Trametinib 0.5 mg and 2 mg tablets

MEQSEL®

Protein kinase inhibitor

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Trametinib 0.5 mg film-coated tablets— yellow, modified oval, biconvex, film-coated tablets with 'GS' debossed on one face and 'TFC' on the opposing face.

Trametinib 2 mg film-coated tablets— pink, round, biconvex, film-coated tablets with 'GS' debossed on one face and 'HMJ' on the opposing face.

Certain dosage strengths and dosage forms may not be available in all countries.

Active substance

0.5 mg film-coated tablets

Each film-coated tablet contains trametinib-dimethylsulfoxide (1:1) equivalent to 0.5 mg trametinib

2 mg film-coated tablets - Each film-coated tablet contains trametinib-dimethylsulfoxide (1:1) equivalent to 2 mg trametinib

Excipients

Tablet core:

Mannitol

Microcrystalline cellulose

Hypromellose

Croscarmellose sodium

Magnesium stearate (vegetable source)

Sodium laurylsulfate

Colloidal silicon dioxide

Tablet film-coating

Hypromellose

Titanium dioxide

Polyethylene glycol

Iron oxide yellow (for 0.5 mg tablets)

Polysorbate 80 and Iron oxide red (for 2 mg tablets).

Pharmaceutical formulations may vary between countries.

INDICATIONS

Unresectable or metastatic melanoma

Meqsel in combination with dabrafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see CLINICAL STUDIES).

Meqsel as a monotherapy is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see CLINICAL STUDIES).

Meqsel as monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (see CLINICAL STUDIES).

Advanced non-small cell lung cancer

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

DOSAGE REGIMEN AND ADMINISTRATION

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

Dose regimen

General target population

Adults

Confirmation of BRAF V600 mutation using an approved/validated test is required for selection of patients appropriate for treatment with Meqsel as monotherapy and in combination with dabrafenib (see CLINICAL STUDIES).

When Meqsel is used in combination with dabrafenib, please refer to the full dabrafenib prescribing information (see DOSAGE REGIMEN AND ADMINISTRATION).

The recommended dose of Meqsel either as monotherapy or in combination with dabrafenib is 2 mg given orally once daily with a full glass of water.

Meqsel should be taken without food, at least one hour before or two hours after a meal (see CLINICAL PHARMACOLOGY).

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

If a dose of Meqsel is missed, it should only be taken if it is more than 12 hours until the next scheduled dose.

Dose adjustments

Meqsel as Monotherapy and in combination with dabrafenib

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

Table 1 Recommended Meqsel dose level reductions

Dose Level	Meqsel Dose
Starting dose	2 mg once daily
First dose reduction	1.5 mg once daily
Second dose reduction	1 mg once daily

Dose adjustment for Meqsel,, below 1 mg once daily is not recommended, whether used as monotherapy or in combination with Rafinlar.

Table 2: Meqsel dose modification schedule

Grade (CTC-AE)*	Dose Modifications
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is grade 0 to1and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy.

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

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 Meqsel dose should not exceed 2 mg once daily.

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

Exceptions where dose modifications are necessary for Meqsel only:

- Left ventricular ejection fraction (LVEF) reduction
- Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED)
- Pneumonitis and Interstitial Lung Disease (ILD)

LVEF Reduction/Left Ventricular Dysfunction management: Meqsel should be interrupted in patients who have an asymptomatic, absolute decrease of > 10 % in LVEF compared to baseline and the ejection fraction below the institution's lower limit of normal (LLN) (see WARNINGS AND PRECAUTIONS). If Meqsel is being used in combination with dabrafenib then therapy with dabrafenib may be continued at the same dose. If the LVEF recovers, treatment with Meqsel may be restarted, but the dose should be reduced by one dose level with careful monitoring. Meqsel should be permanently discontinued with Grade 3 or 4 left ventricular cardiac dysfunction or if repeatedly reduced LVEF does not recover.

Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED) management: If RPED is diagnosed, the dose modification schedule (intolerable) in Table 2 above for Meqsel should be followed and, if Meqsel is being used in combination with dabrafenib, dabrafenib should be continued at the same dose. In patients who experience RVO, treatment with Meqsel should be permanently discontinued (see WARNINGS AND PRECAUTIONS).

Pneumonitis and Interstitial Lung Disease (ILD) management: For events of pneumonitis, follow dose modification guidelines in Table 2 for Meqsel only; no modification of dabrafenib is required when taken in combination with Meqsel.

Refer to the full prescribing information of dabrafenib for dose modification guidelines (see DOSAGE REGIMEN AND ADMINISTRATION).

Special populations

Renal impairment

No dosage adjustment is required in patients with mild or moderate renal impairment. Mild or moderate renal impairment had no significant effect on the population pharmacokinetics of Meqsel (see CLINICAL PHARMACOLOGY, Pharmacokinetics). There are no clinical data in patients with severe renal impairment; therefore, the potential need for starting dose adjustment cannot be determined. Meqsel should be used with caution in patients with severe renal impairment.

Hepatic impairment

No dosage adjustment is required in patients with mild hepatic impairment. In a population pharmacokinetic analysis, Meqsel oral clearance and thus exposure was not significantly different in patients with mild hepatic impairment compared to patients with normal hepatic function (see CLINICAL PHARMACOLOGY, PHARMACOKINETICS). There are no clinical data in patients with moderate or severe hepatic impairment; therefore, the potential need for starting dose adjustment cannot be determined. Meqsel should be used with caution in patients with moderate or severe hepatic impairment.

Pediatric patients (below 18 years)

The safety and efficacy of Meqsel in pediatric patients have not been established. Meqsel is not recommended in this age group.

Geriatric patients (65 years or above)

No dosage adjustment is required in patients over 65 years of age (see CLINICAL PHARMACOLOGY PHARMACOKINETICS).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

When Meqsel is used together with dabrafenib read the full prescribing information for dabrafenib section WARNINGS AND PRECAUTIONS.

LVEF Reduction/Left Ventricular Dysfunction:

Meqsel has been reported to decrease LVEF (see ADVERSE DRUG REACTIONS). In clinical trials, the median time to onset of the first occurrence of left ventricular dysfunction, cardiac failure and LVEF decrease in patients treated with Meqsel as monotherapy or in combination with dabrafenib was between two to five months. Meqsel should be used with caution in patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment with Meqsel with a recommendation of periodic follow-up within eight weeks of initiating therapy, as clinically appropriate. LVEF should continue to be evaluated during treatment with Meqsel as clinically appropriate (see DOSAGE REGIMEN AND ADMINISTRATION).

Haemorrhage:

Haemorrhagic events, including major hemorrhagic events have occurred in patients taking Meqsel as monotherapy and in combination with dabrafenib (see ADVERSE DRUG REACTIONS). Out of the 559 unresectable or metastatic melanoma patients treated with Meqsel in combination with dabrafenib, there were six fatal intracranial hemorrhagic cases (1%). Three cases were from study MEK115306 (COMBI-d) and three cases were from study MEK116513 (COMBI-v). Two out of 93 patients (2%) receiving Meqsel in combination with dabrafenib in a Phase II NSCLC trial had fatal intracranial hemorrhagic events. If patients develop symptoms of haemorrhage they should immediately seek medical care.

Visual Impairment:

Disorders associated with visual disturbances, including chorioretinopathy or retinal pigment epithelial detachment (RPED) and Retinal Vein Occlusion (RVO) have been observed with Meqsel. Symptoms such as blurred vision, decreased acuity, and other visual phenomena have been reported in the clinical trials with Meqsel (see ADVERSE DRUG REACTIONS). Meqsel is not recommended in patients with a history of RVO. A thorough ophthalmological evaluation should be performed at baseline and during treatment with Meqsel, if clinically warranted. If patients report visual disturbances at any time while on Meqsel therapy, additional ophthalmological evaluation should be undertaken. If a retinal abnormality is noted, treatment with Meqsel should be interrupted immediately and referral to a retinal specialist should be considered. If RPED is diagnosed, the dose modification schedule (intolerable) in Table 2 should be followed (see DOSAGE REGIMEN AND ADMINISTRATION). In patients who experience RVO, treatment with Meqsel should be permanently discontinued.

Rash:

In clinical studies, rash has been observed in about 60 % of patients receiving Meqsel as monotherapy and 20 to 30% receiving Meqsel in combination with dabrafenib (see ADVERSE DRUG REACTIONS). The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions.

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

DVT and PE can occur on Meqsel monotherapy and when Meqsel is used in combination with dabrafenib. Patients should be advised to immediately seek medical care if they develop symptoms of pulmonary embolism or deep vein thrombosis.

Pyrexia:

Pyrexia was reported in the clinical trials with Meqsel. The incidence and severity of pyrexia are increased when Meqsel is used in combination with dabrafenib (see ADVERSE DRUG REACTIONS). In patients with unresectable or metastatic melanoma who received the combination dose of Meqsel 2 mg once daily and Rafinlar 150 mg twice daily 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, and hypotension which in some cases can lead to acute renal insufficiency. Serum creatinine and other evidence of renal function should be monitored during and following severe events of pyrexia. Serious non-infectious febrile events have been observed. These events responded well to dose interruption and/or dose reduction and supportive care in clinical trials.

For management of pyrexia see the full prescribing information for dabrafenib (see DOSAGE REGIMEN AND ADMINISTRATION, Dose adjustments).

Colitis and gastrointestinal perforation

Colitis and gastrointestinal perforation, including fatal outcome, have been reported in patients taking Meqsel as monotherapy and in combination with dabrafenib (ADVERSE DRUG REACTIONS). Treatment with Meqsel monotherapy or in combination with dabrafenib should be used with caution in patients with risk factors for gastrointestinal perforation, including a history of diverticulitis, metastases to the gastrointestinal tract and concomitant use of medications with a recognized risk of gastrointestinal perforation.

If patients develop symptoms of colitis and gastrointestinal perforation they should immediately seek medical care.

ADVERSE DRUG REACTIONS

Summary of the safety profile

Unresectable or metastatic melanoma

Meqsel monotherapy

The safety of Meqsel monotherapy was evaluated in an integrated population of 329 patients with BRAF V600 mutant unresectable or metastatic melanoma treated with Meqsel 2 mg orally once daily in studies MEK114267, MEK113583, and MEK111054.. Of these patients, 211 patients were treated with Meqsel for BRAF V600 mutant melanoma in the randomized open-label study MEK114267 (see CLINICAL STUDIES). The most common adverse events (≥ 20 %) for Meqsel were rash, diarrhoea, fatigue, oedema peripheral, nausea, and dermatitis acneiform. In clinical

trials with Meqsel, adverse events of diarrhoea and rash were managed with appropriate supportive care (see DOSAGE REGIMEN AND ADMINISTRATION).

Meqsel and Rafinlar combination therapy:

The safety of Meqsel and Rafinlar combination therapy was evaluated in two randomized Phase III studies of patients with BRAF V600 mutant unresectable or metastatic melanoma treated with Meqsel 2 mg orally once daily and Rafinlar 150 mg orally twice daily (see CLINICAL STUDIES). The most common adverse events (≥20%) for Meqsel and Rafinlar combination therapy were pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, vomiting, peripheral oedema and cough.

Tabulated summary of adverse events from clinical trials in metastatic melanoma:

Adverse events from clinical trials in patients with unresectable or metastatic melanoma are listed by MedDRA system organ class in Table 3 and Table 4 for Meqsel monotherapy and Meqsel in combination with Rafinlar, respectively. Within each system organ class, the adverse events are ranked by frequency, with the most frequent adverse events first. In addition, the corresponding frequency category for each adverse event is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 3 Unresectable or metastatic melanoma-adverse events for Meqsel monotherapy

Adverse events	Frequency category Integrated Safety Data N=329
Infections and Infestations	
Folliculitis	Common
Paronychia	Common
Cellulitis	Common
Rash pustular	Common
Blood and lymphatic system disorders	
Anaemia	Common
Immune system disorders	
Hypersensitivity[1)]	Common
Metabolism and nutrition disorders	
Dehydration	Common
Eye disorders	
Vision blurred	Common
Periorbital oedema	Common
Visual Impairment	Common

Chorioretinopathy	Uncommon
Retinal vein occlusion	Uncommon
Papilloedema	Uncommon
Retinal detachment	Uncommon
Cardiac disorders	
Left ventricular dysfunction	Common
Ejection fraction decreased	Common
Bradycardia	Common
Cardiac failure	Uncommon
Vascular disorders	
Hypertension	Very common
Haemorrhage[2)]	Very common
Lymphoedema	Common
Respiratory, thoracic and mediastinal disorders	
Cough	Very common
Dyspnea	Very common
Epistaxis	Common
Pneumonitis	Common
Interstitial lung disease	Uncommon
Gastrointestinal disorders	
Diarrhoea	Very common
Nausea	Very Common
Vomiting	Very Common
Constipation	Very Common
Abdominal pain	Very Common
Dry mouth	Very Common
Stomatitis	Common
Gastrointestinal perforation	Uncommon
Collitis	Uncommon
Skin and Subcutaneous Tissue Disorders	
Rash	Very common
Dermatitis acneiform	Very common
Dry Skin	Very common
Pruritus	Very common
Alopecia	Very common
Skin chapped	Common
Erythema	Common
Palmar-plantar erythrodysaesthesia syndrome	Common
Skin fissures	Common
Musculoskeletal and connective tissue disorder	
Rhabdomyolysis	Uncommon

Blood creatine phosphokinase increased	Common
General disorders	
Fatigue	Very common
Oedema peripheral	Very common
Pyrexia	Very common
Face oedema	Common
Mucosal inflammation	Common
Asthenia	Common
Investigations	
Aspartate aminotransferase increased	Common
Alanine aminotransferase increased	Common
Blood alkaline phosphatase increased	Common
1) May present with symptoms such as fever, rash, increased liver function tests, and visual disturbances. 2) *The majority of bleeding events were mild. Major events, defined as symptomatic bleeding in a critical area or organ, and fatal intracranial haemorrhages have been reported.*	

Table 4 lists adverse events when Meqsel was used in combination with Rafinlar from the randomized double-blind Phase III study MEK115306 (N=209), and integrated safety data from MEK115306 (N=209) and from the randomized open-label Phase III study MEK 116513 (N=350).

Table 4: Unresectable or metastatic Melanoma -Adverse events for Meqsel in combination with Rafinlar

Adverse events	**Frequency category**	
	MEK115306 (COMBI-d) N=209	**MEK115306 (COMBI-d) plus MEK116513 (COMBI-v) Integrated Safety 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

Adverse events	Frequency category	
	MEK115306 (COMBI-d) N=209	**MEK115306 (COMBI-d) plus MEK116513 (COMBI-v) Integrated Safety Data N=559**
Acrochordon (skin tags)	Common	Uncommon
New primary melanoma	Uncommon	Uncommon
Blood and lymphatic system disorders		
Neutropenia	Very common	Common
Anaemia	Common	Common
Thrombocytopenia	Common	Common
Leukopenia	Common	Common
Immune system disorders		
Hypersensitivity	Uncommon	Uncommon
Metabolic and nutrition disorders		
Decreased appetite	Very common	Very common
Dehydration	Common	Common
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
Bradycardia	Common	Common
Left ventricular dysfunction	Not reported	Uncommon
Cardiac failure	Not reported	Uncommon
Vascular disorders		
Hypertension	Very common	Very common
Haemorrhage[1)]	Very common	Very common
Hypotension	Common	Common
Lymphoedema	Uncommon	Common
Respiratory, thoracic and mediastinal disorders		
Cough	Very common	Very common

Adverse events	Frequency category	
	MEK115306 (COMBI-d) N=209	**MEK115306 (COMBI-d) plus MEK116513 (COMBI-v) Integrated Safety Data N=559**
Dyspnoea	Common	Common
Pneumonitis	Uncommon	Uncommon
Interstitial lung disease	Not reported	Uncommon
Gastrointestinal disorders		
Abdominal pain	Very common	Very common
Constipation	Very common	Very common
Diarrhoea	Very common	Very common
Nausea	Very common	Very common
Vomiting	Very common	Very common
Dry mouth	Common	Common
Stomatitis	Common	Common
Pancreatitis	Uncommon	Uncommon
Gastrointestinal perforation	Not reported	Uncommon
Colitis	Uncommon	Uncommon
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 [2)]	Common	Common
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Very common
Myalgia	Very common	Very common
Pain in extremity	Very common	Very common
Muscle spasms	Common	Common
Blood creatine phosphokinase increased	Common	Common
Rhabdomyolysis	Not reported	Uncommon

Adverse events	Frequency category	
	MEK115306 (COMBI-d) N=209	**MEK115306 (COMBI-d) plus MEK116513 (COMBI-v) Integrated Safety Data N=559**
Renal disorders		
Renal failure	Uncommon	Common
Nephritis	Uncommon	Uncommon
Renal failure acute	Not reported	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
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

1) *The majority of bleeding events were mild. Major events, defined as symptomatic bleeding in a critical area or organ, and fatal intracranial haemorrhages have been reported.*
2) *Photosensitivity cases were also observed in post-marketing experience. All cases reported in the COMBI-d and COMBI-v 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 Meqsel in combination with Rafinlar in unresectable or metastatic melanoma (see CLINICAL STUDIES).

Advanced non-small cell lung cancer (NSCLC)

Meqsel in combination with Rafinlar:

The safety of Meqsel in combination with Rafinlar was evaluated in a Phase II, multicenter, multi-cohort, non-randomized, open label study of patients with BRAF V600E mutation positive metastatic NSCLC (see CLINICAL STUDIES).

In the Meqsel 2 mg orally once daily and Rafinlar 150 mg orally twice daily arms (Cohorts B and C) the most common adverse events (≥20%) reported for Meqsel and Rafinlar combination therapy were pyrexia, nausea, vomiting, peripheral oedema,

diarrhoea, decreased appetite, asthenia, dry skin, chills, cough, fatigue, rash and dyspnea.

Table 5 lists the adverse drug reactions for Meqsel in combination with Rafinlar occurring at an incidence ≥10% for all 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.

Adverse drug reactions are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent adverse drug reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 5: Advanced NSCLC - Adverse drug reactions for Meqsel in combination with Rafinlar

Adverse drug reaction	**Meqsel in combination with Rafinlar N=93**		
	All grades %	**Grades 3/4 %**	**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
Pulmonary embolism	4	2	Common

Adverse drug reaction	Meqsel in combination with Rafinlar N=93		
	All grades %	Grades 3/4 %	Frequency category
Hypertension	8	6	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
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.*

Adverse drug reaction	Meqsel in combination with Rafinlar N=93		
	All grades %	Grades 3/4 %	Frequency category

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 generalized, rash papular, rash macular, rash maculo-papular, and rash pustular.*

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

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

6) *Asthenia also includes fatigue and malaise.*

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

NR: Not Reported

INTERACTIONS

Monotherapy

As Trametinib is metabolized predominantly via deacetylation mediated by hydrolytic enzymes (including carboxylesterases), its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions. Trametinib repeat-dose exposure was not affected by co-administration with a cytochrome P450 (CYP) 3A4 inducer.

Based on *in vitro* and *in vivo* data, Meqsel is unlikely to significantly affect the pharmacokinetics of other medicinal products via interactions with CYP enzymes or transporters (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Repeat dose administration of Meqsel 2 mg once daily had no clinically relevant effect on the single dose C_{max} and AUC of dabrafenib, a CYP2C8/CYP3A4 substrate.

Combination therapy and non-fixed dose combination therapy

Combination with Rafinlar

Co-administration of repeat dosing of Meqsel 2 mg once daily and Rafinlar 150 mg twice daily resulted in a 16% increase in dabrafenib C_{max} and a 23% increase in dabrafenib AUC. A small decrease in Trametinib bioavailability, corresponding to a decrease in AUC of 12%, was estimated when Meqsel is administered in combination with Rafinlar using a population pharmacokinetic analysis. These changes in dabrafenib or trametinib C_{max} and AUC are considered not clinically relevant. See the full prescribing information for dabrafenib for guidelines on drug interactions associated with Rafinlar monotherapy.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

Meqsel can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Meqsel in pregnant women. Reproductive

studies in animals (rats and rabbits) have demonstrated that trametinib induces maternal and developmental toxicity. In rats decreased fetal weight and increased incidences of post implantation loss were observed following maternal exposure to trametinib at concentrations 0.3 and 1.8 times the exposure in humans at the highest recommended dose of 2 mg once daily. In rabbits, decreased fetal weight and increased incidence of variations in ossification and post implantation loss were observed following maternal exposure to trametinib at concentrations 0.09 and 0.3 times the exposure in humans at the highest recommended dose of 2 mg once daily.Pregnant women should be advised of the potential risk to the fetus.

Animal data

In embryo-fetal development studies, rats and rabbits received oral doses of trametinib up to 0.125 mg/kg/day and 0.31 mg/kg/day, respectively, during the period of organogenesis. In rats at ≥0.031 mg/kg/day and 0.125 mg/kg/day, maternal systemic exposures (AUC) were 110 ng*h/mL and 684 ng*h/mL, respectively, corresponding to approximately 0.3 and 1.8 times the exposure in humans at the highest recommended dose of 2 mg once daily. At doses ≥0.031 mg/kg/day developmental toxicity consisted of decreased fetal weights. At a dose of 0.125 mg/kg/day there was maternal toxicity and increases in post implantation loss. In rabbits at ≥0.039 mg/kg/day and 0.15 mg/kg/day, maternal systemic exposures (AUC) were 31.9 ng*h/mL and 127 ng*h/mL, respectively corresponding to approximately 0.09 and 0.3 times the exposures in humans at the highest recommended dose of 2 mg once daily. At doses ≥0.039 mg/kg/day developmental toxicity consisted in decreased fetal body weight and increased incidence of variations in ossification. At doses 0.15 mg/kg/day there t were increases in post-implantation loss, including total loss of pregnancy, compared with control animals.

Lactation

Risk summary

There are no data on the effect of Meqsel on the breast-fed child, or the effect of Meqsel on milk production. Because many drugs are transfered into human milk and because of the potential for adverse reactions in nursing infants from Meqsel, a nursing woman should be advised on the potential risks to the child. The developmental and health benefits of breast-feeding should be considered along with the mother’s clinical need for Meqsel and any potential adverse effects on the breast-fed child from Meqsel or from the underlying maternal condition.

Females and males of reproductive potential

Contraception

Females

Females of reproductive potential should be advised that animal studies have been performed showing Meqsel to be harmful to the developing fetus. Sexually-active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1% pregnancy rates) when taking Meqsel and for atleast 16 weeks after stopping treatment with Meqsel.

Females of reproductive potential receiving Meqsel in combination with dabrafenib should be advised that dabrafenib may decrease the efficacy of oral or any other systemic hormonal contraceptives and an effective alternative method of contraception should be used.

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 Meqsel monotherapy or in combination with Rafinlar and for at least 16 weeks after stopping treatment with Meqsel.

Infertility

There is no information on the effect of Meqsel on human fertility. In animals, no fertility studies have been performed, but adverse effects were seen on female reproductive organs (see NON-CLINICAL SAFETY DATA). Meqsel may impair fertility in humans.

OVERDOSAGE

No cases of overdose have been reported. There were no cases of Meqsel dose above 4 mg once daily reported from the clinical trials. Doses up to 4 mg orally once daily and loading doses of 10 mg orally once daily administered on two consecutive days, have been evaluated in clinical trials.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available. There is no specific treatment for an overdose of trametinib. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Hemodialysis is not expected to enhance the elimination as trametinib is highly bound to plasma proteins.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Meqsel Monotherapy - Melanoma and NSCLC

Trametinib (Meqsel) is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinases 1 (MEK1) and 2 (MEK2) activation and kinase activity. MEK proteins are critical components of the extracellular signal-regulated kinase (ERK) pathway. In melanoma and other cancers, this pathway is often activated by mutated forms of BRAF which activate MEK and stimulate tumour cell growth. Trametinib inhibits MEK kinaseactivity activity, suppresses growth of BRAF V600 mutant melanoma and non-small cell lung cancer (NSCLS) cell lines *in vitro* and demonstrates anti-tumour effects in BRAF V600 mutant melanoma xenograft models.

Meqsel in combination with dabrafenib - Melanoma and NSCLC

Dabrafenib is a potent, selective, ATP-competitive inhibitor of the BRAF (both wild-type and V600 variants) and wild type CRAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway and stimulation of tumor cell growth. Because, co-treatment with Meqsel and Rafinlar results in concomitant inhibition of two kinases in this pathway, BRAF and MEK, the combination provides

superior pathway suppression relative to either agent alone. The combination of trametinib with dabrafenib is synergistic/additive in BRAF V600 mutation positive melanoma and NSCLC cell lines *in vitro* and delays the emergence of resistance *in vivo* in BRAF V600 mutation positive melanoma xenografts.

Pharmacodynamics (PD)

Trametinib suppressed levels of phosphorylated ERK in BRAF V600 mutant melanoma and NSCLC tumour cell lines and melanoma xenografts models.

In patients with BRAF and NRAS mutant melanoma, administration of Meqsel resulted in dose-dependent changes in tumor biomarkers including inhibition of phosphorylated ERK, inhibition of Ki67 (a marker of cell proliferation),and increases in p27 (a marker of apoptosis). The mean trametinib concentrations observed following repeat dose administration of 2 mg once daily exceeds the preclinical target concentration over the 24-hr dosing interval, thereby providing sustained inhibition of the MEK pathway.

Cardiac electrophysiology

Study MEK111054

Initially the QT prolongation potential of trametinib was assessed as part of the first time in human study to determine the relationship between the independently manually-read QTc interval and plasma concentrations of trametinib using a nonlinear mixed effects model. Data were available in 50 patients with a total of 498 matched QTc values. Based on the concentration-QTc analysis, Meqsel showed no apparent potential to alter the QTc interval. At the mean C_{max} value observed at the recommended dose of 2 mg once daily, the median increase in QTc is 2.2 msec (90 % CI: 0.2, 4.0).

To confirm the lack of effect on QTc, the QT prolongation potential of Meqsel was further assessed in a dedicated, stand-alone Phase I study in 35 patients (32 patients completed the study) with solid tumors. Patients received 3 mg matched placebo on study day 1 followed by a 2 mg once daily dose of Meqsel and 2 tablets of 0.5 mg matched placebo on study days 2 to 14. On study day 15, all patients received a single dose of 3 mg Meqsel (supratherapeutic dose). The study showed no potential for Meqsel to alter the QTcF interval after repeat dose administration of 2 mg, including at the supratherapeutic dose of 3 mg on day 15. At a dose 1.5 times the maximum recommended dose, Meqsel does not prolong the QT interval to any clinically relevant extent.

Pharmacokinetics (PK)

Absorption

Trametinib is absorbed orally with median time to achieve peak concentrations of 1.5 hours post-dose. The mean absolute bioavailability of a single 2 mg tablet dose is 72 % relative to an intravenous (IV) microdose. The increase in exposure (C_{max} and AUC) was dose-proportional following repeat dosing. Following administration of 2 mg daily, geometric mean C_{max}, AUC(0-τ) and pre dose concentration were 22.2 ng/ml, 370 ng*hr/ml and 12.1 ng/ml, respectively with a low peak:trough ratio (1.8). Inter-subject variability was low (< 28 %). Administration of a single dose of trametinib with a high-

fat, high-calorie meal resulted in a 70 % and 10 % decrease in C_{max} and AUC, respectively compared to fasted conditions (see DOSAGE REGIMEN AND ADMINISTRATION).

Distribution

Binding of trametinib to human plasma proteins is 97.4 %. Trametinib has a volume of distribution of 1,060 L determined following administration of a 5 microgram IV microdose.

Biotransformation/Metabolism

In vitro and *in vivo* studies demonstrated that trametinib is metabolized predominantly via deacetylation alone or in combination with mono-oxygenation. The deacetylated metabolite was further metabolized by glucuronidation. The deacetylation is mediated by the carboxy-lesterase 1b,1c and 2) and may also be mediated by other hydrolytic enzymes.

Elimination

Trametinib accumulates with repeat daily dosing with a mean accumulation ratio of 6.0 following a 2 mg once daily dose. Mean terminal half-life is 127 hours (5.3 days) after single dose administration. Steady-state was achieved by Day 15. Trametinib plasma IV clearance is 3.21 l/hr.

Total dose recovery is low after a 10-day collection period (< 50 %) following administration of a single oral dose of radiolabelled trametinib as a solution, due to the long half-life. Drug-related material was excreted predominantly in the feces (≥81% of recovered radioactivity) and to a small extent in urine (≤19%). Less than 0.1% of the excreted dose was recovered as parent in urine.

In Vitro evaluation of drug interaction potential

Effects of other drugs on trametinib:

In vitro and *in vivo* data suggest that the pharmacokinetics (PK) of trametinib is unlikely to be affected by other drugs. Trametinib is deacetylated via carboxylesterases and possibly other hydrolytic enzymes. There is little evidence from clinical studies for drug interactions mediated by carboxylesterases. CYP enzymes play a minor role in the elimination of trametinib and the compound is not a substrate of the following transporters: breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, OATP2B1, organic cation transporter (OCT) 1, multidrug resistance-associated protein (MRP) 2, and the multidrug and toxin extrusion protein (MATE) 1. Trametinib is an *in vitro* substrate of the efflux transporter P-glycoprotein (Pgp), but is unlikely to be significantly affected by inhibition of this transporter given its high passive permeability and high bioavailability.

Special Populations

Pediatric population (below 18 years)

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

Geriatric population (65 years or above)

Based on the population pharmacokinetics analysis, age had no relevant clinical effect on Meqsel pharmacokinetics.

Gender/Weight

Based on the population pharmacokinetic analysis, gender and weight were found to influence trametinib oral clearance. Although smaller female subjects are predicted to have higher exposure than heavier male subjects, these differences are unlikely to be clinically relevant and no dose adjustment is warranted.

Race/Ethnicity

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

Renal Impairment

Renal impairment is unlikely to have a clinically relevant effect on trametinib pharmacokinetics given the low renal excretion of trametinib. The pharmacokinetics of trametinib were characterized in 223 patients enrolled in clinical trials with trametinib who had mild renal impairment and 35 patients with moderate renal impairment using a population pharmacokinetic analysis. Mild and moderate renal impairment had no effect on trametinib exposure (< 6 % for either group). No data are available in patients with severe renal impairment (see DOSAGE REGIMEN AND ADMINISTRATION).

Hepatic Impairment

The pharmacokinetics of trametinib were characterized in 64 patients enrolled in clinical trials with trametinib who had mild hepatic impairment (defined by National Cancer Institute classification) using a population pharmacokinetic analysis. Trametinib oral clearance was not significantly different in these patients relative to patients with normal hepatic function. No data are available in patients with moderate or severe hepatic impairment (see DOSAGEE REGIMEN AND ADMINISTRATION).

CLINICAL STUDIES

Unresectable or metastatic melanoma

Meqsel monotherapy

Study MEK114267

The efficacy and safety of Meqsel in patients with BRAF mutant unresectable or metastatic melanoma (V600E and V600K) were evaluated in a randomized open label study. Measurement of patients BRAF V600 mutation status was required. Screening included central testing of BRAF mutation (V600E and V600K) using a BRAF mutation assay conducted on the most recent tumur sample available.

Patients (N = 322) who were treatment naïve or may have received one prior chemotherapy treatment in the metastatic setting [Intent to Treat (ITT) population] were randomized 2:1 to receive trametinib 2 mg once daily or chemotherapy (dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks). Treatment for all patients continued until disease progression, death or withdrawal.

The primary endpoint of the study was to evaluate the efficacy of trametinib compared to chemotherapy with respect to progression-free survival (PFS) in patients with advanced (unresectable or metastatic) BRAF V600E mutation-positive melanoma without a prior history of brain metastases (N = 273) which is considered the primary efficacy population. The secondary endpoints were progression-free survival in the ITT population and overall survival (OS), overall response rate (ORR), and duration of response (DoR) in the primary efficacy population and ITT population. Patients in the chemotherapy arm were allowed to cross-over to the trametinib arm after independent confirmation of progression. Fifty one (47 %) patients with confirmed disease progression in the chemotherapy arm crossed over to receive trametinib.

Baseline characteristics were balanced between treatment groups in the primary efficacy population and the ITT population. In the ITT population, the majority of patients were male (54 %) and all were Caucasian (100 %). The median age was 54 years (22 % were ≥ 65 years), most patients (64%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, and 11 patients (3 %) had a history of brain metastases. Most patients (87 %) in the ITT population had a BRAF V600E mutation and 12 % of patients had a BRAF V600K mutation. Most patients (66 %) had received no prior chemotherapy for advanced or metastatic disease.

The efficacy results in the primary efficacy population were consistent with those in the ITT population; therefore, only the efficacy data for the ITT population are presented in Table 6 and Figure 1.

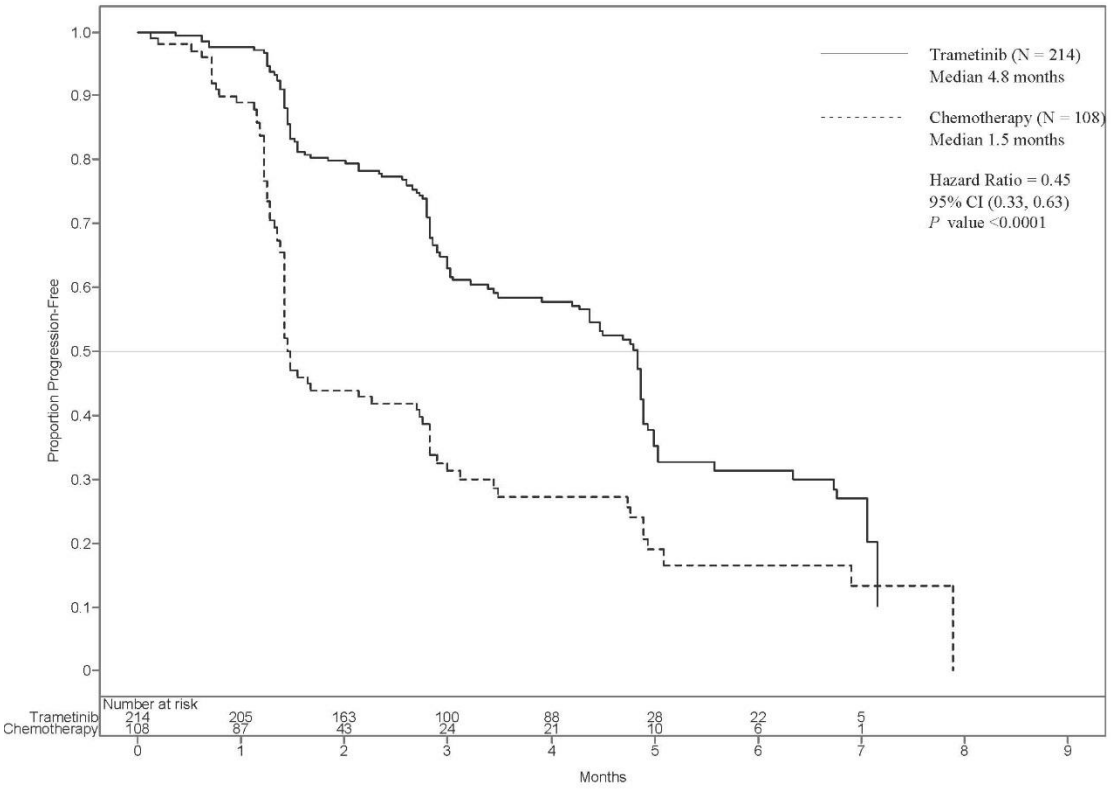
Table 6 MEK114267 - Investigator assessed efficacy results (ITT population).

	Intention-to-treat population	
Endpoints/ Assessments	**Trametinib (N=214)**	**Chemotherapy[a] (N=108)**
Progression-Free Survival		
Median (months)	4.8	1.5
(95% CI)	(4.3, 4.9)	(1.4, 2.7)
Hazard Ratio	0.45	
(95% CI)	(0.33, 0.63)	
P value	<0.0001	
Overall Survival		
Died, n (%)	35 (16)	29 (27)
Hazard Ratio	0.54	
(95% CI)	(0.32, 0.92)	
P value	0.0136	

Survival at 6 months (%) (95% CI)	81 (73, 86)	67 (55, 77)
Overall Response Rate (%)	22	8

ITT = Intent to Treat; PFS = Progression-free survival; CI = Confidence Interval.
[a]Chemotherapy included patients on dacarbazine (DTIC) 1000 mg/m2 every 3 weeks or paclitaxel 175 mg/m2 every 3 weeks.

Figure 1 MEK114267 - Kaplan-Meier investigator-assessed progression-free survival curves (ITT population)



The PFS result was consistent in the subgroup of patients with V600K mutation positive melanoma (HR = 0.50; [95 % CI: 0.18, 1.35], p=0.0788).

In a single arm Phase II study, Meqsel did not demonstrate clinical activity in patients who progressed on a prior BRAF inhibitor therapy in one of the cohorts (see INDICATIONS).

Meqsel in combination with Rafinlar

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

MEK115306 (COMBI-d)

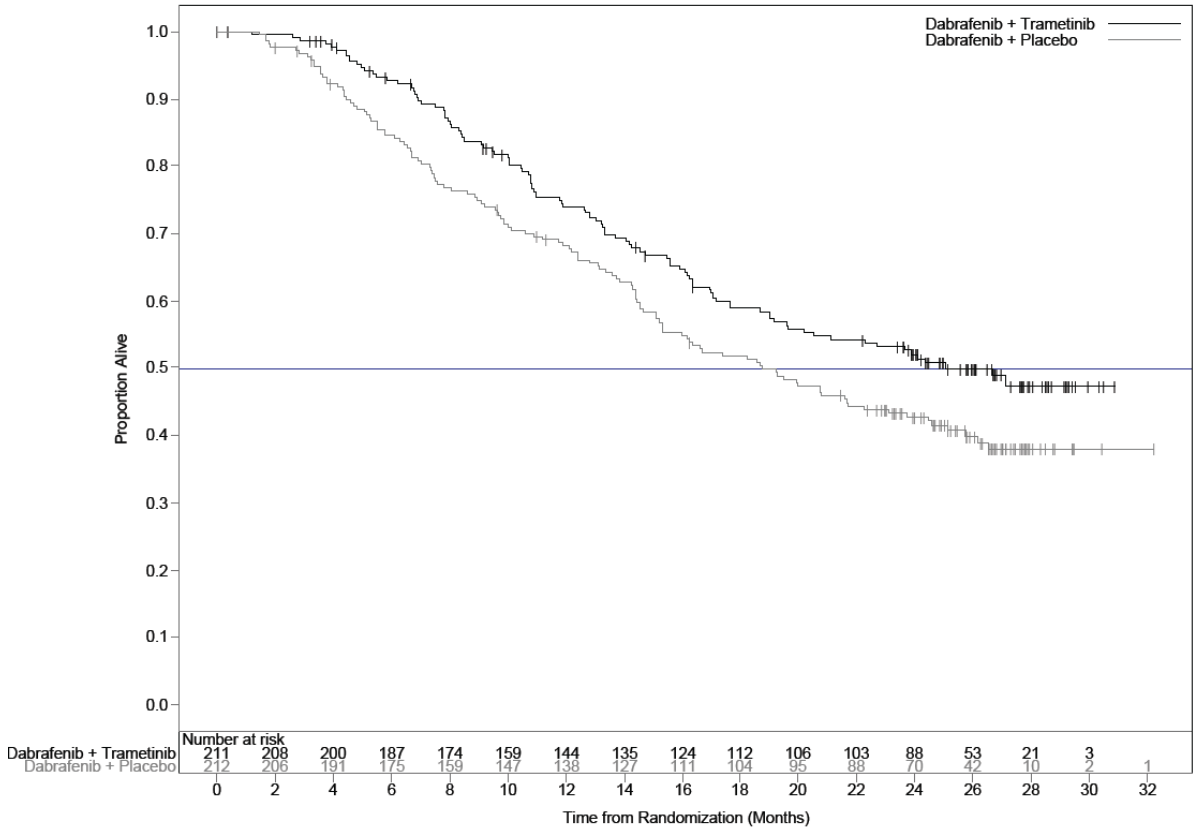
MEK115306 (COMBI-d) was a Phase III, randomized, double-blind study comparing the combination of Meqsel and dabrafenib to dabrafenib and placebo as first-line therapy for patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The primary endpoint 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 randomized 1:1 to either the combination therapy arm (Meqsel 2 mg once daily and Rafinlar 150 mg twice 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. Themajority of patients had an ECOG performance score of 0 (72%) and had Stage IVM1c disease (66%). Most patients (85%) had the BRAF V600E mutation; the remaining 15% of patients had the BRAF V600K mutation.

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

Extended follow-up found the 36-month OS estimate to be 44% for patients who received Meqsel in combination with Rafinlar and 32% for patients who received Rafinlar monotherapy.

Figure 2: COMBI-d - Kaplan-Meier overall survival curves (ITT Population)



Efficacy Results of PFS, ORR and Duration of Response are summarized in Table 7.

Table 7 : Investigator-assessed efficacy results for MEK115306 (COMBI-d) study (primary data cut and final data cut):

Endpoints	Primary Analysis*		Final Analysis*	
	Dabrafenib plus Trametinib N = 211	Dabrafenib N = 212	Dabrafenib plus Trametinib N = 211	Dabrafenib N = 212
Investigator Assessed PFS				
Progressive disease or death, n-(%)	102 (48)	109 (51)	139 (66)	162 (76)
Median, months (95% CI[a])	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)
Hazard Ratio -(95% CI)	0.75 (0.57, 0.99)		0.67 (0.53, 0.84)	
P value (log-rank test)	0.035		<0.001	
Overall Response Rate[b] (%) 95% CI	N=210 67 (59.9, 73.0)	N=210 51 (44.5,58.4)	N=210 69 (61.8, 74.8)	N=210 53 (46.3, 60.2)
Difference in response rate (CR[c] +PR[c]), % 95% CI for difference P value	15[d] 5.9, 24.5 0.0014		15[d] 6.0, 24.5 0.0014	
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)

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

a- Confidence interval

b- Overall Response Rate = Complete Response + Partial Response

c- CR: Complete Response, PR: Partial Response

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

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

NR = Not reached

MEK116513 (COMBI-v)

Study MEK116513 was a two-arm, randomized, open-label, Phase III study comparing Meqsel and dabrafenib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive unresectable or 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 randomized 1:1 to either the combination therapy arm (Meqsel 2 mg once daily and Rafinlar 150 mg twice daily) or the vemurafenib monotherapy arm (960 mg twice daily). Most patients were Caucasians (>96%) and male (55%), with a median age of 55 years (24% were ≥ 65 years). The majority of patients had Stage IV M1c disease (61%). Most patients had LDH ≤ULN (67%), ECOG performance status of 0 (70%), and visceral disease (78%) at baseline. Overall, 54%

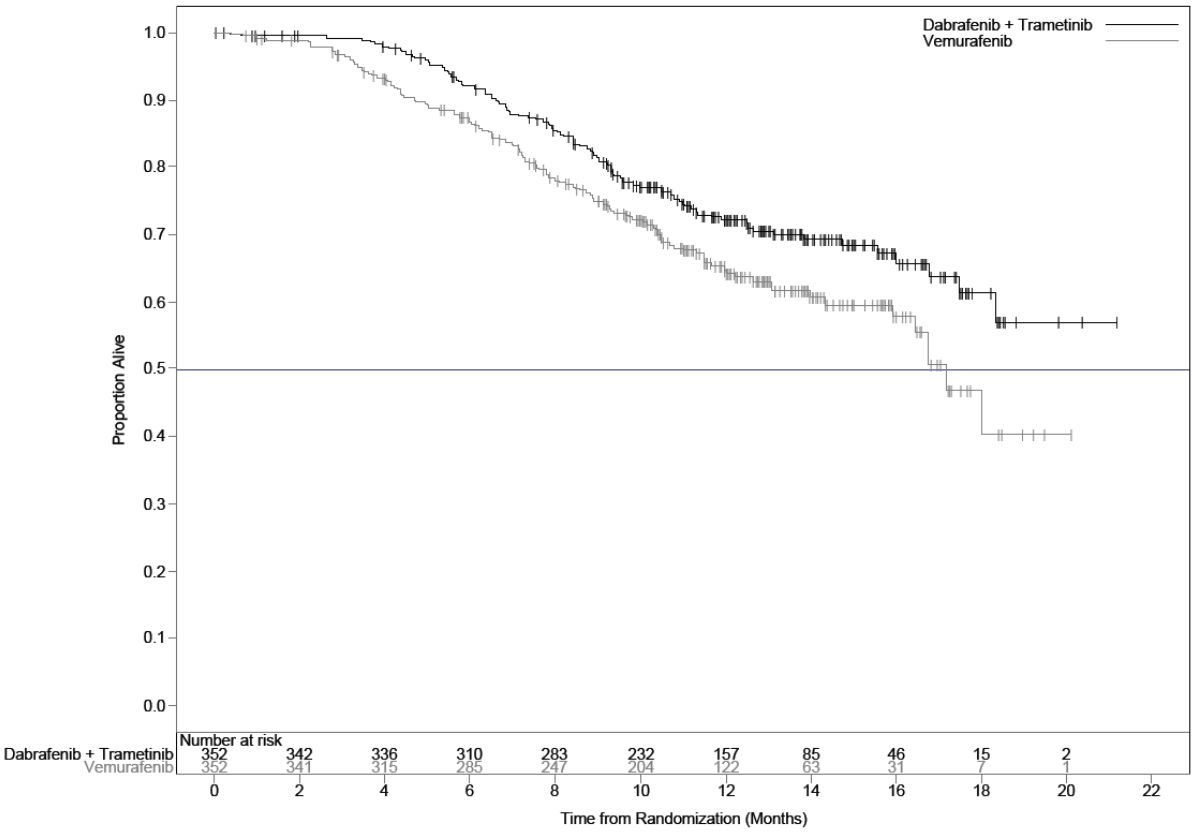
of patients had <3 disease sites at Baseline. The majority of patients had a BRAF V600E mutation (89%).

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

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

Extended follow-up found the 36-month OS estimate to be 45% for patients who received Meqsel in combination with Rafinlar and 31% for patients who received vemurafenib monotherapy.

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



Results of the endpoints for PFS, ORR and Duration of response are summarized in Table 8.

Table 8: Investigator- assessed efficacy results for MEK116513 (COMBI-v) study

Endpoint	**Dabrafenib + Trametinib (N=352)**	**Vemurafenib (N=352)**
Investigator Assessed PFS		
Progressive disease or death, n- (%)	166 (47)	217 (62)
Median, months (95 % CI)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)
Hazard Ratio (95 % CI)	0.56 (0.46, 0.69)	
P value	<0.001	
Overall Response Rate, n (%) 95% CI	226 (64) (59.1, 69.4)	180 (51) (46.1, 56.8)
Difference in response rate (CR+PR), % (95% CI for difference)	13 (5.7, 20.2)	
P value	0.0005	
Duration of Response (months)		
Median (95% CI)	13.8 (11.0, NR)	7.5 (7.3, 9.3)

PFS= Progression Free Survival; NR= Not reached

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

The efficacy and safety of Meqsel in combination with Rafinlar in patients with BRAF mutant-positive melanoma that has metastasized to the brain was studied in a non-randomized 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 or 1.
- 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 10. Secondary endpoints were duration of intracranial response, ORR, PFS and OS. Efficacy results are summarized in Table 9.

Table 9: 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*				

Advanced NSCLC

Study E2201 BRF113928

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

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

Cohorts were enrolled sequentially:

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

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

For 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 Meqsel in combination with Rafinlar for both NSCLC populations was less than or equal to 30%.

The ORR results assessed by IRC were consistent to the investigator assessment (Table 10).

The response was durable with median DoR in the previously treated population reaching 9.8 months (95% CI, 6.9, 16.0) by investigator assessment. For the first-line population, the median DoR and PFS could not yet be estimated (Table11), and 68% of patients with confirmed response were still ongoing in follow-up for duration of response.

Table 10: Efficacy Results in Patients with BRAF V600E NSCLC

Endpoint	Analysis	Combination First Line	Combination Second Line Plus
		N=36[1]	N=57[1]
Overall confirmed response n (%)	By Investigator	22 (61.1%)	38 (66.7%)

(95% CI)		(43.5, 76.9)	(52.9, 78.6)
	By IRC	22 (61.1%) (43.5, 76.9)	36 (63.2%) (49.3, 75.6)
Median DoR, months (95% CI)	By Investigator	NE[2] (8.3, NE)	9.8 (6.9, 16.0)
	By IRC	NE (6.9, NE)	12.6 (5.8, NE)
Median PFS, months (95% CI)	By Investigator	NE (7.0, NE)	10.2 (6.9, 16.7)
	By IRC	NE (7.0, NE)	8.6 (5.2, 16.8)
Median OS, months (95% CI)	-	24.6 (11.7, NE)[3]	18.2 (14.3, NE)

[1] Data cut-off: 8-Aug-2016
[2] NE: Not Evaluable
[3] Event rate for OS calculation was 28% and hence the defined median value still needs to mature

NON-CLINICAL SAFETY DATA

Safety pharmacology and repeat dose toxicity

In mice, lower heart rate, heart weight and left ventricular function were observed without cardiac histopathology after 3 weeks at ≥ 0.25 mg/kg/day trametinib (approximately three times human clinical exposure based on AUC) for up to three weeks. In adult rats, myocardial mineralization and necrosis associated with increased serum phosphorus were seen at doses ≥1 mg/kg/day (approximately 12 times human clinical exposure based on AUC). In juvenile rats, increased heart weight with no histopathology was observed at 0.35 mg/kg/day (approximately twice the adult human clinical exposure based on AUC).

Trametinib was phototoxic in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay at significantly higher concentrations than clinical exposures (IC50 at 2.92 microgram/mL, ≥ 130 times the clinical exposure based on C_{max}), indicating that there is low risk for phototoxicity to patients taking trametinib.

In repeat-dose studies in rats, hepatocellular necrosis and transaminase elevations were seen after 8 weeks at ≥ 0.062 mg/kg/day (approximately 0.8 times human clinical exposure based on AUC).

Carcinogenicity and mutagenicity

Carcinogenicity studies with trametinib have not been conducted. trametinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells and micronuclei in the bone marrow of rats.

Reproductive Toxicity

Embryofetal development and fertility

Trametinib may impair female fertility in humans. In adult and juvenile rat repeat dose studies with trametinib, alterations in follicular maturation, consisting of increases in cystic follicles and decreases in cystic corpora lutea, were observed at ≥ 0.016 mg/kg/day (approximately 0.3 times the human clinical exposure based on AUC).

Additionally, in juvenile rats given trametinib, decreased ovarian weights, slight delays in hallmarks of female sexual maturation (vaginal opening and increased incidence of prominent terminal end buds within the mammary gland) and slight hypertrophy of the surface epithelium of the uterus were observed. All of these effects were reversible following an off-treatment period and attributable to pharmacology. However, in rat and dog toxicity studies up to 13 weeks in duration, there were no treatment effects observed on male reproductive tissues.

Juvenile animal studies

In a juvenile rat toxicity study, the principal toxicities in juvenile rats were on growth (bodyweight and long bone length), adverse microscopic findings included changes in the bone, mineralization and/or degeneration in various organs, primarily stomach at all doses. Adverse findings at the higher doses included in eye, kidney, aortic arch and/or nasal cavity/sinuses, heart, liver and in skin, and higher heart weights and the delay in a physical landmark of sexual maturity in females (vaginal opening).

The majority of findings are reversible with the exception of the bone, serum phosphorus and soft tissue mineralization which progressed/worsened during the off-drug period. Also, kidney tubular basophilia and higher heart weights were still present at end of recovery period.

With the exception of corneal mineralization/dystrophy and increased heart weight, similar effects have been observed in adult animals given trametinib. At the lowest combined dose level evaluated, the systemic exposure is approximately 0.3 times the human exposure at clinical dose of 2 mg/day based on AUC.

Non-fixed dose combination therapy

Trametinib in combination with dabrafenib

Dogs given trametinib and dabrafenib in combination for 4 weeks demonstrated similar toxicities to those observed in comparable monotherapy studies.

Refer to the full prescribing information for Rafinlar

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Meqsel should not be used after the date marked “EXP” on the pack.

Meqsel must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

There are no special requirements for use or handling of this product.

Manufacturer:

See folding box.

Further information is available from:

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