 23 (56.1) ***Male*** 18 (43.9)

Demographic and Baseline Characteristics - StudyG2201 - HGG Cohort:

For patients enrolled in the HGG cohort of Study G2201, 61% were White, 27% were Asian, 7% were race unknown, 2% were Black or African American, and 2% were race not reported. The median time since initial diagnosis of primary site to study entry was 17.4 months. The predominant tumour histologies were pleomorphic xanthoastrocytoma with anaplasia (29%) and diffuse midline glioma (10%). All patients had received at least one form of prior antineoplastic therapy. All patients except one (98%) had prior surgery, with the majority of patients (61%) having residual disease. In total, 90% of patients underwent prior radiotherapy, mostly in the adjuvant setting (49%), and 81% of patients had received chemotherapy, mostly in the adjuvant setting (51%).

The primary efficacy endpoint was ORR (sum of confirmed CR and PR) by Independent review based on RANO 2010 criteria. The primary analysis was performed when all patients had completed at least 32 weeks of therapy.

Efficacy results for the HGG cohort are presented in Table 39:

Table 39 Results of Study G2201 in Pediatric Patients with HGG

	Dabrafenib + Trametinib N=41
Primary Analysis	
Best overall response	
Complete Response (CR), n (%)	12 (29.3)
Partial Response (PR), n (%)	11 (26.8)
ORR[a] % (95% CI)	56.1 (39.7, 71.5)
Duration of response (DoR)	

Kaplan-Meier median (95% CI)	22.2 (7.6, NE)
DoR ≥6 months (%)	78
DoR ≥12 months (%)	48
DoR ≥24 months (%)	22
Final Analysis	
Best overall response	
Complete Response (CR), n (%)	14 (34.1)
Partial Response (PR), n (%)	9 (22.0)
ORR[a] % (95% CI)	56.1 (39.7, 71.5)
Duration of response (DoR)	
Kaplan-Meier median (95% CI) DoR ≥6 months (%) DoR ≥12 months (%) DoR ≥24 months (%)	27.4 (9.2, NE) 83 57 39

[a] Consisting of complete and partial responses

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

General Toxicology

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

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

Dogs given dabrafenib and trametinib in combination for 4 weeks demonstrated decreased serum albumin concentrations consistent with an acute phase response secondary to mild granulomatous changes in the stomach and mesenteric lymph node. Decreases in serum albumin have also been reported in patients receiving combination therapy as compared to those receiving dabrafenib monotherapy in the phase III combination study (see Table 15).

Dogs given dabrafenib and trametinib in combination for 4 weeks also demonstrated decreased lymphoid cellularity of the thymus at a lower dose than in a 3-week dog study in which single agent trametinib was administered.

Carcinogenicity

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

Reproductive and Developmental Toxicity

Dabrafenib is embryo-foetal toxic and teratogenic in animals at doses similar to human clinical exposures. In combined female fertility, early embryonic and embryo-foetal development studies in rats, a reduction in fertility was observed at 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC). There was also delayed skeletal development and reduced foetal body weight at doses ≥ 20 mg/kg/day (≥ 0.5 times human clinical exposure based on AUC). The numbers of ovarian *corpora lutea* were reduced in pregnant females at 300 mg/kg/day. Developmental toxicity including embryo-lethality and ventricular septal defects were also seen at 300 mg/kg/day.

Male fertility studies with dabrafenib have not been conducted. However, in repeat-dose studies, testicular degeneration/depletion was seen in rats and dogs (≥ 0.2 times the human clinical exposure based on AUC). Testicular changes in rat and dog were still present following a 4-week recovery period (see 7 Reproductive Health: Female and Male Potential, Reproduction).

Special Toxicology

Phototoxicity: Dabrafenib was phototoxic in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay and *in vivo* at single doses ≥ 100 mg/kg (> 44 times clinical exposure based on C_{max}) in an oral phototoxicity study in hairless mice.

Juvenile Toxicity

In juvenile toxicity studies in rats, effects on growth (shorter long bone length), renal toxicity (tubular deposits, increased incidence of cortical cysts and tubular basophilia and reversible increases in urea and/or creatinine concentrations) and testicular toxicity (degeneration and tubular dilation) were observed (≥ 0.2 times adult human clinical exposure based on AUC). Renal toxicity, which had not been observed in adult animals, was primarily observed in rats given dabrafenib pre-weaning (< 22 days old). Dabrafenib inhibits LIM kinase 1 (LIMK1) with an IC_{50} value of 11 nM. Literature studies have also demonstrated that LIMK1 knockout (-/-) mice have reduced bone mass and that LIMK1 is required for normal osteoblast differentiation.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTAFINLAR®

dabrafenib capsules

This Patient Medication Information is written for the person who will be taking **TAFINLAR®**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have questions about this medication or want more information about **TAFINLAR**, talk to a healthcare professional.

Your cancer may be treated with TAFINLAR in combination with another medication called trametinib. When you take TAFINLAR with trametinib, read the Patient Medication Information leaflet for trametinib as well as this one.

Serious warnings and precautions box

TAFINLAR should only be prescribed and managed by a healthcare professional who is experienced in the use of anti-cancer drugs. Serious side effects include:

- Taking TAFINLAR may cause severe fever
- TAFINLAR can harm an unborn baby
- Birth control using hormones (pills, injections, or patches) may not work as well while you are taking TAFINLAR
- TAFINLAR has not been studied in patients with moderate or severe liver problems
- Patients taking TAFINLAR have reported secondary cancers

Other serious side effects when taking TAFINLAR with trametinib include:

- Serious bleeding
- Blood clots

What TAFINLAR is used for:

Taking TAFINLAR **by itself** is used to:
- treat a type of skin cancer called melanoma. This type of melanoma cannot be removed by surgery or has spread to other parts of the body.

Taking TAFINLAR **with trametinib** is also used to:
- treat a type of skin cancer called melanoma. This type of melanoma cannot be removed by surgery or has spread to other parts of the body.
- help prevent melanoma from coming back. This is after the skin cancer was completely removed by surgery.
- treat a type of lung cancer. This type of cancer is called non-small cell lung cancer. These drugs are used together when this cancer has spread to other parts of the body.
- treat a type of brain tumour called glioma.

TAFINLAR should only be used for people who have a cancer that has a certain change in a

gene called “BRAF”. Before taking TAFINLAR, you should have your cancer tested for this change. Your healthcare professional will take a tumour tissue sample, to test whether TAFINLAR is suitable for you.

TAFINLAR capsules are not recommended for children less than 6 years of age or weighing less than 26kg.

How TAFINLAR works:
TAFINLAR targets proteins made from the changed (mutated) BRAF gene. This slows down or stops growth of cancer cells.

The ingredients in TAFINLAR are:
Medicinal ingredient: Dabrafenib mesylate
Non-medicinal ingredients: Colloidal silicon dioxide, iron oxide black, iron oxide red, hypromellose, magnesium stearate, microcrystalline cellulose, propylene glycol, shellac, and titanium dioxide.

TAFINLAR comes in the following dosage forms:
Capsules: 50 mg and 75 mg dabrafenib (as dabrafenib mesylate)

Do not use TAFINLAR if:
- you are allergic to dabrafenib mesylate, or any of the other ingredients in TAFINLAR.
- you do not have a particular change (mutation) in a gene called BRAF or if the mutation in BRAF is not known.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TAFINLAR. Talk about any health conditions or problems you may have, including if you:
- are pregnant, may be pregnant or are planning to become pregnant. You must use reliable non-hormonal birth control while receiving TAFINLAR and for at least 2 weeks after you stop TAFINLAR or for at least 16 weeks after stopping TAFINLAR with trametinib treatment. Pills, patches and injections are not effective in preventing pregnancies because they may not work as well while you are taking TAFINLAR; therefore, you should use an alternative effective method of birth control. You must make sure that you do not get pregnant while receiving TAFINLAR. If you do get pregnant, inform your healthcare professional immediately. TAFINLAR can harm an unborn baby.
- are breastfeeding. Do not breastfeed if you are taking TAFINLAR. If you wish to restart breastfeeding after TAFINLAR treatment, you must discuss this with your healthcare professional. Your healthcare professional will tell you when it is safe to breastfeed.
- are a male (who has had a vasectomy or not) with a female partner who is pregnant or may become pregnant. You should use condoms with spermicide during sexual intercourse while taking TAFINLAR and for at least 2 weeks after stopping TAFINLAR or for at least 16 weeks after stopping TAFINLAR with trametinib treatment.
- are a male. Men who take TAFINLAR may have a reduced count of sperm that may not return to normal levels after you stop taking TAFINLAR.
- have or have had a heart rhythm disorder such as irregular heartbeat, prolongation of the QT interval or any risk factors for Torsade de Pointes (dangerous rapid fluttering of the heart) such as diabetes, low potassium, magnesium or calcium levels, or a history of low heart rate, fainting, or loss of consciousness.
- have heart valve problems.

- have elevated blood sugar levels.
- have any liver problems. Your healthcare professional may take blood samples to monitor your liver function while you are taking TAFINLAR.
- have or have ever had any kidney problems.
- plan to have surgery, dental or other medical procedures.
- have any other medical conditions.

BEFORE you use TAFINLAR with trametinib also talk to your healthcare professional if you have:
- had bleeding problems or blood clots.
- heart problems such as heart failure or problems with the way your heart beats.
- unexplained stomach pain. This may be an inflamed pancreas (**pancreatitis**).
- eye problems including blockage of the vein draining the eye or swelling in the eye which may be caused by fluid leakage.
- any skin problems including rash or acne-like rash.
- high blood pressure.
- a low number of white blood cells.
- any lung or breathing problems, including **pneumonitis** (difficulty in breathing often accompanied by a dry cough, shortness of breath and fatigue).

Other warnings you should know about:

Fever (temperature 38°C or higher): Taking TAFINLAR may cause fever. Fever may happen more often or may be more severe when TAFINLAR is taken with trametinib. If you get a fever, or if you feel a fever coming on, stop taking TAFINLAR, or TAFINLAR and trametinib if you are taking both and tell your healthcare professional right away. In some cases, people with fever may develop severe chills, dehydration, low blood pressure, dizziness and kidney problems. Your healthcare professional may recommend that you stop taking TAFINLAR while they treat your fever with other medicines. Your healthcare professional will tell you if and when you can re-start TAFINLAR. You may receive a lower dose or your treatment may be stopped altogether.

Bleeding problems: TAFINLAR, when taken with trametinib, can cause serious bleeding problems, including in your brain, stomach, or bowel, and can lead to death. In some cases, people may develop brain tumours. Call your healthcare professional and get medical help right away if you have any unusual signs of bleeding including:
- headaches, dizziness, or feeling weak
- coughing up blood or blood clots
- vomiting blood or your vomit looks like “coffee grounds”
- red or black stools that look like tar

Blood clots: TAFINLAR, when taken with trametinib, can cause blood clots in your arms and legs, which can travel to your lungs or other parts of the body and can lead to death. Get medical help right away if you have any of the following symptoms:
- chest pain
- sudden shortness of breath or trouble breathing
- pain in your legs with or without swelling
- swelling in your arms or legs, especially one larger than the other
- a cool or pale arm or leg

Changes in your skin: If you notice any skin lesions or experience serious skin reactions while taking this medicine, talk to your healthcare professional as soon as possible.

You may develop a different type of skin cancer called cutaneous squamous cell carcinoma. Usually this cancer does not spread and can be removed with surgery. You can continue treatment with TAFINLAR.

You may also develop new skin cancers (melanomas). These are usually removed by surgery. You can continue treatment with TAFINLAR.

Your healthcare professional will check your skin for any new cancers before you start taking TAFINLAR. Your healthcare professional will also check your skin every 2 months while you take TAFINLAR. Your healthcare professional will check your skin again every 2 or 3 months for 6 months after you stop taking TAFINLAR.

Check your skin regularly while taking TAFINLAR for any of the following:
- new wart
- skin sore or reddish bump that bleeds or does not heal
- new moles or change in size or colour of an existing mole

Tell your healthcare professional as soon as possible if you get any of these symptoms - either for the first time or if they get worse or if you experience any of the following symptoms:
- rash, red skin, blistering of the lips, eyes, or mouth, skin peeling, with or without fever (**Stevens-Johnson syndrome**)
- widespread rash, fever and enlarged lymph nodes (**drug reaction with eosinophilia and systemic symptoms (DRESS).**

Inflammatory disease: TAFINLAR, when taken with trametinib, can cause an inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes called sarcoidosis. Common symptoms may include coughing, shortness of breath, swollen lymph nodes, visual disturbances, fever, fatigue, pain and swelling in the joints, and tender bumps on your skin. **Tell your healthcare professional if you get any of these symptoms**.

Eye problems: TAFINLAR can cause eye problems. These could damage your vision if they are not treated. Eye problems may develop rapidly; symptoms include:
- eye redness and irritation
- blurred vision
- eye pain
- increased sensitivity to light
- floating spots in front of your eyes

TAFINLAR, when taken with trametinib, can also cause uveitis that affects both eyes. This could be a condition known as **Vogt-Koyanagi-Harada-like syndrome**.
Contact your healthcare professional immediately if you get these symptoms. **It is very important to tell your healthcare professional immediately if you develop these symptoms,** especially if you have a painful, red eye that does not clear up quickly. Your healthcare professional will monitor you for eye problems during your treatment. You may also have an examination done with an eye specialist before starting TAFINLAR and again during

your treatment, if needed.

Liver problems: When TAFINLAR is taken with trametinib, it can cause problems with your liver. This may develop into serious conditions such as hepatitis and liver failure. These conditions may be fatal. Your healthcare professional will monitor you periodically. Signs that your liver may not be working properly may include:

- loss of appetite
- nausea
- vomiting
- pain in your stomach (abdomen)
- yellowing of your skin or the whites of your eyes (jaundice)
- dark-coloured urine
- itching of your skin

Decrease in white blood cells (neutropenia): TAFINLAR, when taken with trametinib, can cause a decrease in a certain kind of white blood cells. This may lead to infection, which can be life-threatening. Decrease in white blood cells may also lead to unexpected bruising or bleeding. Your healthcare professional will monitor you for signs of low blood cells. Signs that certain white cell counts are low may include:

- symptoms of infection (fever, chills, sore throat)
- bruise or bleed easily
- cold
- cough

Non-skin cancers: You may develop non-skin cancers while taking TAFINLAR. Your healthcare professional will monitor you for signs of non-skin cancers.

Heart problems: TAFINLAR has an effect on the electrical activity of the heart known as QT prolongation.

High blood sugar (diabetes): TAFINLAR may cause an increase in blood sugar levels or worsening of diabetes. If you are diabetic your healthcare professional may monitor your blood sugar more frequently while you are on TAFINLAR.

Haemophagocytic lymphohistiocytosis or HLH: is a life-threatening blood disorder in which the body's ability to fight an illness (immune system) does not work normally. HLH affects multiple organs and produces several side effects. For more information on HLH and the other side effects, please see the table “Serious side effects and what to do about them”.

Tumour Lysis syndrome or TLS: Treatment with TAFINLAR in combination with trametinib may cause you to develop TLS. This condition, which can be fatal, results from the fast death of cancer cells. For information on TLS side effects, please see the table "Serious side effects and what to do about them”.

Driving and using machines: TAFINLAR can have side effects that may affect your ability to drive or use machines.

Avoid driving or using machines if you have problems with your vision or if you feel tired or weak, or if your energy levels are low.

Discuss with your healthcare professional if you are unsure about anything. Your disease,

symptoms and treatment situation may affect your ability to drive or use machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious drug interactions

TAFINLAR may decrease the effect of hormonal birth control. You may be at risk of getting pregnant if you are taking a hormonal birth control. You should use a different or additional non-hormonal method of birth control while you are taking TAFINLAR.

The following may also interact with TAFINLAR:

- birth control using hormones such as pills, injections, or patches
- warfarin, to thin the blood
- medicines to treat fungal infections, such as ketoconazole
- some antibiotic medicines, such as clarithromycin or rifampin
- dexamethasone
- some medicines to treat HIV, such as ritonavir
- medicines to treat seizures, such as phenytoin, phenobarbital, or carbamazepine
- the anti-depressant medicine nefazodone
- medicines called statins used to treat high cholesterol
- the lipid lowering medicine gemfibrozil
- some medicines (called proton pump inhibitors) that reduce stomach acid (e.g. esomeprazole)
- the herbal product, St. John's wort
- medicines known to cause heart rhythm changes

Tell your healthcare professional if you are taking any of the medicines listed above. Your healthcare professional may decide to adjust your dose. Keep a list of the medicines you take, so you can show it to your healthcare professional when you get a new medicine.

Do not start, stop or change any medicine without talking to your healthcare professional, nurse or pharmacist first.

How to take TAFINLAR:

Take TAFINLAR:

- Exactly as your healthcare professional has told you to. Check with your healthcare professional or pharmacist if you are not sure;
- Twice per day on an empty stomach at least one hour before or two hours after a meal;
- At about the same time each day. Take your TAFINLAR about 12 hours apart, for example in the morning and again in the evening. Do not take the morning and evening doses of TAFINLAR at the same time;
- Swallow the capsules whole with a full glass of water, one after the other;
- Take TAFINLAR for as long as your healthcare professional recommends.
- If you take TAFINLAR with trametinib:
    - Take trametinib with either the morning or the evening dose of TAFINLAR;
    - Take trametinib at about the same time each day and do not take more than one

dose of trametinib a day.

Usual dose:
Taking TAFINLAR by itself: in adults, the recommended daily dose of TAFINLAR is two 75 mg capsules (150 mg), twice a day.

Taking TAFINLAR with trametinib: in adults, the recommended daily dose is two 75 mg capsules of TAFINLAR (150 mg) twice a day with 2 mg of trametinib once a day.

In children 6 years and older, the recommended daily dose of TAFINLAR capsules is based on body weight and is determined by your healthcare professional.

Your healthcare professional may decide that you should take a lower dose if you get side effects or to temporarily interrupt the treatment.

Overdose:

If you think you, or a person you are caring for, have taken too much TAFINLAR, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:
If the missed dose is less than 6 hours late, take it as soon as you remember. If the missed dose is more than 6 hours late, skip that dose and take your next dose at the usual time. Then continue to take your capsules at regular times as usual. **Do not take two doses at once to make up for a missed dose.**

Possible side effects from using TAFINLAR:

These are not all the possible side effects you may have when taking TAFINLAR. If you experience any side effects not listed here, tell your healthcare professional.

- Nausea, vomiting, or diarrhea
- Constipation
- Decreased appetite
- Stomach ache
- Weight increased or decreased
- Dry mouth
- Sore mouth or mouth ulcers
- Chills
- Feeling weak, sick and tired
- Lack of energy
- Tiredness, chills, sore throat, joint or muscle aching (flu-like illness)
- Inflammation of the mucous membranes
- Swelling of the face, the hands, ankles or feet, localized tissue swelling
- Swelling around the eyes
- Low levels of water or fluid (dehydration)
- Headache
- Dizziness

- Thickening of the outer layers of the skin
- Skin effects such as rough scaly patches of skin, brown or yellow to red thickening of skin, skin tags, redness and/or swelling of the skin, rash, dryness, wart-like growths, itching, acne-like problems, skin cracking, rash with pus-filled blisters
- Peeling of the palms, fingers and soles of the feet which may be accompanied by tingling sensation and burning pain
- Increased sensitivity of the skin to sun
- Unusual hair loss or thinning
- Excessive sweating
- Night sweats
- Nasal inflammation
- Urinary tract infections
- Nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles
- Inflammation of the follicles in the skin
- Joint pain, muscle pain, or pain in the hands or feet
- Muscle spasms
- Cough
- Shortness of breath
- High blood pressure
- Low blood pressure
- Slow heart rate
- Problem with the nerves that can produce pain, loss of sensation or tingling in hands and feet/muscle weakness (peripheral neuropathy)

TAFINLAR can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment. These will tell your healthcare professional how TAFINLAR is affecting your blood, liver, kidneys and muscles.

Serious side effects and what to do about them

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Very common			
Dermatitis acneiform: Skin rash, acne-like rash, redness of the face, dry or itching skin	✓		
Fever (temperature 38°C or higher) that may happen with rigors, chills, low blood pressure or kidney problems			✓
Hyponatremia (low blood levels of sodium): tiredness, confusion, muscle twitching, convulsions			✓
Edema: generalised swelling			✓
Papilloma of the skin: small non-cancerous lumps on the skin	✓		
Serious bleeding problems involving:			✓

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
• the brain (headaches, dizziness, feeling weak), • the lungs (coughing up blood or blood clots) • the intestine (vomiting blood or vomit looking like “coffee grounds”, red or black stools that look like tar)			
Common			
Atrioventricular block or bundle branch block (irregular heartbeat): shortness of breath, fatigue, dizziness, near fainting and fainting			✓
Cellulitis (infection of the deeper layers of the skin): red, swollen pain area of skin that can be warm or tender, fever, chills		✓	
Cutaneous squamous cell cancer including keratoacanthomas: skin sore, wart, or reddish bump that bleeds or does not heal		✓	
Ejection fraction decreased (the heart does not pump as well as it should): fatigue, bloating, fluttering in the chest, loss of appetite, nausea, shortness of breath, swelling		✓	
Eye problems: redness, pain, blurred vision, floating spots, sensitivity to light. These eye problems may also include: • **Uveitis or Vogt-Koyanagi-Harada-like syndrome** (inflammation of the inner layer of one or both eyes): red, swollen eye, eye pain, burning or sensitivity to light, blurred vision, headache. • **Chorioretinopathy** (swelling in the eyes caused by leaking fluid): distorted, dimmed or blurred vision, dark area in the middle of your vision • **Retinal detachment** (splitting of the light-sensitive membrane in the back of the eye from its supporting layer): blurred or distorted vision (uncommon)		✓ ✓ ✓	
Hyperglycemia (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue		✓	
Kidney failure (severe kidney problems): confusion; itchiness or rashes; puffiness in your face and hands; swelling in your feet or ankles; urinating less or not at all; weight gain			✓

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
New primary melanoma (mole which has irregular shape, border, or colour, is growing, or changing shape or colour, new skin lesion)		✓	
Pancreatitis (inflammation of the pancreas): severe upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			✓
Panniculitis (inflammation of the fatty layer under the skin): large tender red bumps under the skin		✓	
Tubulointerstitial nephritis: high or low urine output, drowsiness, confusion, nausea as a sign of an inflamed kidney			✓
Venous thromboembolism (blood clots): chest pain, sudden shortness of breath or trouble breathing, pain in your legs with or without swelling, swelling in your arms and legs, or a cool, pale arm or leg			✓
Uncommon			
Allergic Reactions: rash, hives, swelling of the face, lips, tongue, or throat, difficulty swallowing or breathing			✓
Gastrointestinal complications: severe stomach pain, chills, fever, nausea, vomiting of blood, black or bloody stools, holes in the intestinal wall			✓
Pneumonitis (inflammation of the lung): shortness of breath, cough		✓	
Sarcoidosis (inflammatory disease mainly affecting the skin, lungs and eyes): coughing, shortness of breath, swollen lymph nodes, visual disturbances, fever, fatigue, pain and swelling in the joints, tender bumps on your skin		✓	
Unknown			
Guillain-Barré syndrome (a nerve condition): inflammation of the nerves which can result in pain, numbness, muscle weakness and paralysis of the arms and legs		✓	
Haemophagocytic lymphohistiocytosis or HLH (a blood disorder in which your ability to fight off an illness "immune system" does not work normally): multiple symptoms such as fever, swollen glands, bruising, skin rash, enlarged liver and/or spleen, kidney			✓

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
abnormalities, or heart problems occurring at the same time			
Neutrophilic dermatosis (skin problems caused by your immune system): raised, painful, red to dark reddish-purple skin patches or painful skin ulcers or sores that appear mainly on the arms, legs, face, and neck, with a fever		✓	
Tumour lysis syndrome (fast death of cancer cells): multiple symptoms such as irregular heartbeat, decrease in urination, confusion, severe nausea and vomiting, shortness of breath, muscle cramps or spasms, occurring at the same time			✓
Seizures (fits)**:** muscle twitching, changes in emotions, confusion, uncontrollable shaking with or without loss of consciousness		✓	
Skin reaction to tattooed areas: pain, redness, swelling, hardening or thickening of the skin, small raised bumps or itching		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store TAFINLAR between 15°C to 30°C.

Keep out of reach and sight of children.

If you want more information about TAFINLAR:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and

includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.novartis.ca; or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

Date of Authorization: FEB 16, 2026

TAFINLAR is a registered trademark

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTAFINLAR®

dabrafenib tablets for oral suspension

This Patient Medication Information is written for the person who will be taking **TAFINLAR®**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have questions about this medication or want more information about **TAFINLAR**, talk to a healthcare professional.

Your cancer may be treated with TAFINLAR in combination with another medication called trametinib. When you take TAFINLAR with trametinib, read the Patient Medication Information leaflet for trametinib as well as this one.

Serious warnings and precautions box

TAFINLAR should only be prescribed and managed by a healthcare professional who is experienced in the use of anti-cancer drugs. Serious side effects include:

- Taking TAFINLAR may cause severe fever
- TAFINLAR can harm an unborn baby
- Birth control using hormones (pills, injections, or patches) may not work as well while you are taking TAFINLAR
- TAFINLAR has not been studied in patients with moderate or severe liver problems
- Patients taking TAFINLAR have reported secondary cancers

Other serious side effects when taking TAFINLAR with trametinib include:

- Serious bleeding
- Blood clots

What TAFINLAR is used for:

Taking TAFINLAR **by itself** is used to:
- treat a type of skin cancer called melanoma. This type of melanoma cannot be removed by surgery or has spread to other parts of the body.

Taking TAFINLAR **with trametinib** is also used to:
- treat a type of skin cancer called melanoma. This type of melanoma cannot be removed by surgery or has spread to other parts of the body.
- help prevent melanoma from coming back. This is after the skin cancer was completely removed by surgery.
- treat a type of lung cancer. This type of cancer is called non-small cell lung cancer. These drugs are used together when this cancer has spread to other parts of the body.
- treat a type of brain tumour called glioma.

TAFINLAR should only be used for people who have a cancer that has a certain change in a

gene called “BRAF”. Before taking TAFINLAR, you should have your cancer tested for this change. Your healthcare professional will take a tumour tissue sample, to test whether TAFINLAR is suitable for you.

TAFINLAR tablets for suspension are not recommended for children less than 1 year of age or who weigh less than 8 kg.

How TAFINLAR works:
TAFINLAR targets proteins made from the changed (mutated) BRAF gene. This slows down or stops growth of cancer cells.

The ingredients in TAFINLAR are:
Medicinal ingredient: Dabrafenib mesylate
Non-medicinal ingredients: Acesulfame potassium, artificial berry flavour, colloidal silicon dioxide, crospovidone, hypromellose, magnesium stearate, mannitol, and microcrystalline cellulose.

TAFINLAR comes in the following dosage forms:
Tablets for suspension: 10 mg dabrafenib (as dabrafenib mesylate)

Do not use TAFINLAR if:
- you are allergic to dabrafenib mesylate, or any of the other ingredients in TAFINLAR
- you do not have a particular change (mutation) in a gene called BRAF or if the mutation in BRAF is not known.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TAFINLAR. Talk about any health conditions or problems you may have, including if you:
- are pregnant, may be pregnant or are planning to become pregnant. You must use reliable non-hormonal birth control while receiving TAFINLAR and for at least 2 weeks after you stop TAFINLAR or for at least 16 weeks after stopping TAFINLAR with trametinib treatment. Pills, patches and injections are not effective in preventing pregnancies because they may not work as well while you are taking TAFINLAR; therefore, you should use an alternative effective method of birth control. You must make sure that you do not get pregnant while receiving TAFINLAR. If you do get pregnant, inform your healthcare professional immediately. TAFINLAR can harm an unborn baby.
- are breastfeeding. Do not breastfeed if you are taking TAFINLAR. If you wish to restart breastfeeding after TAFINLAR treatment, you must discuss this with your healthcare professional. Your healthcare professional will tell you when it is safe to breastfeed.
- are a male (who has had a vasectomy or not) with a female partner who is pregnant or may become pregnant. You should use condoms with spermicide during sexual intercourse while taking TAFINLAR and for at least 2 weeks after stopping TAFINLAR or for at least 16 weeks after stopping TAFINLAR with trametinib treatment.
- are a male. Men who take TAFINLAR may have a reduced count of sperm that may not return to normal levels after you stop taking TAFINLAR.
- have or have had a heart rhythm disorder such as irregular heartbeat, prolongation of the QT interval or any risk factors for Torsade de Pointes (dangerous rapid fluttering of the heart) such as diabetes, low potassium, magnesium or calcium levels, or a history of low heart rate, fainting, or loss of consciousness.
- have heart valve problems.

- have elevated blood sugar levels.
- have any liver problems. Your healthcare professional may take blood samples to monitor your liver function while you are taking TAFINLAR.
- have or have ever had any kidney problems.
- plan to have surgery, dental or other medical procedures.
- have any other medical conditions.

BEFORE you use TAFINLAR with trametinib also talk to your healthcare professional if you have:
- had bleeding problems or blood clots.
- heart problems such as heart failure or problems with the way your heart beats.
- unexplained stomach pain. This may be an inflamed pancreas (**pancreatitis**).
- eye problems including blockage of the vein draining the eye or swelling in the eye which may be caused by fluid leakage.
- any skin problems including rash or acne-like rash.
- high blood pressure.
- a low number of white blood cells.
- any lung or breathing problems, including **pneumonitis** (difficulty in breathing often accompanied by a dry cough, shortness of breath and fatigue).

Other warnings you should know about:

Fever (temperature 38°C or higher): Taking TAFINLAR may cause fever. Fever may happen more often or may be more severe when TAFINLAR is taken with trametinib. If you get a fever, or if you feel a fever coming on, stop taking TAFINLAR, or TAFINLAR and trametinib if you are taking both and tell your healthcare professional right away. In some cases, people with fever may develop severe chills, dehydration, low blood pressure, dizziness and kidney problems. Your healthcare professional may recommend that you stop taking TAFINLAR while they treat your fever with other medicines. Your healthcare professional will tell you if and when you can re-start TAFINLAR. You may receive a lower dose or your treatment may be stopped altogether.

Bleeding problems: TAFINLAR, when taken with trametinib, can cause serious bleeding problems, including in your brain, stomach, or bowel, and can lead to death. In some cases, people may develop brain tumours. Call your healthcare professional and get medical help right away if you have any unusual signs of bleeding including:
- headaches, dizziness, or feeling weak
- coughing up blood or blood clots
- vomiting blood or your vomit looks like “coffee grounds”
- red or black stools that look like tar

Blood clots: TAFINLAR, when taken with trametinib, can cause blood clots in your arms and legs, which can travel to your lungs or other parts of the body and can lead to death. Get medical help right away if you have any of the following symptoms:
- chest pain
- sudden shortness of breath or trouble breathing
- pain in your legs with or without swelling
- swelling in your arms or legs, especially one larger than the other
- a cool or pale arm or leg

Changes in your skin: If you notice any skin lesions or experience serious skin reactions while taking this medicine, talk to your healthcare professional as soon as possible.

You may develop a different type of skin cancer called cutaneous squamous cell carcinoma. Usually this cancer does not spread and can be removed with surgery. You can continue treatment with TAFINLAR.

You may also develop new skin cancers (melanomas). These are usually removed by surgery. You can continue treatment with TAFINLAR.

Your healthcare professional will check your skin for any new cancers before you start taking TAFINLAR. Your healthcare professional will also check your skin every 2 months while you take TAFINLAR. Your healthcare professional will check your skin again every 2 or 3 months for 6 months after you stop taking TAFINLAR.

Check your skin regularly while taking TAFINLAR for any of the following:
- new wart
- skin sore or reddish bump that bleeds or does not heal
- new moles or change in size or colour of an existing mole

Tell your healthcare professional as soon as possible if you get any of these symptoms - either for the first time or if they get worse or if you experience any of the following symptoms:
- rash, red skin, blistering of the lips, eyes, or mouth, skin peeling, with or without fever (**Stevens-Johnson syndrome**)
- widespread rash, fever and enlarged lymph nodes (**drug reaction with eosinophilia and systemic symptoms (DRESS).**

Inflammatory disease: TAFINLAR, when taken with trametinib, can cause an inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes called sarcoidosis. Common symptoms may include coughing, shortness of breath, swollen lymph nodes, visual disturbances, fever, fatigue, pain and swelling in the joints, and tender bumps on your skin. **Tell your healthcare professional if you get any of these symptoms**.

Eye problems: TAFINLAR can cause eye problems. These could damage your vision if they are not treated. Eye problems may develop rapidly; symptoms include:
- eye redness and irritation
- blurred vision
- eye pain
- increased sensitivity to light
- floating spots in front of your eyes

TAFINLAR, when taken with trametinib, can also cause uveitis that affects both eyes. This could be a condition known as Vogt-Koyanagi-Harada-like syndrome.

Contact your healthcare professional immediately if you get these symptoms. **It is very important to tell your healthcare professional immediately if you develop these symptoms,** especially if you have a painful, red eye that does not clear up quickly. Your healthcare professional will monitor you for eye problems during your treatment. You may also

have an examination done with an eye specialist before starting TAFINLAR and again during your treatment, if needed.

Liver problems: When TAFINLAR is taken with trametinib, it can cause problems with your liver. This may develop into serious conditions such as hepatitis and liver failure. These conditions may be fatal. Your healthcare professional will monitor you periodically. Signs that your liver may not be working properly may include:

- loss of appetite
- nausea
- vomiting
- pain in your stomach (abdomen)
- yellowing of your skin or the whites of your eyes (jaundice)
- dark-coloured urine
- itching of your skin

Decrease in white blood cells (neutropenia): TAFINLAR, when taken with trametinib, can cause a decrease in a certain kind of white blood cells. This may lead to infection, which can be life-threatening. Decrease in white blood cells may also lead to unexpected bruising or bleeding. Your healthcare professional will monitor you for signs of low blood cells. Signs that certain white cell counts are low may include:

- symptoms of infection (fever, chills, sore throat)
- bruise or bleed easily
- cold
- cough

Non-skin cancers: You may develop non-skin cancers while taking TAFINLAR. Your healthcare professional will monitor you for signs of non-skin cancers.

Heart problems: TAFINLAR has an effect on the electrical activity of the heart known as QT prolongation.

High blood sugar (diabetes): TAFINLAR may cause an increase in blood sugar levels or worsening of diabetes. If you are diabetic your healthcare professional may monitor your blood sugar more frequently while you are on TAFINLAR.

Haemophagocytic lymphohistiocytosis or HLH: is a life-threatening blood disorder in which the body's ability to fight an illness (immune system) does not work normally. HLH affects multiple organs and produces several side effects. For more information on HLH and the other side effects, please see the table “Serious side effects and what to do about them”.

Tumour Lysis syndrome or TLS: Treatment with TAFLINLAR in combination with trametinib may cause you to develop TLS. This condition, which can be fatal, results from the fast death of cancer cells. For information on TLS side effects, please see the table "Serious side effects and what to do about them”.

Driving and using machines: TAFINLAR can have side effects that may affect your ability to drive or use machines.

Avoid driving or using machines if you have problems with your vision or if you feel tired or weak, or if your energy levels are low.

Discuss with your healthcare professional if you are unsure about anything. Your disease, symptoms and treatment situation may affect your ability to drive or use machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious drug interactions

TAFINLAR may decrease the effect of hormonal birth control. You may be at risk of getting pregnant if you are taking a hormonal birth control. You should use a different or additional non-hormonal method of birth control while you are taking TAFINLAR.

The following may also interact with TAFINLAR:

- birth control using hormones such as pills, injections, or patches
- warfarin, to thin the blood
- medicines to treat fungal infections, such as ketoconazole
- some antibiotic medicines, such as clarithromycin or rifampin
- dexamethasone
- some medicines to treat HIV, such as ritonavir
- medicines to treat seizures, such as phenytoin, phenobarbital, or carbamazepine
- the anti-depressant medicine nefazodone
- medicines called statins used to treat high cholesterol
- the lipid lowering medicine gemfibrozil
- some medicines (called proton pump inhibitors) that reduce stomach acid (e.g. esomeprazole)
- the herbal product, St. John's wort
- medicines known to cause heart rhythm changes

Tell your healthcare professional if you are taking any of the medicines listed above. Your healthcare professional may decide to adjust your dose. Keep a list of the medicines you take, so you can show it to your healthcare professional when you get a new medicine.

Do not start, stop or change any medicine without talking to your healthcare professional, nurse or pharmacist first.

How to take TAFINLAR:

Take TAFINLAR:

- Exactly as your healthcare professional has told you to. Check with your healthcare professional or pharmacist if you are not sure;
- Twice per day on an empty stomach at least one hour before or two hours after a meal;
- At about the same time each day. Take your TAFINLAR about 12 hours apart, for example in the morning and again in the evening. Do not take the morning and evening doses of TAFINLAR at the same time;
- Take TAFINLAR for as long as your healthcare professional recommends;
- Take trametinib with either the morning or the evening dose of TAFINLAR;
- Take trametinib at about the same time each day and do not take more than one dose of trametinib a day.

TAFINLAR tablets for suspension are to be taken as an oral suspension only and should not be swallowed whole, chewed, or crushed.
Please follow below Instructions for Use on how to prepare and take TAFINLAR tablets for suspension. Talk to your doctor or pharmacist if you are not sure.

INSTRUCTIONS FOR USE of TAFINLAR tablets for suspension

This "Instructions for Use" contains information on how to prepare and take TAFINLAR.

Important Information You Need to Know Before Taking TAFINLAR

- Read these Instructions for Use carefully before you use TAFINLAR for the first time and each time you get a refill. There may be new information.
- These instructions for use do not take the place of talking with your healthcare professional about you or your child's medical condition and treatment.
- Your healthcare professional or pharmacist should show you how to prepare and take or give a dose of TAFINLAR correctly. Always take or give TAFINLAR exactly as your healthcare professional tells you to.
- If you have any questions about how to prepare and take or give a dose of TAFINLAR, contact your healthcare professional or pharmacist.
- Always use the dosing cup that comes with your TAFINLAR pack. If your pack does not contain a dosing cup, contact your healthcare professional or pharmacist.
- If at any time TAFINLAR suspension gets on your or your child's skin, wash the area well with soap and water.
- If at any time TAFINLAR suspension gets in your or your child's eyes, rinse the eyes well with cool water.

IMPORTANT: Use only clean water to rinse. Do not use soap or dishwashing liquid to clean the dosing cup.

- Pregnant or breastfeeding women must avoid cleaning up a spillage due to a risk of harm to the baby.

You will receive your or your child's TAFINLAR prescription in a sealed bottle which contains tablets for suspension. You must dissolve the tablets in water before taking or giving TAFINLAR. Follow the instructions below to mix the tablets in water.

- Your TAFINLAR pack should contain:

1. 1 or 2 bottles containing TAFINLAR tablets for suspension
2. 2 reusable dosing cups

   Instructions leaflet and Patient Medication Information (this document)

You will also need drinking water, which is not included in the TAFINLAR pack.

For administration via swallowing, go to Section A. For administration via feeding tube or via oral syringe, go to Section B.

SECTION A. Preparing and giving TAFINLAR by swallowing directly from the dosing cup

In case of spillage, follow the instructions in the **How to clean up spills** section.

To prepare and administer TAFINLAR, you will need:

- Your prescribed number of TAFINLAR tablets
- Dosing cup
- Stainless steel teaspoon
- Still drinking water

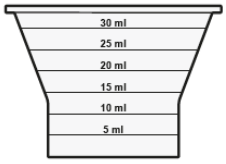
To administer orally (i.e., swallow the suspension), you can drink directly from the dosing cup.

Step 1. Wash and dry your hands before preparing TAFINLAR.

Add cool drinking water up to the markings on the dosing cup, according to the table below.

Note: the amount of water does not need to be exact.

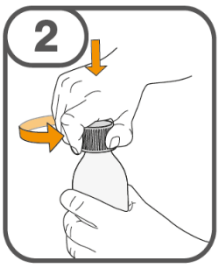
Your dose	**Water volume**
1-4 tablets	Approximately 5 mL
5-15 tablets	Approximately 10 mL

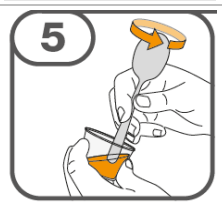


Step 2. Remove the bottle cap by pushing down and turning counterclockwise, as shown.

Do not throw away the cap.

If opening the bottle for the first time, remove the seal from the bottle.



Step 3. Count your prescribed number of tablets. **Note:** The bottle contains 2 plastic canisters to keep the tablets dry. If either canister falls out, put it back into the bottle.	
Put your prescribed number of tablets into the water in your dosing cup.	
Step 4. Place the cap back onto the bottle and turn it clockwise to close it.	
Step 5. Tilt the dosing cup. Gently stir the water and tablets with the handle of a teaspoon until the tablets are fully dissolved. It may take **3 minutes** (or more) to fully dissolve the tablets. Once they are dispersed, the suspension should be cloudy white. **Administer the suspension no later than 30 minutes after the tablets have been dispersed** If more than 30 minutes have passed, dispose of the suspension into the trash and restart from the beginning of Section A. If you are not sure how to dispose of the TAFINLAR oral suspension, ask your healthcare professional	 
Step 6. Drink the suspension from the dosing cup. **IMPORTANT:** after swallowing, there will be drug residue inside the cup. The residue may be difficult to see. Follow steps 7 – 9 to administer all residue and get a full dose.	

Step 7. **Add approximately 5mL of water** to the empty dosing cup.	
Step 8. **Stir** with the handle of a teaspoon to loosen the remaining residue.	
Step 9. Drink the suspension. **Important: If the dose is 1-4 tablets: Perform Steps 7-9 once.** **If the dose is 5-15 tablets: Perform Steps 7-9 twice.** It is important to perform these steps so that you take or give the full dose of TAFINLAR.	

Step 10. Go to the cleaning steps in Section C.

SECTION B. Preparing and giving TAFINLAR via feeding tube or oral syringe

Important administration information
Ensure all the tablets are fully dispersed before administering the suspension.

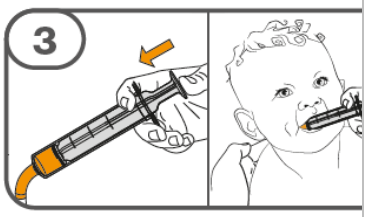
Minimum size of the feeding tube:

Your dose	Minimum size
1 – 3 tablets	10 French
4 – 15 tablets	12 French

Wash and dry your hands before administering TAFINLAR.

In case of spillage, follow the instructions in the **How to clean up spills** section.

Step 1. **Follow Steps 1-5 in Section A to disperse the tablets.** If using a feeding tube, flush the tube with still drinking water then go to Step 2.

Step 2. **Withdraw all of the suspension** from the dosing cup into a syringe compatible with the feeding tube or oral administration. Ask your healthcare professional if you are not sure what syringe to use.	
Step 3. If administering the dose by a feeding tube, dispense the suspension into the feeding tube according to the tube manufacturer's instructions. If administering via oral syringe, place the end of the oral syringe inside the mouth with the tip touching the inside of either cheek. If administering to a child, make sure they are sitting upright. Slowly push the plunger all the way down to deliver the full dose of TAFINLAR. **WARNING:** giving TAFINLAR directly into the throat or pushing the plunger too fast may cause choking.	
Step 4. **Add approximately 5mL of water** to the empty dosing cup	
Step 5. **Stir** with the handle of a teaspoon to loosen the remaining residue.	
Step 6. **Withdraw** the suspension into the syringe.	
Step 7. **Dispense** the suspension into the feeding tube or into the inside of the cheek. **Important: Perform Steps 4-7 a total of three (3) times to give a full dose.** It is important to perform these steps so that you take or give the full dose of TAFINLAR.	

You must **administer all drug residue**. Repeat Step 4 to Step 7 a total of **three times** to give a full dose.

Step 8. After repeating Step 4 to Step 7 a total of three times, flush the feeding tube with still drinking water. Then go to the cleaning steps in Section C.

SECTION C. Cleaning the dosing cup and syringe (if used)

Use only clean water to clean the dosing cup. Do not use soap or dishwashing liquid for the dosing cup.

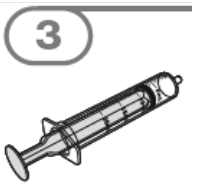
Step 1. Rinse the dosing cup using clean cool water immediately after dosing.
Shake off excess water then wipe dry using clean paper towels.

Note: Always keep the dosing cup away from other kitchen items.

Step 2. Rinse the teaspoon in clean cold water, then wash in warm soapy water and dry using clean paper towels.

Alternatively, you can wash the teaspoon in a dishwasher.

Step 3. Clean the syringe as instructed by your healthcare professional or according to the manufacturer's instructions.



SECTION D. How to throw away (dispose of) TAFINLAR that is expired or no longer needed, or old dosing cups

Throw away (dispose of) unused TAFINLAR tablets or suspension, or old dosing cups into the trash. Do not pour suspension down the drain. Ask your healthcare professional or pharmacist about how to safely throw away TAFINLAR tablets if you are not sure.

How to clean up spills

Follow these steps if you spill any TAFINLAR oral suspension:

1. Put on plastic gloves.
2. Soak up the suspension completely using an absorbent material, such as paper towels soaked with either a mixture of water and household disinfectant or with ethanol 70% (or higher grade).
3. Repeat the cleaning with fresh soaked absorbent material at least three times until the area is clean.

4. Dry the area with paper towels.
5. Throw away all the disposable materials used to clean the spillage into a sealable plastic bag.
6. Dispose of the bag in accordance with local regulations.
7. Wash your hands well with soap and water.

What should I do if TAFINLAR oral suspension comes into contact with my or my child's skin or gets in my eyes?

If at any time TAFINLAR suspension gets on your or your child's skin, wash the area well with soap and water.

If at any time TAFINLAR suspension gets in your or your child's eyes, rinse the eyes well with cool water.

How should I store TAFINLAR

- Store the TAFINLAR bottle with the two plastic canisters inside and the cap tightly closed. The canisters help keep your medicine dry and protect it from moisture.
- Store the bottle and dosing cups in the original packaging
- Store at 15°C to 25°C.
- Keep this medicine out of sight and reach of children.
- After suspension (tablets dispersed in water) in the provided dosing cup, keep the suspension at 15-25°C. Discard suspension if not administered within 30 minutes after preparation.

Usual dose:
The recommended dose of TAFINLAR Tablets for suspension is based on body weight and is determined by your healthcare professional.

Your healthcare professional may decide that you should take a lower dose if you get side effects or to temporarily interrupt the treatment.

Overdose:

If you think you, or a person you are caring for, have taken too much TAFINLAR, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:
If the missed dose is less than 6 hours late, take it as soon as you remember. If the missed dose is more than 6 hours late, skip that dose and take your next dose at the usual time. Then continue to take your capsules at regular times as usual. **Do not take two doses at once to make up for a missed dose.**

Possible side effects from using TAFINLAR:

These are not all the possible side effects you may have when taking TAFINLAR. If you experience any side effects not listed here, tell your healthcare professional.

- Nausea, vomiting, or diarrhea
- Constipation
- Decreased appetite
- Stomach ache
- Weight increased or decreased
- Dry mouth
- Sore mouth or mouth ulcers
- Chills
- Feeling weak, sick and tired
- Lack of energy
- Tiredness, chills, sore throat, joint or muscle aching (flu-like illness)
- Inflammation of the mucous membranes
- Swelling of the face, the hands, ankles or feet, localized tissue swelling
- Swelling around the eyes
- Low levels of water or fluid (dehydration)
- Headache
- Dizziness
- Thickening of the outer layers of the skin
- Skin effects such as rough scaly patches of skin brown or yellow to red thickening of skin, skin tags, redness and/or swelling of the skin, rash, dryness, wart-like growths, itching, acne-like problems, skin cracking, rash with pus-filled blisters
- Peeling of the palms, fingers and soles of the feet which may be accompanied by tingling sensation and burning pain
- Increased sensitivity of the skin to sun
- Unusual hair loss or thinning
- Excessive sweating
- Night sweats
- Nasal inflammation
- Urinary tract infections
- Nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles
- Inflammation of the follicles in the skin
- Joint pain, muscle pain, or pain in the hands or feet
- Muscle spasms
- Cough
- Shortness of breath
- High blood pressure
- Low blood pressure
- Slow heart rate
- Problem with the nerves that can produce pain, loss of sensation or tingling in hands and feet/muscle weakness (peripheral neuropathy)

TAFINLAR can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment. These will tell your healthcare professional how TAFINLAR is affecting your blood, liver, kidneys and muscles.

Serious side effects and what to do about them

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Very common			
Dermatitis acneiform: Skin rash, acne-like rash, redness of the face, dry or itching skin	✓		
Fever (temperature 38°C or higher) that may happen with rigors, chills, low blood pressure or kidney problems			✓
Hyponatremia (low blood levels of sodium): tiredness, confusion, muscle twitching, convulsions			✓
Edema: generalised swelling			✓
Papilloma of the skin: small non-cancerous lumps on the skin	✓		
Serious bleeding problems involving: • the brain (headaches, dizziness, feeling weak), • the lungs (coughing up blood or blood clots) • the intestine (vomiting blood or vomit looking like “coffee grounds”, red or black stools that look like tar)			✓
Common			
Atrioventricular block or bundle branch block (irregular heartbeat): shortness of breath, fatigue, dizziness, near fainting and fainting			✓
Cellulitis (infection of the deeper layers of the skin): red, swollen pain area of skin that can be warm or tender, fever, chills		✓	
Cutaneous squamous cell cancer including keratoacanthomas: skin sore, wart, or reddish bump that bleeds or does not heal		✓	
Ejection fraction decreased (the heart does not pump as well as it should): fatigue, bloating, fluttering in the chest, loss of appetite, nausea, shortness of breath, swelling		✓	
Eye problems: redness, pain, blurred vision, floating spots, sensitivity to light. These eye problems may also include: • **Uveitis or Vogt-Koyanagi-Harada-like syndrome** (inflammation of the inner layer of one or both eyes): red, swollen eye, eye pain, burning or sensitivity to light, blurred vision, headache. ✓ • **Chorioretinopathy** (swelling in the eyes caused by leaking fluid): distorted, dimmed ✓			

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
or blurred vision, dark area in the middle of your vision • **Retinal detachment** (splitting of the light-sensitive membrane in the back of the eye from its supporting layer): blurred or distorted vision (uncommon)		✓	
Hyperglycemia (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue		✓	
Kidney failure (severe kidney problems): confusion; itchiness or rashes; puffiness in your face and hands; swelling in your feet or ankles; urinating less or not at all; weight gain			✓
New primary melanoma (mole which has irregular shape, border, or colour, is growing, or changing shape or colour, new skin lesion)		✓	
Pancreatitis (inflammation of the pancreas): severe upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			✓
Panniculitis (inflammation of the fatty layer under the skin): large tender red bumps under the skin		✓	
Tubulointerstitial nephritis: high or low urine output, drowsiness, confusion, nausea as a sign of an inflamed kidney			✓
Venous thromboembolism (blood clots): chest pain, sudden shortness of breath or trouble breathing, pain in your legs with or without swelling, swelling in your arms and legs, or a cool, pale arm or leg			✓
Uncommon			
Allergic Reactions: rash, hives, swelling of the face, lips, tongue, or throat, difficulty swallowing or breathing			✓
Gastrointestinal complications: severe stomach pain, chills, fever, nausea, vomiting of blood, black or bloody stools, holes in the intestinal wall			✓
Pneumonitis (inflammation of the lung): shortness of breath, cough		✓	
Sarcoidosis (inflammatory disease mainly affecting the skin, lungs and eyes): coughing, shortness of breath, swollen lymph nodes, visual disturbances, fever, fatigue, pain and swelling in the joints, tender bumps on your skin		✓	
Unknown			

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Guillain-Barré syndrome (a nerve condition): inflammation of the nerves which can result in pain, numbness, muscle weakness and paralysis of the arms and legs		✓	
Haemophagocytic lymphohistiocytosis or HLH (a blood disorder in which your ability to fight off an illness "immune system" does not work normally): multiple symptoms such as fever, swollen glands, bruising, skin rash, enlarged liver and/or spleen, kidney abnormalities, or heart problems occurring at the same time			✓
Neutrophilic dermatosis (skin problems caused by your immune system): raised, painful, red to dark reddish-purple skin patches or painful skin ulcers or sores that appear mainly on the arms, legs, face, and neck, with a fever		✓	
Tumour lysis syndrome (fast death of cancer cells): multiple symptoms such as irregular heartbeat, decrease in urination, confusion, severe nausea and vomiting, shortness of breath, muscle cramps or spasms, occurring at the same time			✓
Seizures (fits)**:** muscle twitching, changes in emotions, confusion, uncontrollable shaking with or without loss of consciousness		✓	
Skin reaction to tattooed areas: pain, redness, swelling, hardening or thickening of the skin, small raised bumps or itching		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store TAFINLAR between 15°C to 25°C.
Protect from moisture. Do not remove desiccant.
Keep out of reach and sight of children.

After suspension (tablets dispersed in water) in the provided dosing cup, keep the suspension at 15-25°C. Discard suspension if not administered within 30 minutes after preparation.

If you want more information about TAFINLAR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.novartis.ca; or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

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