# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

Tafinlar 50 mg hard capsules
Tafinlar 75 mg hard capsules
Tafinlar 10 mg dispersible tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

***Note: Tafinlar capsules and dispersible tablets are not interchangeable.***

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

## 3. PHARMACEUTICAL FORM

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

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

Tafinlar 10 mg dispersible tablets

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

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Unresectable or metastatic melanoma

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

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

Adjuvant treatment of melanoma

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

Anaplastic thyroid cancer (ATC)

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

Non-small cell lung cancer (NSCLC)

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

Low-grade glioma

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

High-grade glioma

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

## 4.2 Dose and method of administration

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

Confirmation of BRAF V600 mutation using an approved/validated test is required for selection of patients appropriate for dabrafenib therapy and in combination with trametinib (see section 5.1 - Pharmacodynamic properties).

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

The efficacy and safety of dabrafenib have not been established in patients with wild-type BRAF tumours (see section 5.1 - Pharmacodynamic properties). Dabrafenib should not be used in patients with BRAF wild-type tumours (see section 4.4 - Special warnings and precautions for use).

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

*Duration of treatment*

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

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

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

*Recommended Dosage*

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

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

*Dose modifications*

*Monotherapy and in combination with trametinib*

The management of adverse events/adverse drug reactions may require treatment interruption, dose reduction, or treatment discontinuation (see Table 1, Table 2,Table 3, Table 4 and Table 5). Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (see section 4.4 – Special warnings and precautions for use).

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

Recommended dose level reductions and recommendations for dose modifications are provided in Table 1, and Table 4, respectively. Doses below 50 mg twice daily are not recommended.

**Table 1 Recommended dosing and dose level reductions for dabrafenib capsules in adult patients.**

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

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

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

| Body weight | Recommended starting dosage | First dose reduction | Second dose reduction | Third dose reduction |
|---|---|---|---|---|
| 26 to 37 kg | 75 mg orally twice daily | 50 mg orally twice daily | - | - |
| 38 to 50 kg | 100 mg orally twice daily | 75 mg orally twice daily | 50 mg orally twice daily | - |
| 51 kg or greater | 150 mg orally twice daily | 100 mg orally twice daily | 75 mg orally twice daily | 50 mg orally twice daily |

*Permanently discontinue if unable to tolerate maximum of three dose reductions or a dabrafenib 50 mg capsule orally twice daily*

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

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

| | Recommended Starting Dosage | | Dose Level Reductions | | |
|---|---|---|---|---|---|
| Body weight (kg) | Daily Dose | # of 10 mg tablets twice daily | First Reduction | Second Reduction | Third Reduction |
| | | | # of 10 mg tablets twice daily | | |
| 8 to 9 kg | 20 mg twice daily | 2 | 1 | - | - |
| 10 to 13 kg | 30 mg twice daily | 3 | 2 | 1 | - |
| 14 to 17 kg | 40 mg twice daily | 4 | 3 | 2 | 1 |
| 18 to 21 kg | 50 mg twice daily | 5 | 3 | 2 | 1 |
| 22 to 25 kg | 60 mg twice daily | 6 | 4 | 3 | 2 |
| 26 to 29 kg | 70 mg twice daily | 7 | 5 | 4 | 2 |
| 30 to 33 kg | 80 mg twice daily | 8 | 5 | 4 | 3 |
| 34 to 37 kg | 90 mg twice daily | 9 | 6 | 5 | 3 |
| 38 to 41 kg | 100 mg twice daily | 10 | 7 | 5 | 3 |
| 42 to 45 kg | 110 mg twice daily | 11 | 7 | 6 | 4 |
| 46 to 50 kg | 130 mg twice daily | 13 | 9 | 7 | 4 |
| ≥51 kg | 150 mg twice daily | 15 | 10 | 8 | 5 |

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

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

**Table 4 Recommended dose modifications for dabrafenib (excluding pyrexia)**

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

| Grade (CTC-AE)* | Recommended dabrafenib Dose Modifications |
|---|---|
| Grade 4 | Discontinue permanently, or interrupt therapy until grade 0 – 1 and reduce by one dose level when resuming therapy. |

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

Exceptions where dose modifications are necessary for only dabrafenib:

- Pyrexia
- Uveitis

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

*Detailed dosing modifications for selected adverse reactions*

*New Primary Malignancies:*

For New Primary Cutaneous Malignancies no dose modifications are required. For New Primary Non-Cutaneous Malignancies in patients who develop RAS mutation-positive non-cutaneous malignancies, permanently discontinue dabrafenib.

*Haemorrhagic events:*

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

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

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

*Pyrexia Management*

Follow the dose modifications below. Therapy should be interrupted (dabrafenib when used as monotherapy, and both dabrafenib and trametinib when used in combination) if the patient's temperature is ≥38.0°C, or at the first symptom of pyrexia/pyrexia syndrome. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia/pyrexia syndrome. Initiate treatment with anti-pyretics such as ibuprofen or paracetamol. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection (see section 4.4 – Special warnings and precautions for use). Dabrafenib when used as monotherapy, or both dabrafenib and trametinib when used in combination, should be restarted if patient is symptom free for at least 24 hours either (1) at the same dose level, or (2) reduced by one dose level, if pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient (see table 5). Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia.

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

**Table 5** Recommended dose modifications for dabrafenib

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

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

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

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

**Special populations**

*Paediatric patients (< 18 years of age)*
The safety and efficacy of dabrafenib in combination with trametinib have not been established in paediatric patients younger than 1 year of age with LGG/HGG with BRAF V600E mutation. The safety and effectiveness of dabrafenib as a single agent in paediatric patients have not been established.

Studies in juvenile animals have shown effects of dabrafenib which had not been observed in adult animals (see section 4.4 – Special warnings and precautions for use).

*Patients > 65 years of age*

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

*Renal impairment*
No dose adjustment is required for patients with mild or moderate renal impairment. Based on the population pharmacokinetic analysis, mild and moderate renal impairment had no significant effect on dabrafenib oral clearance or on the concentrations of its metabolites (see

section 5.2 – Pharmacokinetic properties). There are no clinical data in patients with severe renal impairment and the potential need for dose adjustment cannot be determined. dabrafenib should be used with caution in patients with severe renal impairment.

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

**Administration**

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

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

*Hard capsules*

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

*Dispersible tablets*

Dabrafenib dispersible tablets are to be taken as a suspension only and should not be swallowed whole, chewed, or crushed. For instructions on reconstitution of the medicine before administration, see section 6.6.

*Combination therapy*
When dabrafenib and trametinib are taken in combination, take the once-daily dose of trametinib at the same time each day with either the morning dose or the evening dose of dabrafenib.

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

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

BRAF V600 testing

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

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

Pyrexia and serious non-infectious febrile events

Pyrexia was reported in clinical trials with dabrafenib monotherapy and in combination with trametinib (see section 4.8 – Undesirable effects). In a Phase III clinical trial in patients with unresectable or metastatic melanoma, the incidence and severity of pyrexia were increased when dabrafenib was used in combination with trametinib (57% [119/209], 7% Grade 3) as compared to dabrafenib monotherapy (33% [69/211], 2% Grade 3). In a Phase III trial in the adjuvant treatment of melanoma, the incidence and severity of pyrexia were higher in the dabrafenib in combination with trametinib arm (67% [292/435]; 6% Grade 3/4) as compared to the placebo arm (15% [66/432]; <1% Grade 3). In a Phase II trial in patients with rare cancers including ATC, the incidence and severity of pyrexia was 35% (35/100), 4% Grade 3 or 4 across all cohorts. In a Phase II trial in patients with NSCLC the incidence and severity of pyrexia were increased slightly when dabrafenib was used in combination with trametinib (55% [51/93], 5% Grade 3) as compared to dabrafenib monotherapy (37% [31/84], 2% Grade 3). In patients with unresectable or metastatic melanoma who received the combination dose of dabrafenib 150 mg twice daily and trametinib 2 mg once daily and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy. About one-third of the patients receiving combination therapy who experienced pyrexia had three or more events. Pyrexia may be accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency (see section 4.4 – Special warnings and precautions for use and section 4.8 – Undesirable effects).

Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia (see section 4.4 – Special warnings and precautions for use, Renal failure).

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

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

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

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

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

For management of pyrexia, see Section 4.2 Dose and method of administration, Dose Modification Guidelines and the full data sheet for trametinib.

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 dabrafenib as monotherapy and in combination with trametinib (see section 4.8). In a Phase III study in patients with unresectable or metastatic melanoma, 10 % (22/211) of patients receiving dabrafenib monotherapy developed cuSCC with a median time to the first occurrence of approximately 8 weeks. In patients who received the combination dose of dabrafenib in combination with trametinib, 3 % (6/209) of patients developed cuSCC and, events occurred later, with the median time to onset of the first occurrence of 20 to 32 weeks. More than 90 % of patients on dabrafenib who developed cuSCC continued on treatment without dose modification. In a Phase II trial in patients with NSCLC, 18 % (15/84) of patients receiving dabrafenib monotherapy developed cuSCC, with a median time to onset of the first occurrence of approximately 11 weeks. In patients who received dabrafenib in combination with trametinib, only 2% (2/93) of patients developed cuSCC. In a Phase III trial in the adjuvant treatment of melanoma, 1% (6/435) of patients receiving dabrafenib in combination with trametinib as compared to 1% (5/432) of patients receiving placebo developed cuSCC. The median time to onset of the first occurrence of cuSCC in the combination arm was approximately 18 weeks.

Skin examination be performed prior to initiation of dabrafenib and every month throughout treatment with dabrafenib and for up to 6 months after treatment for cuSCC. Monitoring should continue for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy. Cases of cuSCC should be managed by dermatological excision and dabrafenib treatment should be continued without any dose adjustment. Patients should be instructed to immediately inform their physician if new lesions develop.

New primary melanoma

New primary melanomas have been reported in patients treated with dabrafenib. In clinical trials in unresectable or metastatic melanoma, these were identified within the first 5 months of therapy, were managed with excision and did not require treatment modification. In the Phase III clinical trial in the adjuvant treatment of melanoma, new primary melanomas occurred in < 1 % (1/435) of patients receiving the combination of dabrafenib and trametinib as opposed to 1 % (6/432) of patients receiving placebo. Monitoring for skin lesions should occur as described for cuSCC.

Non-cutaneous malignancies

*In vitro* experiments have demonstrated paradoxical activation of MAP-kinase signalling in BRAF wild type cells with RAS mutations when exposed to BRAF inhibitors, which may lead to increased risk of non-cutaneous malignancies in patients treated with dabrafenib. Cases of RAS-driven malignancies have seen with BRAF inhibitors. In the Phase III trial in the adjuvant treatment of melanoma comparing combination of dabrafenib and trametinib to placebo, non-cutaneous secondary malignancies or recurrent malignancies were observed in 1% (5/435) of patients receiving active therapy compared to 1% (3/432) of patients receiving placebo.

Patients should be monitored as clinically appropriate. In patients with a non-cutaneous malignancy that has a RAS mutation the benefits and risks should be considered before continuing treatment with dabrafenib. No dose modification of trametinib is required when taken in combination with dabrafenib.

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

*Uveitis*

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

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

Pancreatitis

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

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

Hyperglycaemia

Hyperglycaemia requiring an increase in the dose of, or initiation of insulin or oral hypoglycaemic 68 agent therapy can occur with dabrafenib. In the pivotal study, five of 12 patients with a history of diabetes required more intensive hypoglycaemic therapy while taking dabrafenib. The incidence of Grade 3 hyperglycaemia based on laboratory values was 6 % (12/187) in patients treated with dabrafenib compared to none of the dacarbazine-treated patients. Monitor serum glucose levels as clinically appropriate during treatment with dabrafenib in patients with pre-existing diabetes or hyperglycaemia. Advise patients to report

symptoms of severe hyperglycaemia such as excessive thirst or any increase in the volume or frequency of urination.

Renal failure

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

*Dabrafenib in combination with trametinib*

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

Haemorrhage

Haemorrhagic events, including major haemorrhagic events have occurred in patients taking trametinib in combination with dabrafenib (see section 4.8 – Undesirable effects). Six out of the 559 unresectable or metastatic melanoma patients (1.1 %) treated with dabrafenib in combination with trametinib in a phase III trial had fatal intracranial haemorrhagic events. Three cases were from study MEK115306 (COMBI-d) and three cases were from study MEK116513 (COMBI-v). No fatal haemorrhagic events occurred in the Phase III study in the adjuvant treatment of melanoma. Two out of 93 patients (2 %) receiving dabrafenib in combination with trametinib in a Phase II trial in patients with metastatic NSCLC had fatal intracranial haemorrhagic events. If patients develop symptoms of haemorrhage they should immediately seek medical care.

Haemophagocytic lymphohistiocytosis (HLH)

In post-marketing experience, HLH has been observed with dabrafenib in combination with trametinib. If HLH is suspected, treatment should be interrupted. If HLH is confirmed, treatment should be discontinued and appropriate management of HLH should be initiated.

Tumour Lysis Syndrome (TLS)

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

Skin toxicity

Severe cutaneous adverse reactions

Cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with dabrafenib 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, dabrafenib and trametinib should be withdrawn.

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

Use in paediatrics (< 18 years of age)
The safety and efficacy of dabrafenib in combination with trametinib have not been established in paediatric patients younger than 1 year of age with LGG/HGG with BRAF V600E mutation. For information of paediatric patients aged 1 to 18 years, refer to section 4.1 – Therapeutic indications, section 4.2 – Dose and method of administration, section 4.8 – Undesirable effects, section 5.1 – Pharmacodynamic properties and section 5.2 – Pharmacokinetic properties. The safety and effectiveness of dabrafenib as a single agent in paediatric patients have not been established.

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

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

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

## 4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on dabrafenib

Based on *in vitro* studies, dabrafenib was shown to be primarily metabolised by cytochrome P450 (CYP) 2C8 and CYP3A4 (see section 5.2 – Pharmacokinetic properties). Dabrafenib's active metabolites hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates. Medicinal products that are strong inhibitors or inducers of CYP2C8 or CYP3A4 are likely to increase or decrease, respectively, dabrafenib concentrations. Alternative agents should be considered during administration with dabrafenib when possible.

Use caution if strong inhibitors (e.g. ketoconazole, nefazodone, clarithromycin, ritonavir, saquinavir, telithromycin, itraconazole, voriconazole, posaconazole, atazanavir, gemfibrozil) are coadministered with dabrafenib.

Avoid coadministration of dabrafenib with potent inducers of CYP2C8 or CYP3A4 (e.g. rifampin, phenytoin, carbamazepine, phenobarbital, St. John's wort (*Hypericum perforatum*)).

*Ketoconazole*
Pharmacokinetic data showed an increase in repeat-dose dabrafenib Cmax (33%) and AUC (71%) upon co-administration with ketoconazole (CYP3A4 inhibitor), and increases of 82% and 68% of hydroxy- and desmethyl-dabrafenib AUC, respectively. A decrease in AUC was noted for carboxy-dabrafenib (decrease of 16%).

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

*Rifampin*

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

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

Effect of dabrafenib on other drugs

Dabrafenib induces CYP3A4- and CYP2C9-mediated metabolism (see section 5.1 – Pharmacodynamic properties and Section 5.2 – Pharmacokinetic properties) and may induce other enzymes, including CYP2B6, CYP2C8, CYP2C19 and UDP glucuronosyltransferases (UGT). Dabrafenib may also induce transporters (e.g. P-glycoprotein (Pgp)). In human hepatocytes, dabrafenib produced dose-dependent increases in CYP2B6 and CYP3A4 mRNA levels up to 32 times the control levels. Co-administration of dabrafenib and medicinal products which are affected by the induction of these enzymes or transporters such as hormonal contraceptives (see section 4.4 – Special warnings and precautions for use and Section 4.6 – Fertility, pregnancy and lactation), dexamethasone, antiretroviral agents, or immunosuppressants may result in decreased concentrations and loss of efficacy. Concomitant use of dabrafenib with these medicinal products should generally be avoided if monitoring for efficacy and dose adjustment is not possible. If co-administration of these medications is necessary, monitor subjects for loss of efficacy or consider substitutions of these medicinal products.

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

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

*Warfarin*
In a separate trial in 14 patients, 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 a small increase in Cmax (18 % and 19 % respectively).

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

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

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

Effects of dabrafenib on substance transport systems
Dabrafenib is an *in vitro* inhibitor of human organic anion transporting polypeptide (OATP) 1B1 (OATP1B1) and OATP1B3 and clinical relevance cannot be excluded. Monitoring is recommended for adverse reactions if dabrafenib is co-administered with drugs that are OATP1B1 or OATP1B3 substrates with a narrow therapeutic index with regards to high peak concentrations.

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

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

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

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

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

## 4.6 Fertility, pregnancy and lactation

Effects on Fertility

*Infertility*

There are no data in humans.

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

Use in Pregnancy (Category D)

Dabrafenib can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of dabrafenib in pregnant women. Reproductive studies in animals (rats) have demonstrated dabrafenib-induced embryofetal development toxicity, including teratogenic effects. In adult female rats dosed with dabrafenib before mating and during gestation, embryofetal toxicities including embryo-lethality, fetal ventricular septal defects, and variation in thymic shape were observed at 300 mg/kg/day, and delayed skeletal development and reduced fetal body weight at ≥20 mg/kg/day (≥0.5 times human clinical exposure based on AUC). Dabrafenib should not be administered to pregnant women unless the potential benefit to the mother outweighs the possible risk to the foetus.

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

*Contraception*

*Females*

Women of reproductive potential should be advised that animal studies have been performed showing dabrafenib to be harmful to the developing fetus. Sexually-active females of reproductive potential are recommended to use effective methods of contraception (methods that result in less than 1% pregnancy rates) when taking dabrafenib and for at least two weeks following discontinuation of dabrafenib. If taking dabrafenib in combination with trametinib, sexually-active females of reproductive potential are recommended to use effective contraception and for at least 16 weeks after stopping treatment.

Dabrafenib may decrease the efficacy of oral or any other systemic hormonal contraceptives and an effective alternate method of contraception should be used (see section 4.5 – Interactions with other medicines and other forms of interactions).

*Males*

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

Use in Lactation

There are no data on the effect of dabrafenib on the breast-fed child, or the effect of dabrafenib on milk production. Because many drugs are transferred into human milk and because of the potential for adverse reactions in a suckling child from dabrafenib, a nursing

mother should be advised of the potential risks to the child. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for dabrafenib and any potential adverse effects on the breast-fed child from dabrafenib or from the underlying maternal condition.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

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

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

*Summary of the safety profile*

*Unresectable or metastatic melanoma*

Dabrafenib monotherapy

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

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

**Table 6 Adverse reactions for dabrafenib monotherapy in unresectable or metastatic melanoma**

| | |
|---|---|
| ***Neoplasms benign and malignant (including cysts and polyps)*** | |
| Very common | Papilloma |
| Common | Acrochordon (skin tags), cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma, seborrheic keratosis, basal cell carcinoma |
| Uncommon | New primary melanoma |
| ***Immune System Disorders*** | |
| Uncommon | Hypersensitivity, panniculitis |
| ***Infections and infestations*** | |
| Common | Nasopharyngitis |
| ***Metabolism and nutrition disorders*** | |
| Very common | Decreased appetite |
| Common | Hypophosphataemia, hyperglycaemia |
| ***Nervous system disorders*** | |

| | |
|---|---|
| Very common | Headache |
| ***Eye disorders*** | |
| Uncommon | Uveitis |
| ***Respiratory, thoracic and mediastinal disorders*** | |
| Very common | Cough |
| ***Gastrointestinal disorders*** | |
| Very common | Nausea, vomiting, diarrhoea |
| Common | Constipation |
| Uncommon | Pancreatitis |
| ***Skin and subcutaneous tissue disorders*** | |
| Very common | Skin effects (rash, hyperkeratosis), alopecia, palmar-plantar erythrodysaesthesia syndrome |
| Common | Skin effects (actinic keratosis, skin lesion, dry skin, erythema), pruritus, photosensitivity reaction[1] |
| Uncommon | Panniculitis |
| ***Musculoskeletal and connective tissue disorders*** | |
| Very common | Arthralgia, myalgia, pain in extremity |
| ***Renal disorders*** | |
| Uncommon | Renal failure, acute renal failure, tubulointerstitial nephritis |
| ***General disorders and administration site conditions*** | |
| Very common | Asthenia, chills, fatigue, pyrexia |
| Common | Influenza-like illness |
| ***Investigations*** | |
| Common | LVEF decrease |
| Uncommon | QT prolongation |

[1] Photosensitivity cases were also observed in post-marketing experience. All cases reported in clinical trials (BRF113683 (BREAK-3), BRF113929 (BREAK-MB), BRF113710 (BREAK-2), BRF113220, and BRF112680) were Grade 1 and no dose modifications were required.

Dabrafenib and trametinib combination therapy

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

Table 7 lists adverse reactions when trametinib was used in combination with dabrafenib from the randomised double-blind Phase III study MEK115306 (n = 209, COMBI-d), and integrated safety data from MEK115306 (n = 209) and from the randomised open-label Phase III study MEK 116513 (n = 350, COMBI-v).

**Table 7 Adverse reactions for dabrafenib in combination with trametinib in unresectable or metastatic melanoma – data from the randomised double-blind phase III combination study MEK115306 (COMBI-d), and integrated safety data from two randomised phase III combination studies, MEK115306 and MEK116513 (COMBI-d and COMBI-v)**

| Adverse reactions | Frequency classification<br>COMBI-d (MEK115306) N=209 | COMBI-d (MEK115306) & COMBI-v (MEK116513) integrated data N=559 |
|---|---|---|
| **Infections and Infestations** | | |
| Urinary tract infection | Very common | Common |
| Nasopharyngitis | Very common | Very common |
| Cellulitis | Common | Common |
| Folliculitis | Common | Common |
| Paronychia | Common | Common |
| Rash pustular | Common | Common |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | | |
| Cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma | Common | Common |
| Papilloma including skin papilloma | Common | Common |
| Seborrhoeic keratosis | Common | Common |
| Acrochordon (skin tags) | Common | Uncommon |
| New primary melanoma | Uncommon | Uncommon |
| **Blood and lymphatic system disorders** | | |
| Neutropenia | Very Common | Common |
| Anaemia | Common | Common |
| Thrombocytopenia | Common | Common |
| Leukopenia | Common | Common |
| **Immune system disorders** | | |
| Hypersensitivity | Uncommon | Uncommon |
| **Metabolic and nutrition disorders** | | |
| Decreased appetite | Very common | Very common |
| Dehydration | Common | Common |
| Hyperglycaemia | Common | Common |
| Hyponatraemia | Common | Common |
| Hypophosphataemia | Common | Common |
| **Nervous system disorders** | | |
| Headache | Very common | Very common |
| Dizziness | Very common | Very common |
| **Eye disorders** | | |
| Vision blurred | Common | Common |
| Visual impairment | Common | Common |
| Chorioretinopathy | Uncommon | Uncommon |
| Uveitis | Uncommon | Uncommon |
| Retinal detachment | Uncommon | Uncommon |
| Periorbital oedema | Uncommon | Uncommon |
| **Cardiac disorders** | | |
| Ejection fraction decreased | Common | Common |
| Left ventricular dysfunction | NR | Uncommon |
| Cardiac failure | NR | Uncommon |
| Bradycardia | Common | Common |
| **Vascular disorders** | | |
| Cardiac failure | NR | Uncommon |
| Hypertension | Very common | Very common |
| Haemorrhage1 | Very common | Very common |

| Adverse reactions | Frequency classification<br>COMBI-d (MEK115306) N=209 | COMBI-d (MEK115306) & COMBI-v (MEK116513) integrated data N=559 |
|---|---|---|
| Hypotension | Common | Common |
| Lymphoedema | Uncommon | Common |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Cough | Very common | Very common |
| Dyspnoea | Common | Common |
| Pneumonitis | Uncommon | Uncommon |
| Interstitial lung disease | NR | Uncommon |
| **Gastrointestinal disorders** | | |
| Gastrointestinal perforation | Not reported | Uncommon |
| Colitis | Uncommon | Uncommon |
| Abdominal pain | Very common | Very common |
| Constipation | Very common | Very common |
| Diarrhoea | Very common | Very common |
| Nausea | Very common | Very common |
| Vomiting | Very common | Very common |
| Dry mouth | Common | Common |
| Stomatitis | Common | Common |
| Pancreatitis | Uncommon | Uncommon |
| **Investigations** | | |
| Alanine aminotransferase increased | Very common | Very common |
| Aspartate aminotransferase increased | Very common | Very common |
| Blood alkaline phosphatase increased | Common | Common |
| Gamma-glutamyltransferase increased | Common | Common |
| **Skin and subcutaneous tissue disorders** | | |
| Dry skin | Very common | Very common |
| Pruritus | Very common | Very common |
| Rash | Very common | Very common |
| Dermatitis acneiform | Very common | Common |
| Erythema | Common | Common |
| Actinic keratosis | Common | Common |
| Night sweats | Common | Common |
| Hyperkeratosis | Common | Common |
| Alopecia | Common | Common |
| Palmar-plantar erythrodysaesthesia syndrome | Common | Common |
| Skin lesion | Common | Common |
| Hyperhidrosis | Common | Common |
| Skin fissures | Common | Common |
| Panniculitis | Common | Common |
| Photosensitivity reaction[1)] | Common | Common |
| **Musculoskeletal and connective tissue disorders** | | |
| Arthralgia | Very common | Very common |
| Myalgia | Very common | Very common |
| Pain in extremity | Very common | Very common |
| Muscle spasms | Common | Common |
| Blood creatine phosphokinase increased | Common | Common |
| Rhabdomyolysis | NR | Uncommon |
| **Renal disorders** | | |

| Adverse reactions | Frequency classification<br>COMBI-d (MEK115306) N=209 | COMBI-d (MEK115306) & COMBI-v (MEK116513) integrated data N=559 |
|---|---|---|
| Renal failure | Uncommon | Common |
| Nephritis | Uncommon | Uncommon |
| Renal failure acute | NR | Uncommon |
| **General disorders and administration site disorders** | | |
| Fatigue | Very common | Very common |
| Oedema peripheral | Very common | Very common |
| Pyrexia | Very common | Very common |
| Chills | Very common | Very common |
| Asthenia | Very common | Very common |
| Mucosal inflammation | Common | Common |
| Influenza-like illness | Common | Common |
| Face oedema | Common | Common |

NR= Not reported

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

*Metastatic melanoma patients with brain metastases*

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

*Adjuvant treatment of melanoma*

Dabrafenib in combination with trametinib

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

In the dabrafenib 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.

Table 8 lists the adverse drug reactions in study BRF115532 (COMBI-AD) occurring at an incidence ≥10% for all grade adverse reactions or at an incidence ≥ 2% for Grade 3 and Grade 4 adverse drugs reactions or adverse events that are medically significant in the dabrafenib in combination with trametinib arm.

**Table 8 Adverse reactions for dabrafenib in combination with trametinib against placebo in adjuvant melanoma**

| Adverse drug reactions | Dabrafenib in combination with trametinib N=435 % | | Placebo N=432 % | | Frequency category (combination arm, all grades) |
|---|---|---|---|---|---|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | |
| **Infections and infestations** | | | | | |
| Nasopharyngitis[1)] | 12 | <1 | 12 | NR | Very common |
| **Blood and lymphatic system disorders** | | | | | |
| Neutropenia[2)] | 10 | 5 | <1 | NR | Very common |
| **Metabolism and nutrition disorders** | | | | | |
| Decreased appetite | 11 | <1 | 6 | NR | Very common |
| **Nervous system disorders** | | | | | |
| Headache[3)] | 39 | 1 | 24 | NR | Very common |
| Dizziness[4)] | 11 | <1 | 10 | NR | Very common |
| **Eye disorders** | | | | | |
| Uveitis | 1 | <1 | <1 | NR | Common |
| Chorioretinopathy[5)] | 1 | <1 | <1 | NR | Common |
| Retinal detachment[6)] | 1 | <1 | <1 | NR | Common |
| **Vascular disorders** | | | | | |
| Haemorrhage[7)] | 15 | <1 | 4 | <1 | Very common |
| Hypertension[8)] | 11 | 6 | 8 | 2 | Very common |
| **Respiratory, thoracic, and mediastinal disorders** | | | | | |
| Cough[9)] | 17 | NR | 8 | NR | Very common |
| **Gastrointestinal disorders** | | | | | |
| Nausea | 40 | <1 | 20 | NR | Very common |
| Diarrhoea | 33 | <1 | 15 | <1 | Very common |
| Vomiting | 28 | <1 | 10 | NR | Very common |
| Abdominal pain[10)] | 16 | <1 | 11 | <1 | Very common |
| Constipation | 12 | NR | 6 | NR | Very common |
| **Skin and subcutaneous tissue disorders** | | | | | |
| Rash[11)] | 37 | <1 | 16 | <1 | Very common |
| Dry skin[12)] | 14 | NR | 9 | NR | Very common |
| Dermatitis acneiform | 12 | <1 | 2 | NR | Very common |
| Erythema[13)] | 12 | NR | 3 | NR | Very common |
| Pruritus[14)] | 11 | <1 | 10 | NR | Very common |
| Palmar-plantar erythrodysaesthesia syndrome | 6 | <1 | 1 | <1 | Common |
| **Musculoskeletal and connective tissue disorders** | | | | | |
| Arthralgia | 28 | <1 | 14 | NR | Very common |
| Myalgia[15)] | 20 | <1 | 14 | NR | Very common |
| Pain in extremity | 14 | <1 | 9 | NR | Very common |
| Muscle spasms[16)] | 11 | NR | 4 | NR | Very common |
| Rhabdomyolysis | <1 | <1 | NR | NR | Uncommon |
| **Renal and urinary disorders** | | | | | |
| Renal failure | <1 | NR | NR | NR | Uncommon |
| **General disorders and administration site conditions** | | | | | |
| Pyrexia[17)] | 63 | 5 | 11 | <1 | Very common |
| Fatigue[18)] | 59 | 5 | 37 | <1 | Very common |

| Adverse drug reactions | Dabrafenib in combination with trametinib N=435 % | | Placebo N=432 % | | Frequency category (combination arm, all grades) |
|---|---|---|---|---|---|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | |
| Chills | 37 | 1 | 4 | NR | Very common |
| Oedema peripheral[19)] | 16 | <1 | 6 | NR | Very common |
| Influenza-like illness | 15 | <1 | 7 | NR | Very common |
| **Investigations** | | | | | |
| Alanine aminotransferase increased[20)] | 17 | 4 | 2 | <1 | Very common |
| Aspartate aminotransferase increased[21)] | 16 | 4 | 2 | <1 | Very common |
| Alkaline phosphatase increased | 7 | <1 | <1 | <1 | Common |
| Ejection fraction decreased | 5 | NR | 2 | <1 | Common |

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

*Locally advanced or metastatic anaplastic thyroid cancer*

*Dabrafenib in combination with trametinib*

The efficacy and safety of dabrafenib in combination with trametinib was studied in a Phase II, nine-cohort, multicenter, non-randomised, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC (see section 5.1 – Pharmacodynamic properties, Clinical studies).

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

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

Table 9 lists the adverse drug reactions for dabrafenib in combination with trametinib occurring at an incidence ≥ 10% for all grade adverse drug reactions or at an incidence ≥ 2% for Grade 3 and Grade 4 adverse drug reactions or events which are medically significant in Study BRF117019.

**Table 9 Adverse reactions for dabrafenib in combination with trametinib in the locally advanced or metastatic anaplastic thyroid cancer ATS population**

| Adverse drug reactions | Dabrafenib in combination with trametinib | | |
|---|---|---|---|
| | All grades n = 100 % | Grades 3/4 n = 100 % | Frequency category |
| **Blood and lymphatic system disorders** | | | |
| Neutropenia[1)] | 15 | 6 | Very common |
| Anaemia | 14 | 2 | Very common |
| Leukopenia[2)] | 13 | NR | Very common |
| **Metabolism and nutrition disorders** | | | |
| Hyperglycaemia | 12 | 3 | Very common |
| Decreased appetite | 11 | NR | Very common |
| Hypophosphataemia | 6 | 3 | Common |
| Hyponatremia | 3 | 3 | Common |
| **Nervous system disorders** | | | |
| Headache | 20 | 2 | Very common |
| Dizziness[3)] | 13 | NR | Very common |
| **Eye disorders** | | | |
| Detachment of retinal pigment epithelium | 1 | NR | Common |
| **Vascular disorders** | | | |
| Haemorrhage[4)] | 16 | NR | Very common |
| Hypertension | 4 | 2 | Common |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Cough[5)] | 21 | NR | Very common |
| **Gastrointestinal disorders** | | | |
| Nausea | 31 | 1 | Very common |
| Vomiting | 22 | 1 | Very common |
| Diarrhoea | 17 | 1 | Very common |
| Constipation | 15 | NR | Very common |
| Dry mouth | 11 | NR | Very common |
| **Skin and subcutaneous tissue disorders** | | | |
| Rash[6)] | 31 | 4 | Very common |
| **Musculoskeletal and connective tissue disorders** | | | |
| Myalgia[7)] | 11 | 1 | Very common |
| Arthralgia | 11 | NR | Very common |
| Rhabdomyolysis | 1 | 1 | Common |
| **General disorders and administration site conditions** | | | |
| Fatigue[8)] | 45 | 5 | Very common |
| Pyrexia | 35 | 4 | Very common |
| Chills | 25 | 1 | Very common |
| Oedema[9)] | 17 | NR | Very common |
| **Investigations** | | | |
| Alanine aminotransferase increased | 13 | 3 | Very common |

| Adverse drug reactions | Dabrafenib in combination with trametinib | | |
|---|---|---|---|
| | All grades n = 100 % | Grades 3/4 n = 100 % | Frequency category |
| Aspartate aminotransferase increased | 12 | 2 | Very common |
| Blood alkaline phosphatase increased | 11 | 3 | Very common |
| Ejection fraction decreased | 3 | 1 | Common |

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

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

*3) Dizziness includes dizziness, vertigo and vertigo positional.*

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

*5) Cough includes cough and productive cough.*

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

*7) Myalgia includes myalgia and musculoskeletal pain.*

*8) Fatigue includes fatigue, asthenia and malaise.*

*9,) Oedema includes oedema and peripheral oedema.*

*NR: not reported*

*Advanced non-small cell lung cancer*

Dabrafenib monotherapy

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

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

Dabrafenib in combination with trametinib

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

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

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

**Table 10 Adverse reactions for dabrafenib in combination with trametinib in advanced NSCLC**

| Adverse drug reactions | Dabrafenib in combination with trametinib | | |
|---|---|---|---|
| | All grades n = 93 % | Grades 3/4 n = 93 % | Frequency category |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | | | |
| Cutaneous squamous cell carcinoma | 3 | 2 | Common |
| **Blood and lymphatic system disorders** | | | |
| Neutropenia[1)] | 15 | 8 | Very common |
| Leukopenia | 6 | 2 | Common |
| **Metabolism and nutrition disorders** | | | |
| Hyponatraemia | 14 | 9 | Very common |
| Dehydration | 8 | 3 | Common |
| **Eye disorders** | | | |
| Detachment of retina/retinal pigment epithelium | 2 | NR | Common |
| **Nervous system disorders** | | | |
| Headache | 16 | NR | Very common |
| Dizziness | 14 | NR | Very common |
| **Cardiac disorders** | | | |
| Ejection fraction decreased | 9 | 4 | Common |
| **Vascular disorders** | | | |
| Haemorrhage[2)] | 26 | 3 | Very common |
| Hypotension | 15 | 2 | Very common |
| Hypertension | 8 | 6 | Common |
| Pulmonary embolism | 4 | 2 | Common |
| **Gastrointestinal disorders** | | | |
| Nausea | 46 | NR | Very common |
| Vomiting | 37 | 3 | Very common |
| Diarrhoea | 33 | 2 | Very common |
| Decreased appetite | 28 | NR | Very common |
| Constipation | 16 | NR | Very common |
| Pancreatitis acute | 1 | NR | Common |
| **Skin and subcutaneous tissue disorders** | | | |
| Erythema | 10 | NR | Very common |
| Dry skin | 32 | 1 | Very common |
| Rash[3)] | 31 | 3 | Very common |
| Pruritus[4)] | 15 | 2 | Very common |
| Hyperkeratosis[5)] | 13 | 1 | Very common |
| **Musculoskeletal and connective tissue disorders** | | | |
| Muscle spasms | 10 | NR | Very common |
| Arthralgia | 16 | NR | Very common |
| Myalgia | 13 | NR | Very common |
| **Renal and urinary disorders** | | | |
| Renal failure | 3 | 1 | Common |
| Tubulointerstitial nephritis | 2 | 2 | Common |
| **General disorders and administration site disorders** | | | |
| Pyrexia | 55 | 5 | Very common |
| Asthenia[6)] | 47 | 6 | Very common |

| Adverse drug reactions | Dabrafenib in combination with trametinib | | |
|---|---|---|---|
| | All grades n = 93 % | Grades 3/4 n = 93 % | Frequency category |
| Oedema[7)] | 35 | NR | Very common |
| Chills | 24 | 1 | Very common |
| **Investigations** | | | |
| Blood alkaline phosphatase increased | 12 | NR | Very common |
| Aspartate aminotransferase increased | 11 | 2 | Very common |
| Alanine aminotransferase increased | 10 | 4 | Very common |

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

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

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

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

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

*6) Asthenia also includes fatigue and malaise.*

*7) Oedema includes generalised oedema and peripheral oedema.*

*NR: Not Reported*

*Post-marketing experience and pooled clinical trials*

The following adverse reactions have been derived from post-marketing experience including spontaneous case reports with dabrafenib monotherapy or in combination with trametinib (Table 11). Because post-marketing ADRs are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency. Where applicable, these ADR frequencies have been calculated from the pooled clinical trials across indications. ADRs are listed according to system organ classes in MedDRA.

**Table 11 Adverse reactions from post-marketing experience and pooled clinical trials across indications**

| Adverse reaction | Dabrafenib in combination with trametinib frequency category | Dabrafenib monotherapy frequency category |
|---|---|---|
| **Cardiac disorders** | | |
| Atrioventricular block[1] | Common | - |
| Bundle branch block[2] | Uncommon | - |
| **Vascular disorders** | | |
| Venous thromboembolism (VTE)[3] | Common | - |
| **Skin and subcutaneous tissue disorders** | | |
| Acute febrile neutrophilic dermatosis (Sweet's syndrome) | Not known | - |
| Tattoo associated skin reaction | Not known | - |
| **Immune system disorders** | | |
| Sarcoidosis | Uncommon | - |
| Haemophagocytic lymphohistiocytosis | Not known | - |
| **Metabolism and nutrition disorders** | | |
| Tumour lysis syndrome | Not known | - |
| **Nervous system disorders** | | |
| Peripheral neuropathy | Common | Common |
| Guillain-Barré syndrome | Uncommon | - |

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

*Description of selected adverse reactions*

*Pyrexia*
Fever has been reported in clinical trials. In 1% of patients in clinical trials, serious non-infectious febrile events were identified defined as fever accompanied by severe rigors, dehydration, hypotension and/or acute renal insufficiency. The onset of these serious non-infectious febrile events was typically within the first month of therapy. Patients with serious non-infectious febrile events responded well to dose interruption and/or dose reduction and supportive care (see section 4.2 – Dose and method of administration and section 4.4 – Special warnings and precautions for use).

*Cutaneous squamous cell carcinoma*
Cutaneous squamous cell carcinomas (including those classified as keratoacanthoma or mixed keratoacanthoma subtype) occurred in 9% (52/578) of patients treated with dabrafenib. Approximately 70% of events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. Ninety-six percent of patients who developed cuSCC continued on treatment without dose modification.

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

*Non-cutaneous malignancy*
Activation of MAP-kinase signalling in BRAF wild type cells which are exposed to BRAF inhibitors may lead to increased risk of non-cutaneous malignancies, including those with RAS mutations (see section 4.4 – Special warnings and precautions for use). Cases of RAS-driven malignancies have been seen with dabrafenib. Patients should be monitored as clinically appropriate.

*Special populations*

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

*Paediatric use*

*Dabrafenib in combination with Trametinib*

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

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

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

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

**Table 12 Most frequent Grade 3/4 Adverse drug reactions (≥2%) for dabrafenib in combination with trametinib in paediatric patients**

| **Adverse drug reactions** | **Dabrafenib in combination with trametinib N=171** |
|---|---|
| | **Grade 3/4 n (%)** |
| Neutropenia[1] | 25 (15) |
| Pyrexia | 19 (11) |
| Transaminases increased[2] | 11(6) |
| Weight Increased | 9 (5) |
| Headache | 5 (3) |

| | |
|---|---|
| Vomiting | 5 (3) |
| Hypotension | 4 (2) |
| Rash[3] | 4 (2) |
| Blood alkaline phosphatase increased | 4 (2) |

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

Reporting of suspected adverse reactions

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

## 4.9 Overdose

Symptoms and Signs

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

Treatment

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

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

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

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

*Mechanism of action*

Dabrafenib monotherapy

Dabrafenib is an ATP-competitive inhibitor of RAF kinases with $IC_{50}$ values of 0.65, 0.5 and 1.84 nM for BRAF V600E, BRAF V600K and BRAF V600D enzymes, respectively. Dabrafenib also inhibits a small number of other kinases, including wild-type BRAF and CRAF with $IC_{50}$ values of 3.2 and 5.0nM, respectively in biochemical assays. Oncologic amino acid variants in BRAF at valine 600 (V600) lead to constitutive activation of the RAS/RAF/MEK/ERK pathway and stimulation of tumour cell growth. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50 % of melanoma and 1-3 % of NSCLC. The most commonly observed BRAF mutation (V600E), and the next most common (V600K) account for 95 % of the BRAF mutations found in all patients with cancers. A number of rare mutations also occur including V600D,

V600G and V600R. Clinical inhibition of the MAPK pathway signalling depends on cellular and genotypic context (see section 4.4 – Special warnings and precautions for use).

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

Dabrafenib in combination with trametinib

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

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

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

*Cardiac electrophysiology*

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

*Determination of BRAF mutation status*

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

*CLINICAL TRIALS*

Unresectable or metastatic melanoma

*Dabrafenib monotherapy*

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

- BRF113683 [BREAK-3]
- BRF113710 [BREAK-2] and

- BRF113929 [BREAK-MB].

Included in these studies were in total 402 patients with BRAF V600E and 49 patients with BRAF V600K mutation. Patients with evidence of active CNS disease (e.g. radiographically unstable or with symptomatic lesions) and those with disease progression in the brain in the last 3 months were excluded from the pivotal Phase III BREAK-3 study.

*BREAK-3: Study in previously untreated patients with BRAF V600E mutation positive advanced (unresectable Stage III) or metastatic (Stage IV) melanoma*

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

The trial enrolled 250 patients randomised 3:1 to receive either dabrafenib 150 mg twice daily or intravenous DTIC 1000 mg/m$^2$ every 3 weeks. The primary objective for this study was to evaluate the efficacy of dabrafenib compared to DTIC with respect to progression-free survival (PFS) per investigator assessment for patients with BRAF V600E mutation positive unresectable or metastatic melanoma. Patients on the DTIC arm were allowed to cross over and receive dabrafenib after independent radiographic confirmation of initial progression. Baseline characteristics were balanced between treatment groups. Sixty percent of patients were male and 99.6 % were Caucasian; the median age was 52 years with 21 % of patients being ≥ 65 years, 98.4 % had had an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1, and 97 % of patients had metastatic disease.

At the pre-specified analysis with a 19 December 2011 data cut, a significant improvement in the primary endpoint of PFS (HR = 0.30; 95% CI 0.18, 0.51; p< 0.0001) was achieved. PFS from the primary analysis is shown in Figure 1. Efficacy results from a post-hoc analysis with 6-months additional follow-up are summarised in Table 13.

**Table 13 Monotherapy efficacy data by Investigator Assessment in previously untreated patients (BREAK-3 study, 25 June 2012)**

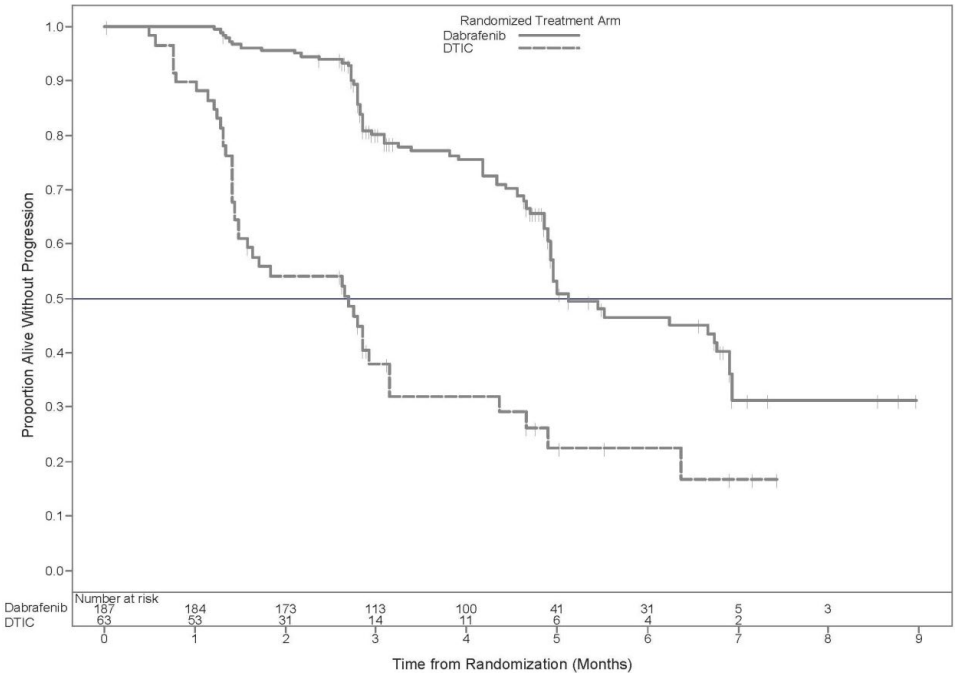
| | **Intention-to-Treat Population** | |
|---|---|---|
| **Endpoints/ Assessment** | **Dabrafenib** | **DTIC** |
| **Progression-free survival** | | |
| Median, months (95 % CI) | 6.9 (5.2, 9.0) | 2.7 (1.5, 3.2) |
| HR (95 % CI) | 0.37 (0.24, 0.58) | |
| **Overall response**[a] | | |
| % (95 % CI)[b] | 59 (51.4, 66.0) | 24 (21.4, 36.2) |
| | P<0.0001 | |
| **Duration of response** | | |
| | N=110 | N=15 |
| Median, months (9 5% CI) | 8.0 (6.6, 11.5) | 7.6 (5.0, 9.7) |

Abbreviations: CI: confidence interval; DTIC: dacarbazine; HR: hazard ratio; NR-not reached

[a.] Defined as complete response + partial response

Confirmed response

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



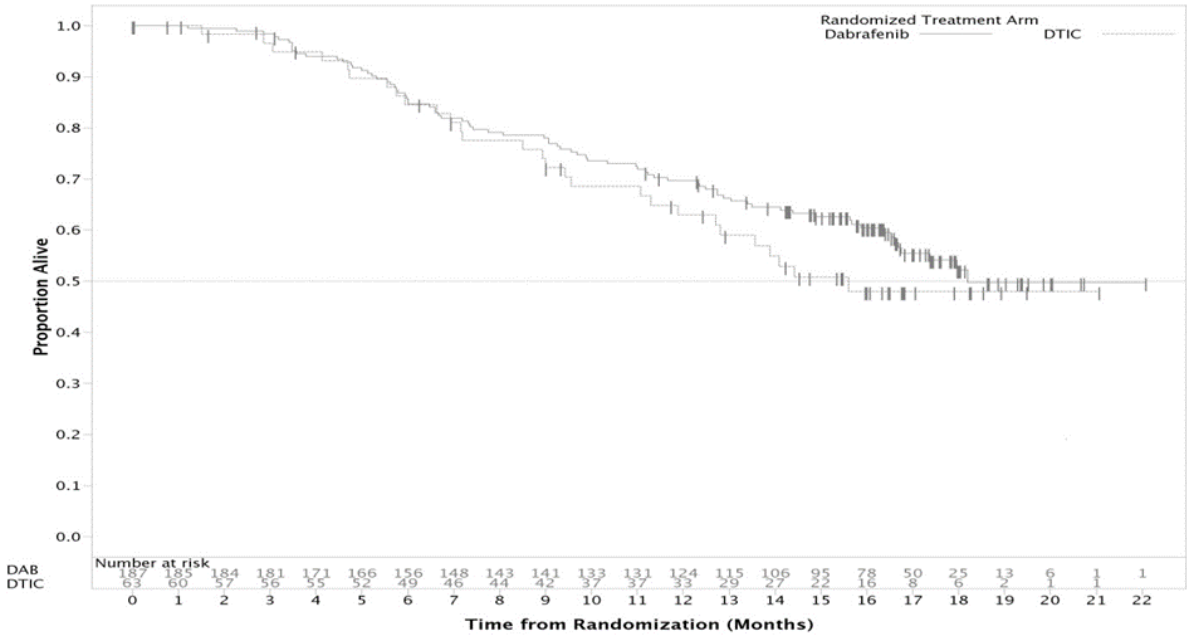

Overall survival data from a further post-hoc analysis based on an 18 December 2012 data cut is provided in Table 14 and shown in Figure 2.

**Table 14 Survival data from a post-hoc analysis (18 December 2012)**

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

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

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




As of 25 June 2012, thirty-five patients (55.6%) of the 63 randomised to DTIC crossed over to dabrafenib. Median PFS after cross-over was 4.4 months.

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

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

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

Patients were given dabrafenib 150 mg twice daily until unacceptable adverse reactions, disease progression, or death. The primary endpoint of the study was overall intracranial response rate (OIRR), which is a measure of response (complete response [CR] + partial response [PR]) of intracranial lesions using modified RECIST criteria as assessed by investigators. The results are summarised in Table 15. Of note, the benefit risk, in terms of intracranial response, relative to surgery or stereotactic radio-surgery has not been studied directly however evidence from cohort B below suggests that prior local treatment does not preclude subsequent benefit from BRAF inhibition.

**Table 15 Efficacy Data in Patients with Brain Metastases (BREAK-MB study)**

| Endpoints/ Assessment | All Treated Patients Population | | | |
|---|---|---|---|---|
| | BRAF V600E (Primary) | | BRAF V600K | |
| | Cohort A N=74 | Cohort B N=65 | Cohort A N=15 | Cohort B N=18 |
| **Overall intracranial response rate** | | | | |
| OIRR **%** (95% CI) [a] | 39 % (28.0, 51.2) | 31 % (19.9, 43.4) | 7 % (0.2, 31.9) | 22 % (6.4, 47.6) |
| p-value | < 0.001 | < 0.001 [b] | | |

| Endpoints/ Assessment | All Treated Patients Population | | | |
|---|---|---|---|---|
| | BRAF V600E (Primary) | | BRAF V600K | |
| | Cohort A N=74 | Cohort B N=65 | Cohort A N=15 | Cohort B N=18 |
| **Duration of intracranial response median months** | N=29 | N=20 | N=1 | N=4 |
| Median, months (95% CI) | 4.6 (2.8, NR) | 6.5 (4.6, 6.5) | 2.9 (NR, NR) | 3.8 (NR, NR) |
| **Overall response** OR % (95% CI) [a] | 38 % (26.8, 49.9) | 31 % (19.9, 43.4) | 0 (0, 21.8) | 28 % (9.7, 53.5) |
| **Duration of response** | N=28 | N=20 | NA | N=5 |
| Median, months (95% CI) | 5.1 (3.7, NR) | 4.6 (4.6, 6.5) | | 3.1 (2.8, NR) |
| **Progression-free survival** Median, months (95% CI) | 3.7 (3.6, 5.0) | 3.8 (3.6, 5.5) | 1.9 (0.7, 3.7) | 3.6 (1.8, 5.2) |
| **Overall survival** Median, months (95% CI) | 7.6 (5.9, NR) | 7.2 (5.9, NR) | 3.7 (1.6, 5.2) | 5.0 (3.5, NR) |

Abbreviations: CI: confidence interval; NR: not reached; NA: not applicable

a = Confirmed response.

b =This study was designed to support or reject the null hypothesis of OIRR ≤ 10 % (based on historical results) in favour of the alternative hypothesis of OIRR ≥ 30% in $BRAF^{V600E}$ positive patients.

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

BRF113710 (BREAK-2) was a multi-centre, global, open-label, single-arm, Phase II study that enrolled 92 patients with histologically confirmed metastatic melanoma (Stage IV) with confirmed BRAF V600E or V600K mutation-positive melanoma. Patients were treatment-naïve (n=15) or received prior treatment (n=77) in the metastatic setting (i.e., chemotherapy, immunotherapy, prior targeted therapy, etc.).

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

*Dabrafenib in combination with trametinib*

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

MEK115306 (COMBI-d)

MEK115306 (COMBI-d) was a Phase III, randomised, double-blind study comparing the combination of dabrafenib and trametinib to dabrafenib and placebo as first-line therapy for patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The primary endpoint of the study was investigator assessed progression-free survival (PFS) with a key secondary endpoint of Overall Survival (OS).

Patients were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ ULN) and BRAF mutation (V600E versus V600K).

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

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

**Table 16 Overall Survival results for Study MEK115306 (COMBI-d)**

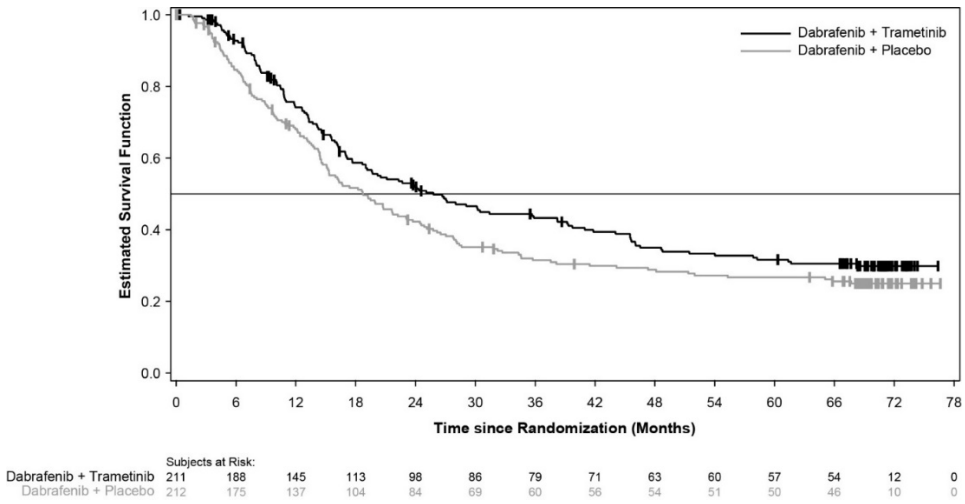
| | **OS analysis*** | | **3-year OS analysis*** | | **5-year OS analysis*** | |
|---|---|---|---|---|---|---|
| | **Dabrafenib + trametinib (n=211)** | **Dabrafenib + placebo (n=212)** | **Dabrafenib + trametinib (n=211)** | **Dabrafenib + placebo (n=212)** | **Dabrafenib + trametinib (n=211)** | **Dabrafenib + placebo (n=212)** |
| **Number of Patients** | | | | | | |
| Died (event), n (%) | 99 (47) | 123 (58) | 114 (54) | 139 (66) | 135 (64) | 151 (71) |
| **Estimates of OS (months)** | | | | | | |
| Median (95% CI) | 25.1 (19.2, NR) | 18.7 (15.2, 23.7) | 26.7 (19.0, 38.2) | 18.7 (15.2, 23.1) | 25.8 (19.2, 38.2) | 18.7 (15.2, 23.1) |
| Hazard ratio (95% CI) | 0.71 (0.55, 0.92) | | 0.75 (0.58, 0.96) | | 0.80 (0.63, 1.01) | |
| p-value | 0.011 | | NA | | NA | |
| **Overall survival Estimate, % (95% CI)** | **Dabrafenib + trametinib (n=211)** | | | **Dabrafenib + placebo (n=212)** | | |

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

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

NR = Not reached, NA = Not applicable

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




Clinically meaningful improvements for the primary endpoint of PFS were sustained over a 5 year timeframe in the combination arm compared to dabrafenib monotherapy. Clinically meaningful improvements were also observed for overall response rate (ORR) and a longer duration of response (DoR) was observed in the combination arm compared to dabrafenib monotherapy (Table 17).

**Table 17 Investigator-assessed efficacy results for MEK115306 (COMBI-d) study**

| Endpoints | Primary Analysis* | | Updated Analysis* | | 3 Year Analysis* | | 5 Year Analysis* | |
|---|---|---|---|---|---|---|---|---|
| | Dabrafenib + trametinib (n=211) | Dabrafenib + placebo (n=212) | Dabrafenib + trametinib (n=211) | Dabrafenib + placebo (n=212) | Dabrafenib + trametinib (n=211) | Dabrafenib + placebo (n=212) | Dabrafenib + trametinib (n=211) | Dabrafenib + placebo (n=212) |
| Investigator Assessed PFS | | | | | | | | |
| Progressive disease or death, n (%) | 102 (48) | 109 (51) | 139 (66) | 162 (76) | 153 (73) | 168[f] (79) | 160 (76) | 166[f] (78) |
| Median, months (95% CI[a]) | 9.3 (7.7, 11.1) | 8.8 (5.9, 10.9) | 11.0 (8.0, 13.9) | 8.8 (5.9, 9.3) | 10.2 (8.0, 12.8) | 7.6 (5.8, 9.3) | 10.2 (8.1, 12.8) | 8.8 (5.9, 9.3) |
| Hazard Ratio (95% CI) | 0.75 (0.57, 0.99) | | 0.67 (0.53, 0.84) | | 0.71 (0.57, 0.88) | | 0.73 (0.59, 0.91) | |
| *P* value (log-rank test) | 0.035 | | <0.001 | | NA | | NA | |
| Overall Response Rate[b] (%) 95% CI | 67 (59.9, 73.0) | 51 (44.5,58.4) | 69 (61.8, 74.8) | 53 (46.3, 60.2) | 68 (61.5, 74.5) | 55 (47.8, 61.5) | 69 (62.5, 75.4) | 54 (46.8, 60.6) |
| Difference in response rate (CR[c] +PR[c]), % 95% CI for difference *P* value | 15[d] 5.9, 24.5 0.0015 | | 15[d] 6.0, 24.5 0.0014[g] | | NA | | NA | |
| Duration of Response (months) | | | | | | | | |
| *Median (95% CI)* | 9.2[e] (7.4, NR) | 10.2[e] (7.5, NR) | 12.9 (9.4,19.5) | 10.6 (9.1,13.8) | 12.0 (9.3, 17.1) | 10.6 (8.3, 12.9) | 12.9 (9.3, 18.4) | 10.2 (8.3, 13.8) |

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

*a - Confidence interval*

*b - Overall Response Rate = Complete Response + Partial Response*

*c - CR: Complete Response, PR: Partial Response*

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

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

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

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

*NR = Not reached*

*NA=Not applicable*

*MEK116513 (COMBI-v)*

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

A total of 704 patients were randomised 1:1 to either the combination therapy arm (dabrafenib 150 mg twice daily and trametinib 2 mg once daily) or the vemurafenib monotherapy arm (960 mg twice daily). Most patients were white (> 96 %) and male (55 %), with a median age of 55 years (24 % were ≥ 65 years). The majority of patients had Stage IV M1c disease (61 %). Most patients had LDH ≤ULN (67 %), ECOG performance status of 0 (70 %), and visceral disease (78 %) at baseline. Overall, 54 % of patients had < 3 disease sites at Baseline. The majority of patients had a BRAF V600E mutation (89 %).

An OS analysis at 5 years demonstrated continued benefit for the combination of dabrafenib and trametinib compared with vemurafenib monotherapy; the median OS for the combination arm was approximately 8 months longer than the median OS for vemurafenib monotherapy (26.0 months versus 17.8 months) with 5 year survival rates of 36% for the combination versus 23% for vemurafenib monotherapy (Table 18, Figure 4). The Kaplan-Meier OS curve appears to stabilise from 3 years to 5 years (see Figure 4). The 5-year overall survival rate was 46% (95% CI: 38.8, 52.0) in the combination arm versus 28% (95% CI: 22.5, 34.6) in the vemurafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 9.3, 23.3) in the combination arm versus 10% (95% CI: 5.1, 17.4) in the vemurafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline.

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

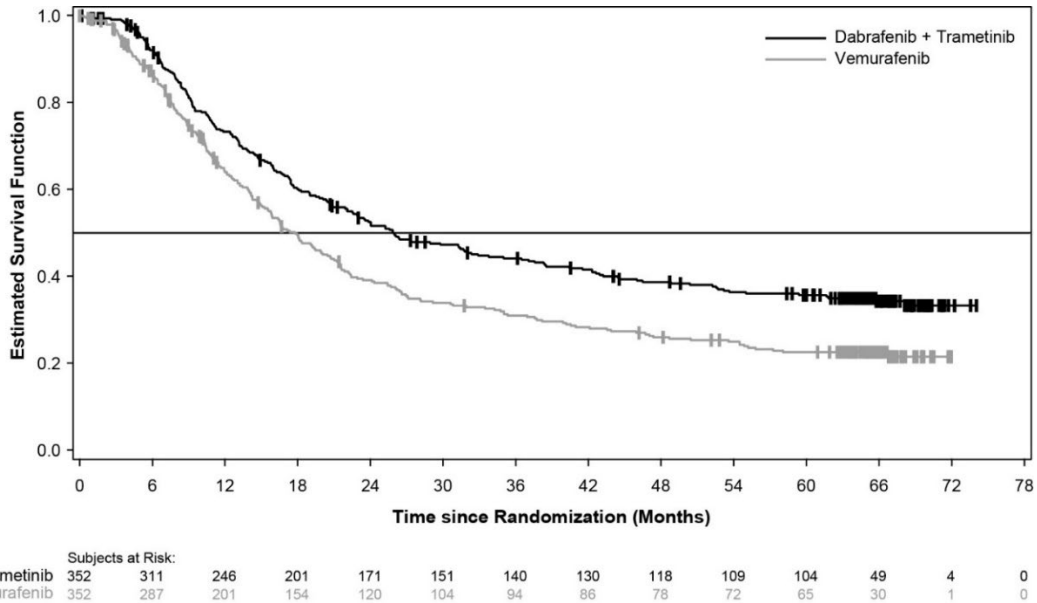


**Table 18 Overall Survival results for Study MEK116513 (COMBI-v)**

| | OS analysis* | | 3-year OS analysis* | | 5-year OS analysis* | |
|---|---|---|---|---|---|---|
| | **Dabrafenib + trametinib (n=352)** | **Vemurafenib (n=352)** | **Dabrafenib + trametinib (n=352)** | **Vemurafenib (n=352)** | **Dabrafenib + trametinib (n=352)** | **Vemurafenib (n=352)** |
| **Number of patients** | | | | | | |
| Died (event), n (%) | 100 (28) | 122 (35) | 190 (54) | 224 (64) | 216 (61) | 246 (70) |
| **Estimates of OS (months)** | | | | | | |
| Median (95% CI) | NR (18.3, NR) | 17.2 (16.4, NR) | 26.1 (22.6, 35.1) | 17.8 (15.6, 20.7) | 26.0 (22.1, 33.8) | 17.8 (15.6, 20.7) |
| Adjusted hazard ratio (95% CI) | 0.69 (0.53, 0.89) | | 0.68 (0.56, 0.83) | | 0.70 (0.58, 0.84) | |
| p-value | 0.005 | | NA | | NA | |
| **Overall survival Estimate, % (95% CI)** | **Dabrafenib + Trametinib (n=352)** | | | | **Vemurafenib (n=352)** | |
| At 1 year | 72 (67, 77) | | | | 65 (59, 70) | |
| At 2 years | 53 (47.1, 57.8) | | | | 39 (33.8, 44.5) | |
| At 3 years | 44 (38.8, 49.4) | | | | 31 (25.9, 36.2) | |
| At 4 years | 39 (33.4, 44.0) | | | | 26 (21.3, 31.0) | |
| At 5 years | 36 (30.5, 40.9) | | | | 23 (18.1, 27.4) | |

NR = Not reached, NA = Not applicable

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

Clinically meaningful improvements for the secondary endpoint of PFS were sustained over a 5-year timeframe in the combination arm compared to vemurafenib monotherapy. Clinically meaningful improvements were also observed for overall response rate (ORR) and a longer duration of response (DoR) was observed in the combination arm compared to vemurafenib monotherapy (Table 19).

**Table 19 Investigator-assessed efficacy results for MEK116513 (COMBI-v) study**

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

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

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

*PFS = Progression Free Survival; NR = Not reached*

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

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

A total of 125 patients were enrolled into four cohorts:

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

The primary endpoint of the study was intracranial response in Cohort A, defined as the percentage of patients with a confirmed intracranial response assessed by the investigator using modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Efficacy results are summarised in Table 20. Secondary endpoints were duration of intracranial response, ORR, PFS and OS. Efficacy results are summarised in Table 20.

**Table 20 COMBI-MB - Efficacy data by investigator assessment**

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

*Study BRF115532 / CDRB436F2301 (COMBI-AD)*

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

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

A total of 870 patients were randomised to the combination therapy (n=438) and placebo (n=432) arms. Most patients were Caucasian (99%) and male (55%), with a median age of 51 years (18% were ≥65 years). The study included patients with all sub-stages of Stage III disease prior to resection; 18% of these patients had lymph node involvement only identifiable by microscope and no primary tumour ulceration. The majority of patients had a BRAF V600E mutation (91%).

The median duration of follow-up at the time of the primary analysis was 2.83 years in the dabrafenib and trametinib combination arm and 2.75 years in the placebo arm.

Results for the primary analysis of RFS are presented in Table 21. The study showed a statistically significant difference for the primary outcome of investigator-assessed RFS between treatment arms, with an estimated 53% risk reduction in the dabrafenib and trametinib combination arm as compared to the placebo arm (HR=0.47; 95% CI: 0.39, 0.58; $p=1.53\times10^{-14}$). Results were consistent across subgroups, including stratification factors for disease stage and BRAF V600 mutation type. Median RFS was 16.6 months for the placebo arm and was not reached for the combination arm at the time of the primary analysis.

**Table 21 COMBI-AD Primary analysis – Relapse-free survival results**

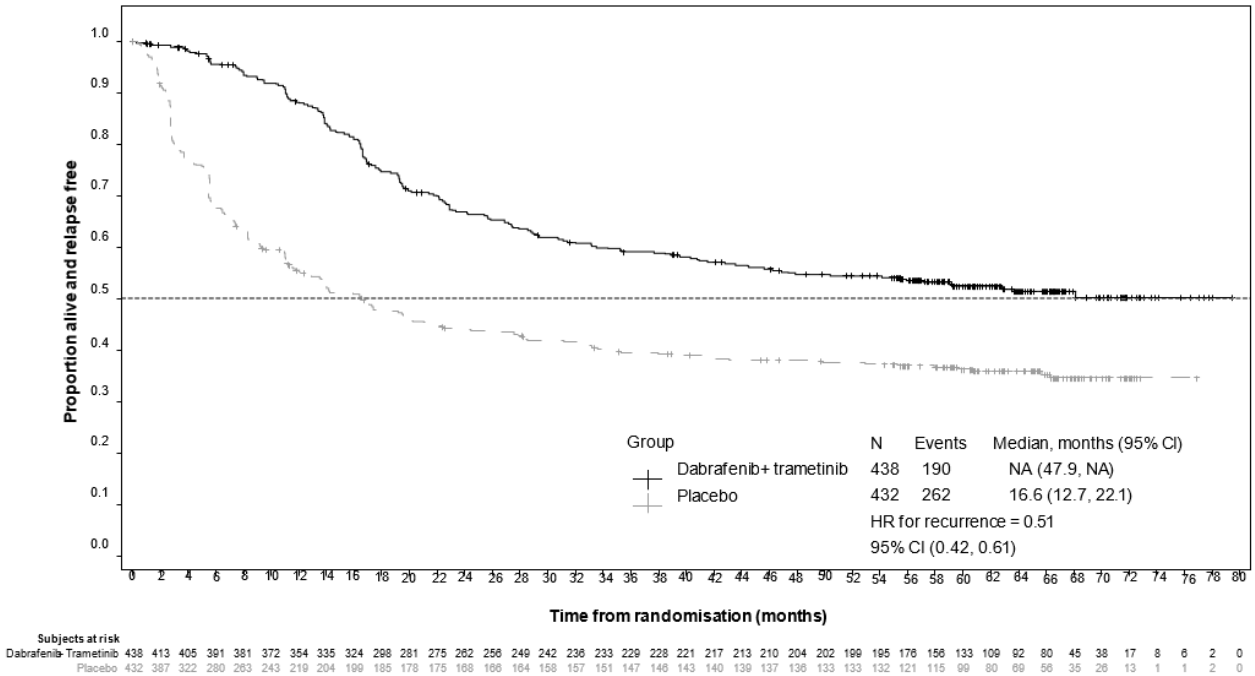
| RFS parameter | Dabrafenib + trametinib N=438 | | Placebo N=432 |
|---|---|---|---|
| Number of events, n (%) | 166 (38%) | | 248 (57%) |
| Recurrence | 163 (37%) | | 247 (57%) |
| Relapsed with distant metastasis | 103 (24%) | | 133 (31%) |
| Death | 3 (<1%) | | 1 (<1%) |
| Median (months) | NE | | 16.6 |
| (95% CI) | (44.5, NE) | | (12.7, 22.1) |
| Hazard ratio[1] | | 0.47 | |
| (95% CI) | | (0.39, 0.58) | |
| p-value[2] | | $1.53\times10^{-14}$ | |
| 1-year rate (95% CI) | 0.88 (0.85, 0.91) | | 0.56 (0.51, 0.61) |
| 2-year rate (95% CI) | 0.67 (0.63, 0.72) | | 0.44 (0.40, 0.49) |
| 3-year rate (95% CI) | 0.58 (0.54, 0.64) | | 0.39 (0.35, 0.44) |

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

[2] P-value is obtained from the two-sided stratified log-rank test (stratification factors were disease stage – IIIA vs. IIIB vs. IIIC – and BRAF V600 mutation type – V600E vs. V600K)
NE = not estimable

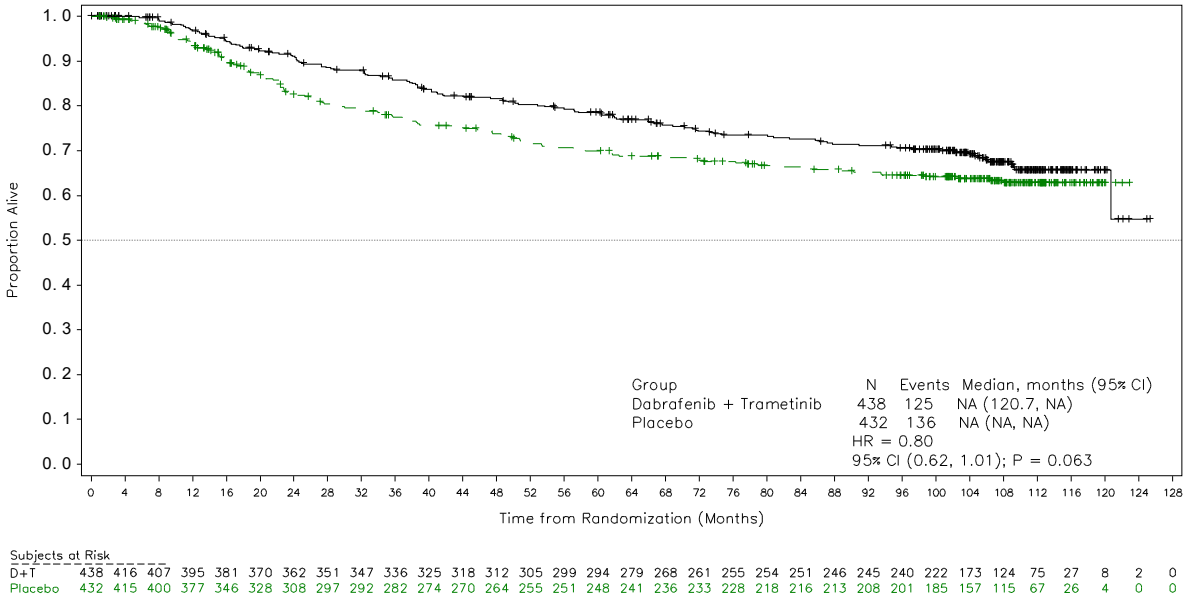
Based on updated data with an additional 29 months of follow-up compared to the primary analysis (minimum follow-up of 59 months), the RFS benefit was maintained with an estimated HR of 0.51 ([95% CI: (0.42, 0.61)] (Figure 5). The 5-year RFS rate was 52% (95% CI: 48, 58) in the combination arm compared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

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




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

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




Advanced NSCLC

*Study E2201 (BRF113928)*

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

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

Cohorts were enrolled sequentially:

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

Among the total of 93 patients who were enrolled in the combination therapy in Cohorts B and C most patients were Caucasians (n = 79, 85%). There was a similar female to male ratio (54% vs 46%). The median age was 64 years in patients who had at least one prior therapy

and 68 years in patients who were treatment naïve for their advanced disease. Most patients (n=87, 94%) enrolled in the combination therapy treated Cohorts had an ECOG performance status of 0 or 1. Twenty-six (26) patients (28%) had never smoked. Ninety-one (91) patients (97.8%) had a non-squamous histology. In the pre-treated population, 38 patients (67%) had one line of systemic anti-cancer therapy for metastatic disease.

**Primary analysis**

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

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

The final analysis of efficacy performed 5 years after last subject first dose is presented in Table 22.

**Table 22 Efficacy Results in Patients with BRAF V600E NSCLC**

| Endpoint | Analysis | Combination First Line | Combination Second Line Plus |
|---|---|---|---|
| | | N=36 | N=57 |
| Overall confirmed response n (%) (95 % CI) | By Investigator | 23 (63.9%) (46.2, 79.2) | 39 (68.4%) (54.8, 80.1) |
| | By IRC | 23 (63.9%) (46.2, 79.2) | 36 (63.2%) (49.3, 75.6) |
| Median DoR, months (95 % CI) | By Investigator | 10.2 (8.3, 15.2) | 9.8 (6.9, 18.3 ) |
| | By IRC | 15.2 (7.8, 23.5) | 12.6 (5.8, 26.2) |
| Median PFS, months (95 % CI) | By Investigator | 10.8 (7.0, 14.5) | 10.2 (6.9, 16.7) |
| | By IRC | 14.6 (7.0, 22.1) | 8.6 (5.2, 16.8) |
| Median OS, months (95 % CI) | - | 17.3 (12.3, 40.2) | 18.2 (14.3, 28.6 ) |

*Dabrafenib Monotherapy*

At the time of the primary objective analysis for Cohort A, ORR as per investigator assessment was observed in 32.1 % of second-line plus all treated patients (95 % CI: 21.9, 43.6). Partial response was the best response among all these patients. At a subsequent data

cut for mature DoR, the estimated median DoR was 9.6 months (95% CI: 5.4, 15.2). The estimated median PFS was 5.5 months (95 % CI: 3.4, 7.3). With an additional 18 months of follow-up from the primary objective analysis for Cohort A to determine a mature OS, the estimated median OS was 12.7 months (95 % CI: 7.3, 16.3).

Locally advanced or metastatic anaplastic thyroid cancer

*Study BRF117019 / CDRB436X2201*

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

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

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

For the primary endpoint, the investigator-assessed ORR was 56 % (95% CI: 38.1, 72.1) in the ATC cohort. The ORR results assessed by IRC and investigator-assessment were consistent (Table 23).

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

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

**Table 23 Efficacy Results in Patients with BRAF V600E ATC**

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

| Endpoint | Analysis By Investigator[1] ATC Cohort N= 36 | Analysis By IRC ATC Cohort N= 36 |
|---|---|---|
| Median OS, months (95% CI) | 14.5 (6.8, 23.2) | |

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

## Other Studies

### Pyrexia Management Analysis

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

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

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

Study DRB436G2201

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

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

confirm the BRAF V600E mutation.

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

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

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

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

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

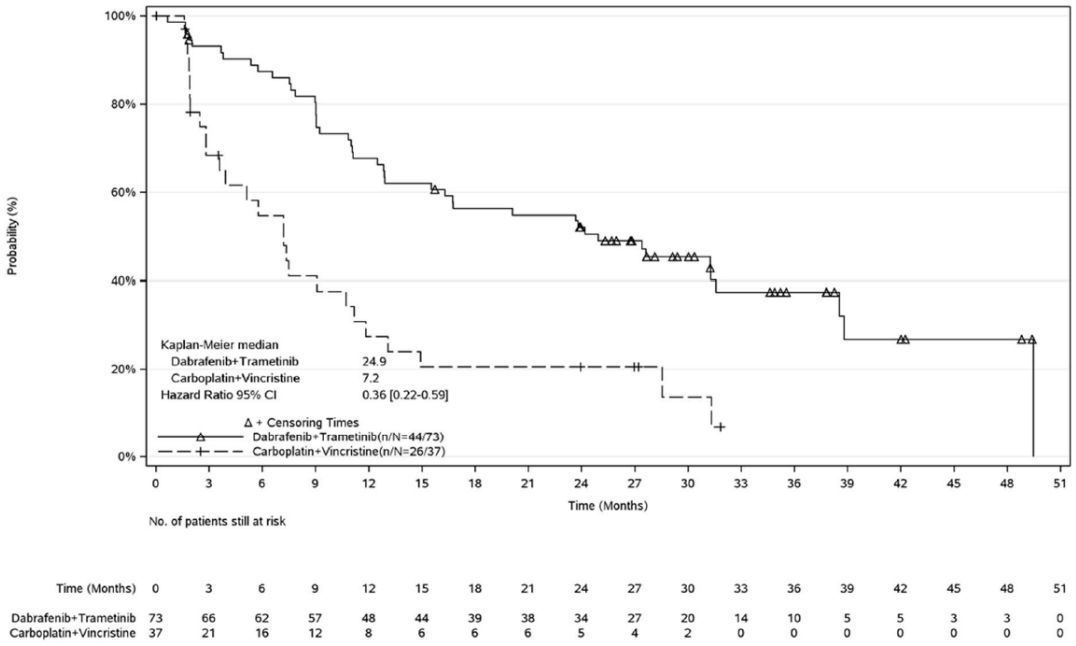
**Table 24 Response and progression-free survival based on independent review in Study G2201 (LGG cohort, primary analysis)**

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

*CBR=clinical benefit rate; CI=confidence interval; CR=complete response; NE=not estimable; ORR=overall response rate; PD=progressive disease; PR=partial response; SD=stable disease.*
*[1] 4 patients randomised to C+V discontinued prior to receiving treatment.*
*[2] Based on Clopper-Pearson exact confidence interval.*
*[3] Odds ratio (D+T vs C+V) and 95% CI are from a logistic regression with treatment as the only covariate, i.e. it is the odds of observing a response in the D+T arm compared to the odds of observing a response in the C+V arm. Odds ratio >1 favours D+T.*
*[4] Based on Kaplan-Meier method.*
*[5] Based on proportional hazards model.*

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

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




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

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

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

## 5.2 Pharmacokinetic properties

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

*Absorption*

Dabrafenib is absorbed orally with median time to achieve peak plasma concentration of 2 hours post-dose. Mean absolute bioavailability of oral dabrafenib is 95 % (90 % CI: 81 %, 110 %). Dabrafenib exposure ($C_{max}$ and AUC) increased in a dose proportional manner between 12 mg and 300 mg following single-dose administration, but the increase was slightly less than dose-proportional after repeat twice daily dosing. There was a decrease in exposure observed with repeat dosing, likely due to induction of its own metabolism. Mean accumulation AUC Day 18/Day 1 ratios averaged 0.73. Following administration of 150 mg

twice daily, geometric mean $C_{max}$, $AUC_{(0-\tau)}$ and predose concentration ($C\tau$) at steady state were 1478 ng/mL, 4341 ng*hour/mL and 26 ng/mL, respectively.

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

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

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

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

Fecal excretion is the major route of elimination after oral dose, accounting for 71 % of a radioactive dose while urinary excretion accounted for 23 % of radioactivity as metabolites.

*Special populations*
*Hepatic Impairment*
A population pharmacokinetic analysis in 65 patients with mild hepatic impairment indicates that mildly elevated bilirubin and/or AST levels (based on National Cancer Institute [NCI] classification) does not significantly affect dabrafenib oral clearance. In addition, mild hepatic impairment, as defined by bilirubin and AST, did not have a significant effect on dabrafenib metabolite plasma concentrations. No data are available in patients with moderate to severe hepatic impairment. As hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites, administration of dabrafenib should be undertaken with caution in patients with moderate to severe hepatic impairment (see section 4.2 – Dose and method of administration).

*Renal Impairment*
The pharmacokinetics of dabrafenib were characterised in 233 patients with mild renal impairment (GFR 60-89 mL/min/1.73 $m^2$) and 30 patients with moderate renal impairment (GFR 30-59 mL/min/1.73 $m^2$) enrolled in clinical trials, using a population analysis. The

effect of mild to moderate renal impairment on dabrafenib clearance was small (< 6 % for both categories) and was not clinically relevant. No data are available in patients with severe renal impairment (see section 4.2 – Dose and method of administration).

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

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

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

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

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

## 5.3 Preclinical safety data

Safety pharmacology
In combined female fertility, early embryonic and embryofetal development studies in rats numbers of ovarian corpora lutea were reduced in pregnant females at 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC), but there were no effects on oestrous cycle, mating or fertility. Developmental toxicity including embryo-lethality and ventricular septal defects and variation in thymic shape were seen at 300 mg/kg/day, and delayed skeletal development and reduced foetal body weight at ≥ 20 mg/kg/day (≥ 0.5 times human clinical exposure based on AUC).

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

In juvenile toxicity studies in rats, effects on growth (shorter long bone length), renal toxicity (tubular deposits, increased incidence of cortical cysts and tubular basophilia and reversible

increases in urea and/or creatinine concentrations) and testicular toxicity (degeneration and tubular dilation) were observed.

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

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

An increase in cutaneous malignancies has been observed with BRAF inhibitors with preliminary evidence suggesting this occurs in patients harbouring other MAPK pathway mutations, including RAS, in skin (see section 4.4 – Special warnings and precautions for use).

## 6. PHARMACEUTICAL PARTICULARS
### 6.1 List of excipients

Hard capsule
TAFINLAR hard capsules also contain:

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

Dispersible tablet

TAFINLAR dispersible tablets also contain:

- mannitol
- microcrystalline cellulose
- crospovidone
- hypromellose
- acesulfame potassium
- magnesium stearate
- colloidal anhydrous silica
- artificial berry flavour 59454 AP0551 (Proprietary Ingredient No. 05-35-10)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

Hard capsule

3 years.

Dispersible tablet

2 years

**In use shelf-life**: Once tablets are dispersed in water, use within 30 minutes.

**6.4 Special precautions for storage**

Hard capsule

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

Dispersible tablet

Store Tafinlar dispersible tablets below 25°C. Store in original container in order to protect from moisture. Do not remove desiccant.

**6.5 Nature and contents of container**

Hard capsule

Tafinlar capsules are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 28 or 120 capsules*. The bottle contains a desiccant.

Dispersible tablet

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

*Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

Hard capsule

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

Dispersible tablet

The oral suspension is prepared with approximately 5mL of water for 1 to 4 tablets, and

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

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

## 7. MEDICINE SCHEDULE

Prescription medicine.

## 8. SPONSOR

**Novartis New Zealand Limited**
PO Box 99102 Newmarket Auckland 1149

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

## 9. DATE OF FIRST APPROVAL

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

**10 mg dispersible tablets:** 8th December 2025

## 10. DATE OF REVISION OF THE TEXT

15 December 2025.

## SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|---|---|
| 4.8 | Safety updates for special populations – paediatric patients, based on the final analysis of study G2201 in paediatric glioma. |
| 5.1 | Efficacy updates for paediatric glioma (LGG, HGG) following final analysis from study G2201.<br><br>Efficacy updates for COMBI-AD (DRB436F2301) following final analysis. |