FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Melanoma

MEQSEL as monotherapy or in combination with dabrafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation *[see Warnings and Precautions (5) and Clinical Pharmacology (11.1)]*.

Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy *[see Clinical Pharmacology (11.1)]*.

1.2 Adjuvant treatment of melanoma

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

1.3 BRAF V600E Mutation-Positive Metastatic NSCLC

MEQSEL is indicated, in combination with dabrafenib, for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation *[see Dosage and Administration (2.1)]*.

1.4 BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors

MEQSEL is indicated, in combination with dabrafenib, for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options *[see Dosage and Administration (2.1)]*.

1.5 Limitations of Use

MEQSEL is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition *[see Indications and Usage (1.4), Clinical Pharmacology (11.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Melanoma

- Treatment with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.
- Before taking trametinib, patients must have confirmation of BRAF V600 mutation using a validated test.

NSCLC

Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEQSEL and dabrafenib *[see Clinical Studies (13.3)]*.

Solid Tumors

Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEQSEL and dabrafenib *[see Clinical Studies (13.5)]*.

2.2 Recommended Dosage

MEQSEL Tablets

Adult Patients

The recommended dosage for MEQSEL tablets in adult patients, either used as monotherapy or in combination with dabrafenib, is 2 mg once daily. The recommended dose of dabrafenib, when used in combination with trametinib, is 150 mg twice daily.

Pediatric Patients *(Solid Tumors only)*

The recommended dosage for MEQSEL tablets in pediatric patients who weigh at least 26 kg is based on body weight (Table 1) *[see Dosage and Administration (2.3)]*. A recommended dosage of MEQSEL tablets has not been established in patients who weigh less than 26 kg.

Table 1. Recommended Dosage for MEQSEL Tablets in Pediatric Patients (Weight-based)

Body Weight	Recommended Dosage
26 to 37 kg	1 mg orally once daily
38 to 50 kg	1.5 mg orally once daily
51 kg or greater	2 mg orally once daily

Duration of treatment

- The recommended duration of treatment for patients with unresectable or metastatic melanoma, solid tumors or metastatic NSCLC is until disease progression or unacceptable toxicity.
- In the adjuvant melanoma setting, patients should be treated for a period of 12 months unless there is disease recurrence or unacceptable toxicity.

Refer to the dabrafenib prescribing information for recommended dabrafenib dosing information.

2.3 Administration

- Take MEQSEL at the same time each day, approximately 24 hours apart.
- Take MEQSEL tablets on an empty stomach (at least 1 hour before or 2 hours after a meal) *[see Clinical Pharmacology (11.3)]*. Do not take a missed dose of MEQSEL within 12 hours of the next dose of MEQSEL.
- If vomiting occurs after MEQSEL administration, do not take an additional dose. Take the next dose at its scheduled time.
- Do not crush or break MEQSEL tablets.

2.4 Dosage Modifications for Adverse Reactions

Dose reductions for adverse reactions associated with MEQSEL are presented in Table 2.

Table 2. Recommended Dosage Reductions for MEQSEL Tablets for Adverse Reactions

Recommended Dosage	1 mg orally once daily	1.5 mg orally once daily	2 mg orally once daily
First dose reduction	0.5 mg orally once daily	1 mg orally once daily	1.5 mg orally once daily
Second dose reduction	N/A	0.5 mg orally once daily	1 mg orally once daily
Subsequent modification	Permanently discontinue MEQSEL tablets if unable to tolerate a maximum of two dose reductions.		

Dosage modifications for adverse reactions associated with MEQSEL are presented in Table 3.

Table 3. Recommended Dosage Modifications for MEQSEL for Adverse Reactions

Severity of Adverse Reaction[a]	Dosage Modification for MEQSEL[b]
Hemorrhage [see Warnings and Precautions (5.2)]	

• Grade 3	Withhold MEQSEL. • If improved, resume MEQSEL at lower dose. • If not improved, permanently discontinue MEQSEL.
• Grade 4	Permanently discontinue MEQSEL.
Venous Thromboembolic Events [see Warnings and Precautions (5.4)]	
• Uncomplicated deep venous thrombosis (DVT) or pulmonary embolism (PE)	Withhold MEQSEL for up to 3 weeks. • If improved to Grade 0-1, resume MEQSEL at lower dose. • If not improved, permanently discontinue MEQSEL.
• Life-threatening PE	Permanently discontinue MEQSEL.
Cardiomyopathy [see Warnings and Precautions (5.5)]	
• Asymptomatic, absolute decrease in left ventricular ejection fraction (LVEF) of 10% or greater from baseline that is below the institutional lower limit of normal (LLN)	Withhold MEQSEL for up to 4 weeks. • If improved to normal LVEF value, resume MEQSEL at lower dose. • If not improved to normal LVEF value, permanently discontinue MEQSEL.
• Symptomatic cardiomyopathy • Absolute decrease in LVEF of greater than 20% from baseline that is below the institutional LLN	Permanently discontinue MEQSEL.
Ocular Toxicities [see Warnings and Precautions (5.6)]	
• Retinal pigment epithelial detachments (RPED)	Withhold MEQSEL for up to 3 weeks. • If improved, resume MEQSEL at same or lower dose. • If not improved, permanently discontinue MEQSEL or resume MEQSEL at lower dose.
• Retinal vein occlusion (RVO)	Permanently discontinue MEQSEL.
Pulmonary [see Warnings and Precautions (5.7)]	
• Interstitial lung disease (ILD)/pneumonitis	Permanently discontinue MEQSEL.
Febrile Reactions [see Warnings and Precautions (5.8)]	
• Fever of 100.4°F to 104°F (or first symptoms in case of recurrence)	Withhold MEQSEL until fever resolves, then resume MEQSEL at same or lower dose.
• Fever higher than 104°F • Fever complicated by rigors, hypotension, dehydration, or renal failure	• Withhold MEQSEL until febrile reactions resolve for at least 24 hours, then resume MEQSEL at lower dose. Or • Permanently discontinue MEQSEL.
Skin Toxicities [see Warnings and Precautions (5.9)]	
• Intolerable Grade 2 • Grade 3 or 4	Withhold MEQSEL for up to 3 weeks. • If improved, resume MEQSEL at lower dose. • If not improved, permanently discontinue MEQSEL.
• Severe cutaneous adverse reactions (SCARs)	Permanently discontinue MEQSEL.
Other Adverse Reactions[c]	
• Intolerable Grade 2 • Any Grade 3	Withhold MEQSEL. • If improved to Grade 0-1, resume MEQSEL at lower dose. • If not improved, permanently discontinue MEQSEL.
• First occurrence of any Grade 4	• Withhold MEQSEL until improves to Grade 0-1, then resume at lower dose. Or • Permanently discontinue MEQSEL.
• Recurrent Grade 4	Permanently discontinue MEQSEL.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.
[b] See Tables 2 and 3 for recommended dose reductions of MEQSEL.

[c] Dose modifications are not recommended for MEQSEL when administered with dabrafenib for the following adverse reactions of dabrafenib: non-cutaneous malignancies and uveitis. Dose modification of MEQSEL is not required for new primary cutaneous malignancies.

Refer to the dabrafenib prescribing information for dose modifications for adverse reactions associated with dabrafenib.

3 DOSAGE FORMS AND STRENGTHS

MEQSEL tablets:

- 0.5 mg tablets: Yellow, ovaloid, biconvex, unscored film-coated tablets with beveled edges and with the Novartis logo debossed on one side and 'TT' on the other side.
- 2 mg tablets: Pink, round, biconvex, unscored film-coated tablets with beveled edges and with the Novartis logo debossed on one side and 'LL' on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 New Primary Malignancies

Cutaneous Malignancies

MEQSEL Administered with Dabrafenib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, cutaneous squamous cell carcinomas (cuSCCs) and keratoacanthomas occurred in 2% of patients. Basal cell carcinoma and new primary melanoma occurred in 3% and < 1% of patients, respectively.

MEQSEL Administered with Dabrafenib (Pediatric): In the pooled safety population, new primary melanoma occurred in < 1% of patients.

Perform dermatologic evaluations prior to initiation of MEQSEL when used with dabrafenib, every 2 months while on therapy, and for up to 6 months following discontinuation of the combination.

Non-Cutaneous Malignancies

Based on its mechanism of action, dabrafenib may promote growth and development of malignancies with activation of RAS through mutation or other mechanisms; refer to the prescribing information for dabrafenib.

In the pooled safety population of MEQSEL administered with dabrafenib, non-cutaneous malignancies occurred in 1% of patients.

Monitor patients receiving MEQSEL and dabrafenib closely for signs or symptoms of non-cutaneous malignancies. No dose modification is required for MEQSEL in patients who develop non-cutaneous malignancies.

5.2 Hemorrhage

Hemorrhages, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur with MEQSEL. Fatal cases have been reported.

MEQSEL Administered with Dabrafenib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, hemorrhagic events occurred in 17% of patients; gastrointestinal hemorrhage occurred in 3% of patients;

intracranial hemorrhage occurred in 0.6% of patients; fatal hemorrhage occurred in 0.5% of patients. The fatal events were cerebral hemorrhage and brainstem hemorrhage.

MEQSEL Administered with Dabrafenib (Pediatric): In the pooled safety population, hemorrhagic events occurred in 25% of patients; the most common type of bleeding was epistaxis (16%). Serious events of bleeding occurred in 3.6% of patients and included gastrointestinal hemorrhage (1.2%), cerebral hemorrhage (0.6%) uterine hemorrhage (0.6%), post-procedural hemorrhage (0.6%), and epistaxis (0.6%).

Permanently discontinue MEQSEL for all Grade 4 hemorrhagic events and for any Grade 3 hemorrhagic events that do not improve. Withhold MEQSEL for Grade 3 hemorrhagic events; if improved, resume MEQSEL at the next lower dose level.

5.3 Colitis and Gastrointestinal Perforation

Colitis and gastrointestinal perforation, including fatal outcomes, have been reported in patients taking:

MEQSEL Monotherapy and Administered with Dabrafenib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)],* colitis occurred in < 1% of patients and gastrointestinal perforation occurred in < 1% of patients.

MEQSEL Administered with Dabrafenib (Pediatric): In the pooled safety population, colitis events occurred in <1% of patients.

Monitor patients closely for colitis and gastrointestinal perforations.

5.4 Venous Thromboembolic Events

MEQSEL Administered with Dabrafenib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, deep vein thrombosis (DVT) and pulmonary embolism (PE) occurred in 2% of patients.

MEQSEL Administered with Dabrafenib (Pediatric): In the pooled safety population, embolism events occurred in < 1% of patients.

Advise patients to immediately seek medical care if they develop symptoms of DVT or PE, such as shortness of breath, chest pain, or arm or leg swelling. Permanently discontinue MEQSEL for life-threatening PE. Withhold MEQSEL for uncomplicated DVT and PE for up to 3 weeks; if improved, MEQSEL may be resumed at a lower dose level *[see Dosage and Administration (2.4)]*.

5.5 Cardiomyopathy

Cardiomyopathy, including cardiac failure, can occur with MEQSEL.

MEQSEL Administered with Dabrafenib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) ≥ 10% from baseline and below the institutional lower limit of normal (LLN), occurred in 6% of patients. Development of cardiomyopathy resulted in dose interruption or discontinuation of MEQSEL in 3% and < 1% of patients, respectively. Cardiomyopathy resolved in 45 of 50 patients who received MEQSEL administered with dabrafenib.

MEQSEL Administered with Dabrafenib (Pediatric): In the pooled safety population, cardiomyopathy, defined as a decrease in LVEF ≥ 10% from baseline and below the institutional LLN, occurred in 9% of patients.

Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of MEQSEL as a single agent or with dabrafenib, one month after initiation, and then at 2- to 3-month intervals while on treatment. For an asymptomatic absolute decrease in LVEF of 10% or greater from baseline that is below the institutional LLN, withhold MEQSEL for up to 4 weeks. If improved to normal LVEF value, resume at a lower dose. If no improvement to normal LVEF value within 4 weeks, permanently discontinue MEQSEL. For symptomatic cardiomyopathy or an absolute decrease in LVEF of greater than 20% from baseline that is below the institutional LLN, permanently discontinue MEQSEL *[see Dosage and Administration (2.4)]*.

5.6 Ocular Toxicities

Retinal Vein Occlusion

In the pooled safety population *[see Adverse Reactions (6.1)]* of MEQSEL monotherapy, the incidence of retinal vein occlusion (RVO) was 0.6%. In the pooled safety population *[see Adverse Reactions (6.1)]* of MEQSEL administered with dabrafenib, there were no cases of RVO. RVO may lead to macular edema, decreased visual function, neovascularization, and glaucoma.

Urgently (within 24 hours) perform ophthalmological evaluation for patient-reported loss of vision or other visual disturbances. Permanently discontinue MEQSEL in patients with documented RVO *[see Dosage and Administration (2.4)]*.

Retinal Pigment Epithelial Detachment

Retinal pigment epithelial detachment (RPED) can occur with MEQSEL. Retinal detachments may be bilateral and multifocal, occurring in the central macular region of the retina or elsewhere in the retina. In melanoma and NSCLC trials, routine monitoring of patients to detect asymptomatic RPED was not conducted; therefore, the true incidence of this finding is unknown.

MEQSEL Administered with Dabrafenib (Pediatric): In the pooled safety population, RPED events occurred in < 1% of patients.

Perform ophthalmological evaluation periodically and at any time a patient reports visual disturbances. Withhold MEQSEL if RPED is diagnosed. If resolution of the RPED is documented on repeat ophthalmological evaluation within 3 weeks, resume MEQSEL at same or reduced dose. If no improvement after 3 weeks, resume MEQSEL at reduced dose or permanently discontinue MEQSEL *[see Dosage and Administration (2.4)]*.

5.7 Interstitial Lung Disease/Pneumonitis

In the pooled safety population *[see Adverse Reactions (6.1)]* of MEQSEL monotherapy, interstitial lung disease or pneumonitis occurred in 2% of patients. In the pooled safety population *[see Adverse Reactions (6.1)]* of MEQSEL administered with dabrafenib, ILD or pneumonitis occurred in 1% of patients.

Withhold MEQSEL in patients presenting with new or progressive pulmonary symptoms and findings, including cough, dyspnea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Permanently discontinue MEQSEL for patients diagnosed with treatment-related ILD or pneumonitis *[see Dosage and Administration (2.4)]*.

5.8 Serious Febrile Reactions

Serious febrile reactions and fever of any severity accompanied by hypotension, rigors or chills, dehydration, or renal failure, can occur when MEQSEL is administered with dabrafenib.

MEQSEL Administered with Dabrafenib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, fever occurred in 58% of patients. Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration or renal failure occurred in 5% of patients. Fever was complicated by hypotension in 4%, dehydration in 3%, syncope in 2%, renal failure in 1%, and severe chills/rigors in < 1% of patients.

MEQSEL Administered with Dabrafenib (Pediatric): In the pooled safety population *[see Adverse Reactions (6.1)],* pyrexia occurred in 66% of patients.

Withhold MEQSEL when used as monotherapy, and both MEQSEL and dabrafenib when used in combination, if the patient's temperature is ≥ 100.4°F. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia *[see Adverse Reactions (6.1)]*. Fever may be complicated by hypotension, rigors or chills, dehydration, or renal failure. Evaluate for signs and symptoms of infection and monitor serum creatinine and other evidence of renal function during and following severe pyrexia. If appropriate, MEQSEL, or both MEQSEL and dabrafenib

when used in combination, may be restarted if the patient has recovered from the febrile reaction for at least 24 hours, either at same or lower dose *[see Dosage and Administration (2.4)]*. Administer antipyretics as secondary prophylaxis when resuming MEQSEL if patient had a prior episode of severe febrile reaction or fever associated with complications. Administer corticosteroids (e.g., prednisone 10 mg daily) for at least 5 days for second or subsequent pyrexia if temperature does not return to baseline within 3 days of onset of pyrexia, or for pyrexia associated with complications, such as dehydration, hypotension, renal failure, or severe chills/rigors, and there is no evidence of active infection.

5.9 Serious Skin Toxicities

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with MEQSEL administered with dabrafenib *[see Adverse Reactions (6.2)]*.

MEQSEL Administered with Dabrafenib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, other serious skin toxicity occurred in < 1% of patients.

MEQSEL Administered with Dabrafenib (Pediatric): In the pooled safety population, serious adverse events of skin and subcutaneous tissue disorders occurred in 1.8% of patients.

Monitor for new or worsening serious skin reactions. Permanently discontinue MEQSEL for SCARs *[see Dosage and Administration (2.4)]*. For other skin toxicities, withhold MEQSEL for intolerable or severe skin toxicity. Resume MEQSEL at a lower dose in patients with improvement or recovery from skin toxicity within 3 weeks. Permanently discontinue MEQSEL if skin toxicity has not improved in 3 weeks *[see Dosage and Administration (2.4)]*.

5.10 Hyperglycemia

MEQSEL Administered with Dabrafenib (Adult): In the pooled safety population *[see Adverse Reactions (6.1)]*, 15% of patients with a history of diabetes who had received MEQSEL with dabrafenib required more intensive hypoglycemic therapy. Grade 3 and Grade 4 hyperglycemia occurred in 2% of patients.

MEQSEL Administered with Dabrafenib (Pediatric): In the pooled safety population, Grade 3 and Grade 4 hyperglycemia events occurred in < 1% of patients.

Monitor serum glucose levels upon initiation and as clinically appropriate when MEQSEL is administered with dabrafenib in patients with preexisting diabetes or hyperglycemia. Initiate or optimize anti-hyperglycemic medications as clinically indicated.

5.11 Risks Associated with Combination Treatment

MEQSEL is indicated for use in combination with dabrafenib. Review the prescribing information for dabrafenib for information on the serious risks of dabrafenib prior to initiation of MEQSEL with dabrafenib.

5.12 Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) has been observed in the post-marketing setting when MEQSEL was administered with dabrafenib. If HLH is suspected, interrupt treatment. If HLH is confirmed, discontinue treatment and initiate appropriate management of HLH.

5.13 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, MEQSEL can cause fetal harm when administered to a pregnant woman. Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 0.3 times the human exposure at the recommended adult clinical dose. Advise pregnant women of the potential risk to a fetus. Advise female patients of reproductive potential to use effective contraception during treatment with MEQSEL and for 4 months after treatment *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- New Primary Malignancies *[see Warnings and Precautions (5.1)]*
- Hemorrhage *[see Warnings and Precautions (5.2)]*
- Colitis and Gastrointestinal Perforation *[see Warnings and Precautions (5.3)]*
- Venous Thromboembolic Events *[see Warnings and Precautions (5.4)]*
- Cardiomyopathy *[see Warnings and Precautions (5.5)]*
- Ocular Toxicities *[see Warnings and Precautions (5.6)]*
- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.7)]*
- Serious Febrile Reactions *[see Warnings and Precautions (5.8)]*
- Serious Skin Toxicities *[see Warnings and Precautions (5.9)]*
- Hyperglycemia *[see Warnings and Precautions (5.10)]*
- Hemophagocytic Lymphohistiocytosis *[see Warnings and Precautions (5.12)]*

There are additional adverse reactions associated with dabrafenib. Refer to the dabrafenib prescribing information for additional information.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Safety Pools

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to MEQSEL 2 mg orally, once daily as a single agent in 329 patients with various solid tumors enrolled in METRIC, MEK113583, and MEK111054. Among these 329 patients who received MEQSEL as a single agent, 33% were exposed for 6 months or longer and 9% were exposed for greater than one year.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to MEQSEL 2 mg orally, once daily, administered in combination with dabrafenib 150 mg orally, twice daily, in 1087 patients enrolled in COMBI-d, COMBI-v, COMBI-AD, and BRF113928 with unresectable or metastatic melanoma, adjuvant melanoma, or NSCLC. Among these 1087 patients who received MEQSEL administered with dabrafenib, 70% were exposed for 6 months or longer and 21% were exposed for greater than one year.

Pediatric Safety Pool

The pediatric pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to weight-based MEQSEL orally, once daily administered in combination with dabrafenib in 166 pediatric patients across two trials: a multi-center, open-label, multi-cohort study in pediatric patients with BRAF V600E mutation-positive glioma requiring systemic therapy (Study G2201; n = 123) and a multi-center, open-label, multi-cohort study in pediatric patients with refractory or recurrent solid tumors with MAPK pathway activation (Study X2101; n = 43) *[see Clinical Studies (13.5)]*. Among 166 patients who received MEQSEL administered with dabrafenib, 85% were exposed for 6 months and 69% were exposed for greater than one year. The most common (> 20%) adverse reactions were pyrexia (66%), rash (54%), headache (40%), vomiting (38%), musculoskeletal pain (36%), fatigue (31%), dry skin (31%), diarrhea (30%), nausea (26%), epistaxis and other bleeding events (25%), abdominal pain (24%), and dermatitis acneiform (23%). The most common (> 2%) Grade 3 or 4 laboratory abnormalities were decreased neutrophil count (20%), increased alanine aminotransferase (3.1%), and increased aspartate aminotransferase (3.1%).

Unresectable or Metastatic BRAF V600E or V600K Mutation-Positive Melanoma

MEQSEL as a Single Agent

The safety of MEQSEL was evaluated in the METRIC study, a randomized, open-label trial of patients with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma who received MEQSEL (N = 211) 2 mg orally once daily or chemotherapy (N = 99) (either dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks) *[see Clinical Studies (13.1)]*. Patients with abnormal LVEF, history of acute coronary syndrome within 6 months, or current evidence of Class II or greater congestive heart failure were excluded. The median duration of treatment with MEQSEL was 4.3 months.

In this study, 9% of patients who received MEQSEL experienced adverse reactions resulting in permanent discontinuation of trial medication. The most frequent adverse reactions resulting in permanent discontinuation of MEQSEL were decreased LVEF, pneumonitis, renal failure, diarrhea, and rash. Adverse reactions led to dose reductions in 27% of patients treated with MEQSEL. Rash and decreased LVEF were the most frequent reasons cited for dose reductions of MEQSEL. Table 4 and Table 5 present adverse reactions and laboratory abnormalities, respectively, of MEQSEL as a single agent in the METRIC study.

Table 4. Select Adverse Reactions Occurring in ≥ 10% of Patients Who Received MEQSEL and at a Higher Incidence (≥ 5%) Than in the Chemotherapy Arm or ≥ 2% (Grades 3 or 4) Adverse Reactions in the METRIC Study

Adverse Reactions	MEQSEL N = 211		Chemotherapy N = 99	
	All Grades[a] (%)	Grades 3 and 4[b] (%)	All Grades[a] (%)	Grades 3 and 4[b] (%)
Skin and subcutaneous tissue				
Rash	57	8	10	0
Acneiform dermatitis	19	< 1	1	0
Dry skin	11	0	0	0
Pruritus	10	2	1	0
Paronychia	10	0	1	0
Gastrointestinal				
Diarrhea	43	0	16	2
Stomatitis[c]	15	2	2	0
Abdominal pain[d]	13	1	5	1
Vascular				
Lymphedema[e]	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage[f]	13	< 1	0	0

[a] NCI CTCAE version 4.0.
[b] Grade 4 adverse reactions limited to rash (n = 1) in trametinib arm and diarrhea (n = 1) in chemotherapy arm.
[c] Includes stomatitis, aphthous stomatitis, mouth ulceration, and mucosal inflammation.
[d] Includes abdominal pain, lower abdominal pain, upper abdominal pain, and abdominal tenderness.
[e] Includes lymphedema, edema, and peripheral edema.
[f] Includes epistaxis, gingival bleeding, hematochezia, rectal hemorrhage, melena, vaginal hemorrhage, hemorrhoidal hemorrhage, hematuria, and conjunctival hemorrhage.

Table 5. Laboratory Abnormalities Occurring at a Higher Incidence in Patients Who Received MEQSEL in the METRIC Study [Between-Arm Difference of ≥ 5% (All Grades) or ≥ 2% (Grades 3 or 4)[a]]

Laboratory Abnormality	MEQSEL N = 211		Chemotherapy N = 99	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)

Increased AST	60	2	16	1
Hypoalbuminemia	42	2	23	1
Increased ALT	39	3	20	3
Anemia	38	2	26	3
Increased alkaline phosphatase	24	2	18	3

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] Only Grade 3 adverse reactions were reported in either treatment arm.

Other clinically important adverse reactions for MEQSEL in a pool of MEQSEL monotherapy clinical studies observed in less than 10% of patients who received MEQSEL were:

Cardiac: Bradycardia, atrioventricular block, bundle branch block

Gastrointestinal: Dry mouth

Infections and Infestations: Folliculitis, rash pustular, cellulitis

Musculoskeletal and Connective Tissue: Rhabdomyolysis

Nervous System: Dizziness, dysgeusia, peripheral neuropathy

Ocular: Blurred vision, dry eye

MEQSEL with Dabrafenib

The safety of MEQSEL when administered with dabrafenib was evaluated in 559 patients with previously untreated, unresectable or metastatic, BRAF V600 mutation-positive melanoma who received MEQSEL in two trials, the COMBI-d study (n = 209), a multi-center, double-blind, randomized (1:1), active-controlled trial and the COMBI-v study (n = 350), a multi-center, open-label, randomized (1:1), active-controlled trial. In both trials, patients received MEQSEL 2 mg orally once daily and dabrafenib 150 mg orally twice daily until disease progression or unacceptable toxicity. Both trials excluded patients with abnormal LVEF, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure, history of RVO or RPED, QTcB interval ≥ 480 msec, uncontrolled hypertension, uncontrolled arrhythmias, active brain metastases, or known history of glucose-6-phosphate dehydrogenase deficiency *[see Clinical Studies (13.1)]*.

Among these 559 patients, 197 (35%) were exposed to MEQSEL for > 6 months to 12 months while 185 (33%) were exposed to MEQSEL for > 1 year. The median age was 55 years (range: 18 to 91), 57% were male, and 98% were White, 72% had baseline ECOG performance status of 0 and 28% had ECOG performance status of 1, 64% had M1c disease, 35% had elevated lactate dehydrogenase (LDH) at baseline, and 0.5% had a history of brain metastases.

The most common adverse reactions (≥ 20%) for MEQSEL in patients who received MEQSEL plus dabrafenib in the COMBI-d and COMBI-v studies were: pyrexia, nausea, rash, chills, diarrhea, vomiting, hypertension, and peripheral edema.

The demographics and baseline tumor characteristics of patients enrolled in the COMBI-d study are summarized in Clinical Studies *[see Clinical Studies (13.1)]*. Patients who received MEQSEL plus dabrafenib had a median duration of exposure of 11 months (range: 3 days to 30 months) to MEQSEL. Among the 209 patients who received MEQSEL plus dabrafenib, 26% were exposed to MEQSEL for > 6 months to 12 months while 46% were exposed to MEQSEL for > 1 year.

In the COMBI-d study, adverse reactions leading to discontinuation of MEQSEL occurred in 11% of patients who received MEQSEL plus dabrafenib; the most frequent were pyrexia (1.4%) and decreased ejection fraction (1.4%). Adverse reactions leading to dose reductions of MEQSEL occurred in 18% of patients who received MEQSEL plus dabrafenib; the most frequent were pyrexia (2.9%), neutropenia (1.9%), decreased ejection fraction (1.9%), and rash (1.9%). Adverse reactions leading to dose interruptions of MEQSEL occurred in 46% of patients who received MEQSEL plus dabrafenib; the most frequent were pyrexia (18%), chills (7%), vomiting (6%), and decreased ejection fraction (4.8%).

Table 6 and Table 7 present selected adverse reactions and laboratory abnormalities, respectively, of MEQSEL observed in the COMBI-d study.

Table 6. Adverse Reactions Occurring in ≥ 10% (All Grades) of Patients Who Received MEQSEL with Dabrafenib and at a Higher Incidence* Than in Patients Who Received Single-Agent Dabrafenib in COMBI-d[a]

Adverse Reactions	Pooled MEQSEL plus Dabrafenib N = 559		COMBI-d Study			
			MEQSEL plus Dabrafenib N = 209		Dabrafenib N = 211	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
General						
Pyrexia	54	5	57	7	33	1.9
Chills	31	0.5	31	0	17	0.5
Peripheral edema[b]	21	0.7	25	1.4	11	0.5
Gastrointestinal						
Nausea	35	0.4	34	0.5	27	1.4
Diarrhea	31	1.3	30	1.4	16	0.9
Vomiting	27	1.1	25	1.0	14	0.5
Abdominal pain[c]	18	0.9	26	1.0	14	2.4
Skin and subcutaneous tissue						
Rash[d]	32	1.1	42	0	27	1.4
Vascular						
Hypertension	26	11	25	6	16	6
Hemorrhage[e]	18	2.0	19	1.9	15	1.9
Nervous system						
Dizziness	11	0.2	14	0	7	0

* ≥ 5% for All Grades or ≥ 2% for Grades 3–4 incidence in patients who received MEQSEL with dabrafenib compared with patients who received dabrafenib as a single agent.

[a] NCI CTCAE version 4.0.

[b] Includes peripheral edema, edema, lymphedema, localized edema, and generalized edema.

[c] Includes abdominal pain, upper abdominal pain, lower abdominal pain, and abdominal discomfort.

[d] Includes rash, generalized rash, pruritic rash, erythematous rash, papular rash, vesicular rash, macular rash, maculo-papular rash, and follicular rash.

[e] Most common events (≥ 1%) include epistaxis, hematochezia, decreased hemoglobin, purpura, and rectal hemorrhage. Grade 4 events were limited to hepatic hematoma and duodenal ulcer hemorrhage (each n = 1 in the pooled combination arm).

Other clinically important adverse reactions for MEQSEL across the COMBI-d and COMBI-v studies (N = 559) observed in less than 10% of patients who received MEQSEL in combination with dabrafenib were:

Cardiac: Bradycardia, atrioventricular block, bundle branch block

Immune System: Sarcoidosis

Musculoskeletal and Connective Tissue: Rhabdomyolysis

Nervous System: Peripheral neuropathy, Guillain-Barré syndrome

Skin and Subcutaneous Tissue: Photosensitivity

Table 7. Laboratory Abnormalities Worsening from Baseline Occurring at ≥ 10% (All Grades) of Patients Who Received MEQSEL with Dabrafenib and at a Higher Incidence* Than in Patients Who Received Single-Agent Dabrafenib in COMBI-d

Laboratory Abnormality	Pooled MEQSEL plus Dabrafenib N = 559[a]		COMBI-d Study			
			MEQSEL plus Dabrafenib N = 209[b]		Dabrafenib N = 211[b]	
	All Grades (%)	Grades 3 and 4[c] (%)	All Grades (%)	Grades 3 and 4[c] (%)	All Grades (%)	Grades 3 and 4[c] (%)
Chemistry						
Hyperglycemia	60	4.7	65	6	57	4.3
Hypoalbuminemia	48	1.1	53	1.4	27	0
Hyponatremia	25	8	24	6	14	2.9
Hepatic						
Increased AST	59	4.1	60	4.3	21	1.0
Increased blood alkaline phosphatase	49	2.7	50	1.0	25	0.5
Increased ALT	48	4.5	44	3.8	28	1.0
Hematology						
Neutropenia	46	7	50	6	16	1.9
Anemia	43	2.3	43	2.4	38	4.3
Lymphopenia	32	8	38	9	28	7
Thrombocytopenia	21	0.7	19	0.5	10	0.5

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

* ≥ 5% for All Grades or ≥ 2% for Grades 3–4 incidence in patients who received MEQSEL with dabrafenib compared with patients who received dabrafenib as a single agent.

[a] For these laboratory tests, the denominator is 556.

[b] For these laboratory tests, the denominator is 208 for the combination arm, 207-209 for the dabrafenib arm.

[c] Grade 4 adverse reactions limited to lymphopenia and hyperglycemia (each n = 4), increased ALT and increased AST (each n = 3), neutropenia (n = 2), and hyponatremia (n = 1) in the pooled combination arm; neutropenia, lymphopenia, increased ALT, increased AST, and hyperglycemia (each n = 1) in the COMBI-d study combination arm; neutropenia, thrombocytopenia, increased ALT, and increased AST (each n = 1) in the dabrafenib arm.

Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma

The safety of MEQSEL when administered with dabrafenib was evaluated in 435 patients with Stage III melanoma with BRAF V600E or V600K mutations following complete resection who received at least one dose of study therapy in the COMBI-AD study *[see Clinical Studies (13.2)]*. Patients received MEQSEL 2 mg orally once daily and dabrafenib 150 mg orally twice daily for 12 months. The trial excluded patients with abnormal LVEF; history of acute coronary syndromes, coronary angioplasty, or stenting within 6 months; Class II or greater congestive heart failure; QTc interval ≥ 480 msec; treatment refractory hypertension; uncontrolled arrhythmias; or history of RVO.

Patients who received MEQSEL in combination with dabrafenib had a median duration of exposure of 11 months (range: 0 to 12) to MEQSEL. Among the 435 patients who received MEQSEL in combination with dabrafenib, 72% were exposed to MEQSEL for > 6 months. The median age of patients who received MEQSEL in combination with dabrafenib was 50 years (range: 18 to 89), 56% were male, 99% were White, 92% had baseline ECOG performance status of 0, and 8% had baseline ECOG performance status of 1.

The most common adverse reactions (≥ 20%) in patients who received MEQSEL in combination with dabrafenib were: pyrexia, fatigue, nausea, headache, rash, chills, diarrhea, vomiting, arthralgia, and myalgia.

Adverse reactions resulting in discontinuation and dose interruptions of MEQSEL occurred in 24% and 54% of patients, respectively; the most frequent for each were pyrexia and chills. Adverse reactions leading to dose reductions of MEQSEL occurred in 23% of patients; the most frequent were pyrexia and decreased ejection fraction.

Table 8 summarizes the adverse reactions that occurred in at least 20% of the patients who received MEQSEL in combination with dabrafenib.

Table 8. Adverse Reactions Occurring in ≥ 20% of Patients in the COMBI-AD Study[a]

Adverse Reactions	MEQSEL plus Dabrafenib N = 435		Placebo N = 432	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
General				
Pyrexia[b]	63	5	11	< 1
Fatigue[c]	59	5	37	< 1
Chills	37	1	4	0
Gastrointestinal				
Nausea	40	< 1	20	0
Diarrhea	33	< 1	15	< 1
Vomiting	28	< 1	10	0
Nervous system				
Headache[d]	39	1	24	0
Skin and subcutaneous tissue				
Rash[e]	37	< 1	16	< 1
Musculoskeletal and connective tissue				
Arthralgia	28	< 1	14	0
Myalgia[f]	20	< 1	14	0

[a] NCI CTCAE version 4.0.
[b] Includes pyrexia and hyperpyrexia.
[c] Includes fatigue, asthenia, and malaise.
[d] Includes headache and tension headache.
[e] Includes rash, rash maculo-papular, rash macular, rash generalized, rash erythematous, rash papular, rash pruritic, nodular rash, rash vesicular, and rash pustular.
[f] Includes myalgia, musculoskeletal pain, and musculoskeletal chest pain.

Other clinically important adverse reactions for MEQSEL in the COMBI-AD study observed in less than 20% of patients who received MEQSEL in combination with dabrafenib were: blurred vision (6%), decreased ejection fraction (5%), peripheral neuropathy (2.5%), rhabdomyolysis (< 1%), atrioventricular block (< 1%), Guillain-Barré syndrome (< 1%), and sarcoidosis (< 1%).

The laboratory abnormalities are summarized in Table 9.

Table 9. Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients in the COMBI-AD Study

Laboratory Abnormality	MEQSEL plus Dabrafenib[a] N = 435		Placebo[a] N = 432	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Chemistry				
Hyperglycemia	63	3	47	2
Hypophosphatemia	42	7	10	< 1
Hypoalbuminemia	25	< 1	< 1	0
Hepatic				
Increased AST	57	6	11	< 1
Increased ALT	48	5	18	< 1
Increased blood alkaline phosphatase	38	1	6	< 1
Hematology				
Neutropenia	47	6	12	< 1
Lymphopenia	26	5	6	< 1
Anemia	25	< 1	6	< 1

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] The incidence is based on the number of patients who had both a baseline and at least one on-study laboratory measurement: MEQSEL plus dabrafenib (range: 429 to 431) and placebo arm (range: 426 to 428).

Trial COMBI-APlus (Pyrexia Management Study)

COMBI-APlus evaluated the impact of pyrexia-related outcomes of a revised pyrexia management algorithm in patients who received dabrafenib administered with trametinib in the adjuvant treatment of BRAF V600 mutation-positive melanoma after complete resection. The pyrexia management algorithm interrupted both dabrafenib and trametinib when patient's temperature is ≥ 100.4°F.

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

Metastatic, BRAF V600E Mutation-Positive Non-Small Cell Lung Cancer

The safety of MEQSEL when administered with dabrafenib was evaluated in 93 patients with previously untreated (n = 36) and previously treated (n = 57) metastatic BRAF V600E mutation-positive NSCLC in a multi-center, multi-cohort, non-randomized, open-label trial (Study BRF113928). Patients received MEQSEL 2 mg orally once daily and dabrafenib 150 mg orally twice daily until disease progression or unacceptable toxicity. The trial excluded patients with abnormal LVEF, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure, QTc interval ≥ 480 msec, treatment refractory hypertension, uncontrolled arrhythmias, active brain metastases, history of ILD or pneumonitis, or history or current RVO *[see Clinical Studies (13.3)]*.

Among these 93 patients, 53 (57%) were exposed to MEQSEL and dabrafenib for > 6 months and 27 (29%) were exposed to MEQSEL and dabrafenib for ≥ 1 year. The median age was 65 years (range: 41 to 91), 46% were male, 85% were White; 32% had baseline ECOG performance status of 0 and 61% had ECOG performance status of 1; 98% had non-squamous histology; and 12% were current smokers, 60% were former smokers, and 28% had never smoked.

The most common adverse reactions (≥ 20%) in these 93 patients were: pyrexia, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough, and dyspnea.

Adverse reactions leading to discontinuation of MEQSEL occurred in 19% of patients; the most frequent were pyrexia (2.2%), decreased ejection fraction (2.2%), and respiratory distress (2.2%). Adverse reactions leading to dose reductions of MEQSEL occurred in 30% of patients; the most frequent were pyrexia (5%), nausea (4.3%), vomiting (4.3%), diarrhea (3.2%), and neutropenia (3.2%). Adverse reactions leading to dose interruptions of MEQSEL occurred in 57% of patients; the most frequent were pyrexia (16%), vomiting (10%), neutropenia (8%), nausea (5%), and decreased ejection fraction (5%).

Table 10 and Table 11 present adverse reactions and laboratory abnormalities, respectively, of MEQSEL in combination with dabrafenib in Study BRF113928.

Table 10. Adverse Reactions Occurring in ≥ 20% (All Grades) of Patients Treated with MEQSEL plus Dabrafenib in Study BRF113928[a]

Adverse Reactions	MEQSEL plus Dabrafenib N = 93	
	All Grades (%)	Grades 3 and 4 (%)
General		
Pyrexia	55	5
Fatigue[b]	51	5
Edema[c]	28	0
Chills	23	1.1
Gastrointestinal		
Nausea	45	0
Vomiting	33	3.2
Diarrhea	32	2.2
Decreased appetite	29	0
Skin and subcutaneous tissue		
Dry skin	31	1.1
Rash[d]	28	3.2
Vascular		
Hemorrhage[e]	23	3.2
Respiratory system		
Cough	22	0
Dyspnea	20	5

[a]NCI CTCAE version 4.0.
[b]Includes fatigue, malaise, and asthenia.
[c]Includes peripheral edema, edema, and generalized edema.
[d]Includes rash, rash generalized, rash papular, rash macular, rash maculo-papular, and rash pustular.
[e]Includes hemoptysis, hematoma, epistaxis, purpura, hematuria, subarachnoid hemorrhage, gastric hemorrhage, urinary bladder hemorrhage, contusion, hematochezia, injection site hemorrhage, pulmonary hemorrhage, and retroperitoneal hemorrhage.

Other clinically important adverse reactions for MEQSEL in Study BRF113928 observed in less than 20% of patients who received MEQSEL administered with dabrafenib were:

Cardiac: Atrioventricular block

Nervous System: Peripheral neuropathy

Table 11. Treatment-Emergent Laboratory Abnormalities Occurring in ≥ 20% (All Grades) of Patients Who Received MEQSEL plus Dabrafenib in Study BRF113928

Laboratory Abnormality	MEQSEL plus Dabrafenib N = 93	
	All Grades (%)	Grades 3 and 4 (%)
Chemistry[a]		
Hyperglycemia	71	9
Hyponatremia	57	17
Hypophosphatemia	36	7
Increased creatinine	21	1.1
Hepatic[a]		
Increased blood alkaline phosphatase	64	0
Increased AST	61	4.4
Increased ALT	32	6
Hematology[b]		
Leukopenia	48	8
Anemia	46	10
Neutropenia	44	8
Lymphopenia	42	14

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]For these laboratory tests, the denominator is 90.
[b]For these laboratory tests, the denominator is 91.

Advanced BRAF V600E Mutation-Positive Tumors

Study BRF117019

The safety of MEQSEL when administered with dabrafenib was evaluated in a multi-cohort, multi-center, non-randomized, open-label study in adult patients with cancers with the BRAF V600E mutation (Study BRF117019). A total of 206 patients were enrolled in the trial, 36 of whom were enrolled in the ATC cohort, 105 were enrolled in specific solid tumor cohorts, and 65 in other malignancies *[see Clinical Studies (13.5)]*. Patients received MEQSEL 2 mg orally once daily and dabrafenib 150 mg orally twice daily until disease progression or unacceptable toxicity.

Among these 206 patients, 101 (49%) were exposed to MEQSEL for ≥ 1 year and 103 (50%) were exposed to dabrafenib for ≥ 1 year. The median age was 60 years (range: 18 to 89); 56% were male; 79% were White; and 34% had baseline ECOG performance status of 0 and 60% had ECOG performance status of 1.

Serious adverse reactions occurred in 45% of patients who received MEQSEL in combination with dabrafenib. Serious adverse reactions in > 5% of patients included pyrexia (11%) and pneumonia (6%). Fatal adverse reactions occurred in 3.9% of patients who received MEQSEL in combination with dabrafenib. Fatal adverse reactions that occurred in > 1% of patients included sepsis (1.9%).

Permanent treatment discontinuation due to an adverse reaction occurred in 13% of patients. Adverse reactions which resulted in permanent treatment discontinuation in > 1% of patients included nausea (1.5%).

Dosage interruptions due to an adverse reaction occurred in 55% of patients. Adverse reactions which required dosage interruption in > 5% of patients included pyrexia (22%), chills (9%), fatigue (6%), neutropenia (6%), and nausea (5%).

Dose reductions due to an adverse reaction occurred in 44% of patients. Adverse reactions which required dose reductions in > 5% of patients included pyrexia (18%), chills (8%), and fatigue (6%).

The most common (≥ 20%) adverse reactions, including laboratory abnormalities, are listed in Table 12 and Table 13.

Table 12 summarizes the adverse reactions in Study BRF117019.

Table 12. Adverse Reactions (≥ 20%) in Adult Patients Treated with MEQSEL Plus Dabrafenib in Study BRF117019

Adverse Reactions	MEQSEL plus Dabrafenib[a] (N = 206)	
	All Grades (%)	Grade 3 or 4 (%)
General		
Pyrexia	55	4.95
Fatigue[b]	50	5
Chills	30	0.5
Peripheral edema[c]	22	0
Gastrointestinal		
Nausea	40	1.5
Constipation	27	0
Vomiting	27	1.5
Diarrhea	26	2.93
Skin and subcutaneous tissue		
Rash[d]	40	2.4
Nervous system		
Headache	30	1.5
Vascular		
Hemorrhage[e]	29	4.4
Respiratory system		
Cough[f]	29	0
Musculoskeletal and connective tissue		
Myalgia[g]	24	0.5
Arthralgia	23	0.5

[a] NCI CTCAE version 4.0.
[b] Includes fatigue, asthenia, and malaise.
[c] Includes peripheral edema and peripheral swelling.
[d] Includes rash, rash maculo-papular, rash erythematous, rash pustular, and rash papular.
[e] Includes epistaxis, hematuria, contusion, hematoma, hemoptysis, conjunctival hemorrhage, hematochezia, rectal hemorrhage, hemorrhoidal hemorrhage, melaena, purpura, eye contusion, eye hemorrhage, gastric hemorrhage, gingival bleeding, hematemesis, hemorrhage intracranial, hemorrhagic stroke, hemothorax, increased tendency to bruise, large intestinal hemorrhage, mouth hemorrhage, petechiae, pharyngeal hemorrhage, prothrombin time prolonged, pulmonary hematoma, retinal hemorrhage, vaginal hemorrhage, and vitreous hemorrhage.
[f] Includes cough and productive cough.
[g] Includes myalgia, musculoskeletal chest pain, and musculoskeletal pain.

Clinically relevant adverse reactions for MEQSEL in Study BRF117019 observed in less than 20% of patients who received MEQSEL in combination with dabrafenib were: peripheral neuropathy (9%), decreased ejection fraction (8%), atrioventricular block (2.9%), uveitis (1.9%), hypersensitivity (1.9%) and Guillain-Barré syndrome (< 1%).

Table 13 summarizes the laboratory abnormalities in Study BRF117019.

Table 13. Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Adult Patients Treated with MEQSEL Plus Dabrafenib in Study BRF117019

Laboratory Abnormality	MEQSEL plus Dabrafenib[a]	
	All Grades (%)	Grade 3 or 4 (%)
Chemistry		
Hyperglycemia	61	8
Decreased sodium	35	10
Decreased magnesium	24	0
Increased creatinine	21	1.5
Hepatic		
Increased alkaline phosphatase	51	5
Increased AST	51	4.6
Increased ALT	39	3
Hematology		
Decreased hemoglobin	44	9

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] The denominator used to calculate the rate varied from 199 to 202 based on the number of patients with a baseline value and at least one post-treatment value.

BRAF V600E Mutation-Positive Solid Tumors in Pediatric Patients

Study CTMT212X2101 (X2101)

The safety of MEQSEL when administered with dabrafenib was evaluated in Study X2101, a multi-center, open-label, multi-cohort study in pediatric patients (n = 48) with refractory or recurrent solid tumors activation *[see Clinical Studies (13.5)].* The median duration of exposure to MEQSEL in Parts C (dose escalation) and D (cohort expansion) was 20.8 and 24.4 months, respectively. The median duration of exposure to dabrafenib in Parts C and D was 20.8 and 24.9 months, respectively. The median age of pediatric patients who received MEQSEL with dabrafenib was 9 years (range: 1 to 17).

Serious adverse reactions occurred in 46% of patients who received MEQSEL in combination with dabrafenib. Serious adverse reactions in > 5% of patients included pyrexia (25%) and decreased ejection fraction (6%). Permanent treatment discontinuation due to an adverse reaction occurred in 21% of patients. Adverse reactions which resulted in permanent treatment discontinuation in > 3% of patients included increased ALT (6%), increased AST (4.2%) and decreased ejection fraction (4.2%). Dosage interruptions due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage interruption in > 5% of patients included pyrexia (56%), vomiting (19%), neutropenia (13%), rash (13%), decreased ejection fraction (6%), and uveitis (6%). Dose reductions due to an adverse reaction occurred in 25% of patients. Adverse reactions which required dose reductions in > 5% of patients included pyrexia (13%).

The most common (≥ 20%) adverse reactions, including laboratory abnormalities, are listed in Table 14 and Table 15.

Table 14 summarizes the adverse reactions in Study X2101.

Table 14. Adverse Reactions (≥ 20%) in Pediatric Patients Treated with MEQSEL Plus Dabrafenib in Study X2101

Adverse Reactions	MEQSEL plus Dabrafenib[a] (N = 48)	
	All Grades (%)	Grade 3 or 4 (%)
General		
Pyrexia	75	17

Fatigue[b]	48	0
Skin and subcutaneous tissue		
Rash[c]	73	2.1
Dry skin	48	0
Dermatitis acneiform[d]	40	0
Gastrointestinal		
Vomiting	52	4.2
Diarrhea	42	2.1
Abdominal pain[e]	33	4.2
Nausea	33	2.1
Constipation	23	0
Respiratory system		
Cough	44	0
Nervous system		
Headache	35	0
Vascular		
Hemorrhage[f]	33	0
Infections and infestations		
Paronychia	23	0

[a] NCI CTCAE version 4.0.
[b] Includes fatigue, asthenia, and malaise.
[c] Includes rash, rash maculo-papular, rash erythematous, rash papular, rash pustular, and rash macular.
[d] Includes dermatitis acneiform and acne.
[e] Includes abdominal pain and abdominal pain upper.
[f] Includes epistaxis, hematuria, contusion, hematoma, petechiae, rectal hemorrhage, and red blood cell count decreased.

Clinically relevant adverse reactions for MEQSEL in Study X2101 observed in less than 20% of patients (N=48) who received MEQSEL in combination with dabrafenib were: atrioventricular block (2.1%).

Table 15 summarizes the laboratory abnormalities in Study X2101.

Table 15. Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Pediatric Patients Treated with MEQSEL Plus Dabrafenib in Study X2101

Laboratory Abnormality	**MEQSEL plus Dabrafenib[a]**	
	All Grades (%)	**Grade 3 or 4 (%)**
Chemistry		
Hyperglycemia	65	2.2
Hypoalbuminemia	48	2.1
Hypocalcemia	40	2.1
Decreased phosphate	38	0
Decreased magnesium	33	2.1
Hypernatremia	27	0
Hypokalemia	21	2.1
Hepatic		
Increased AST	55	4.2
Increased ALT	40	6
Increased alkaline phosphatase	28	6
Increased total bilirubin	21	2.1
Hematology		
Decreased hemoglobin	60	6
Decreased neutrophils	49	28

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] The denominator used to calculate the rate varied from 39 to 48 based on the number of patients with a baseline value and at least one post-treatment value.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of MEQSEL in combination with dabrafenib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac: Atrioventricular block complete. This adverse reaction was also observed with MEQSEL monotherapy.

Immune System: Hemophagocytic lymphohistiocytosis (HLH) *[see Warnings and Precautions (5.12)]*

Skin and Subcutaneous Tissue: SCAR (including DRESS and SJS) *[see Warnings and Precautions (5.9)]*

7 DRUG INTERACTIONS

MEQSEL is indicated for use in combination with dabrafenib. Refer to the dabrafenib prescribing information for additional risk information that applies to combination use treatment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (11.1)]* and findings from animal reproduction studies, MEQSEL can cause fetal harm when administered to a pregnant woman. There is insufficient data in pregnant women exposed to MEQSEL to assess the risks. Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 0.3 times the human exposure at the recommended adult clinical dose *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In reproductive toxicity studies, administration of trametinib to rats during the period of organogenesis resulted in decreased fetal weights at doses greater than or equal to 0.031 mg/kg/day [approximately 0.3 times the human exposure at the recommended adult dose based on area under the curve (AUC)]. In rats, at a dose resulting in exposures 1.8-fold higher than the human exposure at the recommended adult dose, there was maternal toxicity and an increase in post-implantation loss.

In pregnant rabbits, administration of trametinib during the period of organogenesis resulted in decreased fetal body weight and increased incidence of variations in ossification at doses greater than or equal to 0.039 mg/kg/day (approximately 0.08 times the human exposure at the recommended adult dose based on AUC). In rabbits administered trametinib at 0.15 mg/kg/day (approximately 0.3 times the human exposure at the recommended adult dose based on AUC) there was an increase in post-implantation loss, including total loss of pregnancy, compared with control animals.

8.2 Lactation

Risk Summary

There are no data on the presence of trametinib in human milk, or the effects of trametinib on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with MEQSEL and for 4 months following the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating MEQSEL.

Contraception

Based on data from animal studies and its mechanism of action, MEQSEL can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Females

Advise female patients of reproductive potential to use effective contraception during treatment with MEQSEL and for 4 months after the last dose.

Males

To avoid potential drug exposure to pregnant partners and female partners of reproductive potential, advise male patients (including those who have had vasectomies) with female partners of reproductive potential to use condoms during treatment with MEQSEL and for 4 months after the last dose.

Infertility

Females

Advise female patients of reproductive potential that MEQSEL may impair fertility. Increased follicular cysts and decreased corpora lutea were observed in female rats at dose exposures equivalent to 0.3 times the human exposure at the recommended adult dose *[see Nonclinical Toxicology (12.1)]*.

8.4 Pediatric Use

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors

The safety and effectiveness of MEQSEL in combination with dabrafenib have been established in pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. Use of MEQSEL in combination with dabrafenib for these indications is supported by evidence from studies X2101 that enrolled 171 patients (1 to < 18 years of age) with BRAF V600 mutation-positive advanced solid tumors, of which 4 (2.3%) patients were 1 to < 2 years of age, 39 (23%) patients were 2 to < 6 years of age, 54 (32%) patients were 6 to < 12 years of age, and 74 (43%) patients were 12 to < 18 years of age *[see Adverse Reactions (6.1), Clinical Pharmacology (11.3), Clinical Studies (13.5)]*.

The safety and effectiveness of MEQSEL in combination with dabrafenib have not been established for these indications in pediatric patients < 6 years old.

The safety and effectiveness of MEQSEL as a single agent in pediatric patients have not been established.

Juvenile Animal Toxicity Data

In a repeat-dose toxicity study in juvenile rats, decreased bone length and corneal dystrophy were observed at doses resulting in exposures as low as 0.3 times the human exposure at the recommended adult dose based on AUC. Additionally, a delay in sexual maturation was noted at doses resulting in exposures as low as 1.6 times the human exposure at the recommended adult dose based on AUC.

8.5 Geriatric Use

Of the 214 patients with melanoma who received single agent MEQSEL in the METRIC study, 27% were aged 65 years and older and 4% were over 75 years old *[see Clinical Studies (13.1)]*. This study of single agent MEQSEL in melanoma did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger adults.

Of the 994 patients with melanoma who received MEQSEL plus dabrafenib in the COMBI-d, COMBI-v, and COMBI-AD studies *[see Clinical Studies (13.1, 13.2)]*, 21% were aged 65 years and older and 5% were aged 75 years and older. No overall differences in the effectiveness of MEQSEL plus dabrafenib were observed in geriatric patients as compared to younger adults across these melanoma studies. The incidences of peripheral edema (26% vs. 12%) and anorexia (21% vs. 9%) increased in geriatric patients as compared to younger adults in these studies.

Of the 93 patients with NSCLC who received MEQSEL in Study BRF113928, there were insufficient numbers of geriatric patients aged 65 years and older to determine whether they respond differently from younger adults *[see Clinical Studies (13.3)]*.

8.6 Hepatic Impairment

No dose adjustment is recommended in patients with mild (bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or bilirubin > 1x to 1.5x ULN and any AST) hepatic impairment.

A recommended dosage of MEQSEL has not been established for patients with moderate (bilirubin > 1.5x to 3x ULN and any AST) or severe (bilirubin > 3x to 10x ULN and any AST) hepatic impairment. Consider the risk-benefit profile of MEQSEL related to dosing prior to determining whether to administer MEQSEL to patients with moderate or severe hepatic impairment.

In patients with moderate hepatic impairment, 3 patients who received a starting dose of 1.5 mg orally once daily and two patients who received a starting dose of 2 mg orally once daily did not experience dose limiting toxicities (DLTs) during the first cycle of therapy.

In patients with severe hepatic impairment, 3 patients who received a starting dose of 1 mg orally once daily did not experience DLTs during the first cycle; one patient who received a starting dose of 1.5 mg orally once daily experienced a DLT (grade 3 acneiform rash).

Compared to patients with normal hepatic function, there was no increase in exposure of trametinib in patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (11.3)]*.

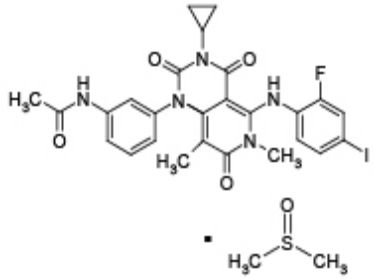
9 OVERDOSAGE

The highest doses of MEQSEL evaluated in clinical trials were 4 mg orally once daily and 10 mg administered orally once daily on 2 consecutive days followed by 3 mg once daily. In seven patients treated on one of these two schedules, there were two cases of RPEDs for an incidence of 28%.

Since trametinib is highly bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with MEQSEL.

10 DESCRIPTION

Trametinib dimethyl sulfoxide is a kinase inhibitor. The chemical name is acetamide, N-[3-[3-cyclopropyl-5-[(2-fluoro-4- iodophenyl)amino]-3,4,6,7-tetrahydro-6,8-dimethyl- 2,4,7-trioxopyrido[4,3-d]pyrimidin-1(2H)-yl]phenyl]-, compound with 1,1'-sulfinylbis[methane] (1:1). It has a molecular formula $C_{26}H_{23}FIN_5O_4 \bullet C_2H_6OS$ with a molecular mass of 693.53 g/mol. Trametinib dimethyl sulfoxide has the following chemical structure:



Trametinib dimethyl sulfoxide is a white to almost white powder. It is practically insoluble in the pH range of 2 to 8 in aqueous media.

MEQSEL (trametinib) tablets for oral use are supplied as 0.5 mg and 2 mg tablets for oral administration. Each 0.5 mg tablet contains 0.5635 mg trametinib dimethyl sulfoxide equivalent to 0.5 mg of trametinib non-solvated parent. Each 2 mg tablet contains 2.254 mg trametinib dimethyl sulfoxide equivalent to 2 mg of trametinib non-solvated parent.

The inactive ingredients of MEQSEL tablets are: *Tablet Core:* colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate (vegetable source), mannitol, microcrystalline cellulose, and sodium lauryl sulfate. *Coating:* hypromellose, iron oxide red (2 mg tablets), iron oxide yellow (0.5 mg tablets), polyethylene glycol, polysorbate 80 (2 mg tablets), and titanium dioxide.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Trametinib is a reversible inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. BRAF V600E mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2. Trametinib inhibits cell growth of various BRAF V600 mutation-positive tumors in vitro and in vivo.

Trametinib and dabrafenib target two different kinases in the RAS/RAF/MEK/ERK pathway. Use of trametinib and dabrafenib in combination resulted in greater growth inhibition of BRAF V600 mutation-positive tumor cell lines in vitro and prolonged inhibition of tumor growth in BRAF V600 mutation-positive tumor xenografts compared with either drug alone.

In the setting of BRAF-mutant colorectal cancer, induction of EGFR-mediated MAPK pathway re-activation has been identified as a mechanism of intrinsic resistance to BRAF inhibitors *[see Indications and Usage (1.5)].*

11.2 Pharmacodynamics

Administration of MEQSEL tablets 1 mg and 2 mg to patients with BRAF V600 mutation-positive melanoma 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).

Cardiac Electrophysiology

The heart rate-corrected QT (QTc) prolongation potential of trametinib was assessed in a dedicated study in 32 patients who received placebo on Day 1 and MEQSEL tablets 2 mg once daily on Days 2-14 followed by MEQSEL tablets 3 mg on Day 15. No large changes in the mean QTc interval (i.e., > 20 ms) were detected in the study.

A decrease from baseline in HR by 9 beats/min (90% CI: -11.4 to -6.1) and an increase from baseline in PR by 20 ms (90% CI: 13.0 to 27.4) relative to placebo was observed at two hours post-dose in the same study.

In clinical trials in patients who received MEQSEL with dabrafenib, QTc prolongation > 500 ms occurred in 0.8% of patients and QTc increased by > 60 ms from baseline in 3.8% of patients.

11.3 Pharmacokinetics

The pharmacokinetics of trametinib were characterized following a single dose and multiple doses in patients with solid tumors and BRAF V600 mutation-positive metastatic melanoma. Following administration of MEQSEL tablets 0.125 mg (0.0625 times the approved recommended adult dosage) to 4 mg (2 times the approved recommended adult dosage) daily, both C_{max} and AUC increase proportionally with dose. Intersubject variability in AUC and C_{max} at steady state is 22% and 28%, respectively.

Absorption

The median time to achieve peak plasma concentrations (T_{max}) is 1.5 hours post-dose. The mean absolute bioavailability of MEQSEL tablets is 72%.

Effect of Food

Following administration of MEQSEL tablets, a high-fat, high-calorie meal (approximately 1000 calories) decreased trametinib AUC by 24%, C_{max} by 70%, and delayed T_{max} by approximately 4 hours as compared with fasted conditions.

Distribution

Trametinib is 97.4% bound to human plasma proteins. The apparent volume of distribution (V_c/F) is 214 L.

Elimination

The estimated elimination half-life is 3.9 to 4.8 days. The apparent clearance is 4.9 L/h.

Metabolism

Trametinib is metabolized predominantly via deacetylation alone or with mono-oxygenation or in combination with glucuronidation biotransformation pathways in vitro. Deacetylation is mediated by carboxylesterases (i.e., carboxylesterase 1b/c and 2) and may also be mediated by other hydrolytic enzymes.

Following a single dose of [^{14}C]-trametinib, approximately 50% of circulating radioactivity is represented as the parent compound; however, ≥ 75% of drug-related material in plasma is the parent compound based on metabolite profiling after repeat dosing of trametinib.

Excretion

Following oral administration of [^{14}C]-trametinib, greater than 80% of excreted radioactivity was recovered in the feces while less than 20% of excreted radioactivity was recovered in the urine with less than 0.1% of the excreted dose as parent.

Specific Populations

Age (18 to 93 years), sex, body weight (36 to 170 kg), and renal impairment (eGFR 15 to 89 mL/min/1.73 m^2) have no clinically significant effect on the exposure of trametinib. There are insufficient data to evaluate potential differences in the exposure of trametinib by race or ethnicity.

Pediatric Patients: The pharmacokinetics of trametinib in glioma and other solid tumors were evaluated in 244 patients aged 1 to < 18 years following a single dose or multiple doses. Pharmacokinetic parameters in patients aged 1 to < 18 years are within range of values previously observed in adults given the same dose based on weight. Weight (6 to 156 kg) was found to have a statistically significant effect on trametinib oral clearance in this population.

Patients with Hepatic Impairment: Hepatic impairment (defined by bilirubin and AST levels) had no significant effect in trametinib exposure or apparent drug clearance compared with patients with normal hepatic function.

Drug Interaction Studies

Effect of Dabrafenib on Trametinib: Coadministration of MEQSEL tablets 2 mg daily with dabrafenib resulted in no change in AUC of trametinib.

Effect of Trametinib on CYP Substrates: Coadministration of MEQSEL tablets 2 mg once daily with a sensitive CYP3A4 substrate had no clinically relevant effect on the AUC and C_{max} of the sensitive CYP3A4 substrate.

Based on in vitro studies, trametinib is an inhibitor of CYP2C8, but is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at a clinically relevant systemic concentration.

Effect of Transporters on Trametinib: Trametinib is a substrate of P-glycoprotein (P-gp) and BSEP. Inhibition of P-gp is unlikely to result in a clinically important increase in trametinib concentrations as trametinib exhibits high passive permeability and bioavailability.

Trametinib is not a substrate of BCRP, OATP1B1, OATP1B3, OATP2B1, OCT1, MRP2, or MATE1 in vitro.

Effect of Trametinib on Transporters: Based on in vitro studies, trametinib is not an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, BSEP, MRP2, or MATE1 at a clinically relevant systemic concentration.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

Trametinib may impair fertility in humans. In female rats given trametinib for up to 13 weeks, increased follicular cysts and decreased corpora lutea were observed at doses ≥ 0.016 mg/kg/day (approximately 0.3 times the human exposure at the recommended adult dose based on AUC). In rat and dog toxicity studies up to 13 weeks in duration, there were no treatment effects observed on male reproductive tissues *[see Use in Specific Populations (8.3)]*.

13 CLINICAL STUDIES

13.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

MEQSEL as a Single Agent

The safety and efficacy of MEQSEL were evaluated in an international, multi-center, randomized (2:1), open-label, active-controlled trial (the METRIC study; NCT01245062) in 322 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma. In the METRIC study, patients were not permitted to have more than one prior chemotherapy regimen for advanced or metastatic disease; prior treatment with a BRAF inhibitor or MEK inhibitor was not permitted. Patients were randomized to receive MEQSEL 2 mg orally once

daily (N = 214) or chemotherapy (N = 108) consisting of either dacarbazine 1000 mg/m^2 intravenously every 3 weeks or paclitaxel 175 mg/m^2 intravenously every 3 weeks. Treatment continued until disease progression or unacceptable toxicity. Randomization was stratified according to prior use of chemotherapy for advanced or metastatic disease (yes vs. no) and LDH level (normal vs. greater than ULN). Tumor tissue was evaluated for BRAF mutations at a central testing site using a clinical trial assay. Tumor samples from 289 patients (196 patients treated with MEQSEL and 93 chemotherapy-treated patients) were also tested retrospectively. The major efficacy outcome measure was progression-free survival (PFS) as assessed by the investigator.

The median age for randomized patients was 54 years, 54% were male, greater than 99% were White, and all patients had baseline ECOG performance status of 0 or 1. Most patients had metastatic disease (94%), had M1c disease (64%), had elevated LDH (36%), had no history of brain metastasis (97%), and received no prior chemotherapy for advanced or metastatic disease (66%). The distribution of BRAF V600 mutations was BRAF V600E (87%), V600K (12%), or both (less than 1%). The median durations of follow-up prior to initiation of alternative treatment were 4.9 months for patients treated with MEQSEL and 3.1 months for patients treated with chemotherapy. Fifty-one (47%) patients crossed over from the chemotherapy arm at the time of disease progression to receive MEQSEL.

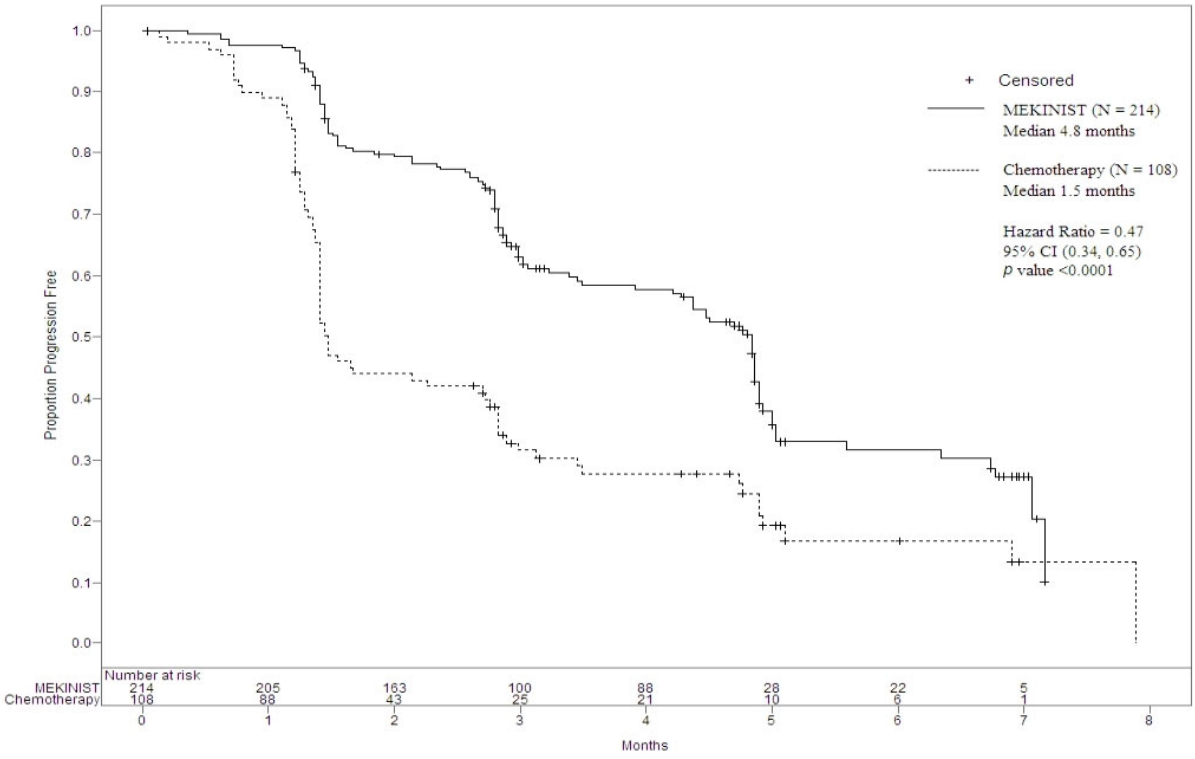
The METRIC study demonstrated a statistically significant increase in PFS in the patients treated with MEQSEL. Table 16 and Figure 1 summarize the PFS results.

Table 16. Efficacy Results in the METRIC Study

Investigator-Assessed Endpoints	**MEQSEL N = 214**	**Chemotherapy N = 108**
Progression-Free Survival		
Number of events (%)	117 (55%)	77 (71%)
Progressive disease	107 (50%)	70 (65%)
Death	10 (5%)	7 (6%)
Median, months (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
HR[a] (95% CI)	0.47 (0.34, 0.65)	
P-value (log-rank test)	< 0.0001	
Confirmed Tumor Responses		
Overall response rate (95% CI)	22% (17%, 28%)	8% (4%, 15%)
Complete response, n (%)	4 (2%)	0
Partial response, n (%)	43 (20%)	9 (8%)
Duration of Response		
Median DoR, months (95% CI)	5.5 (4.1, 5.9)	NR (3.5, NR)

Abbreviations: CI, confidence interval; DoR, duration of response; HR, hazard ratio; NR, not reached.
[a]Pike estimator.

Figure 1. Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival (ITT Population) in the METRIC Study



In supportive analyses based on independent radiologic review committee (IRRC) assessment, the PFS results were consistent with those of the primary efficacy analysis.

MEQSEL with Dabrafenib

COMBI-d Study

The safety and efficacy of MEQSEL administered with dabrafenib were evaluated in an international, randomized, double-blind, active-controlled trial (the COMBI-d study; NCT01584648). The COMBI-d study compared dabrafenib plus MEQSEL to dabrafenib plus placebo as first-line treatment for patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive MEQSEL 2 mg once daily plus dabrafenib 150 mg twice daily or dabrafenib 150 mg twice daily plus matching placebo. Randomization was stratified by LDH level (> ULN vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome measure was investigator-assessed progression-free survival (PFS) per RECIST v1.1 with additional efficacy outcome measures of overall survival (OS) and confirmed overall response rate (ORR).

In the COMBI-d study, 423 patients were randomized to MEQSEL plus dabrafenib (n = 211) or dabrafenib plus placebo (n = 212). The median age was 56 years (range: 22 to 89), 53% were male, > 99% were White, 72% had ECOG performance status of 0, 4% had Stage IIIc, 66% had M1c disease, 65% had normal LDH, and 2 patients had a history of brain metastases. All patients had tumor containing BRAF V600E or V600K mutations as determined by centralized testing; 85% had BRAF V600E mutation-positive melanoma and 15% had BRAF V600K mutation-positive melanoma.

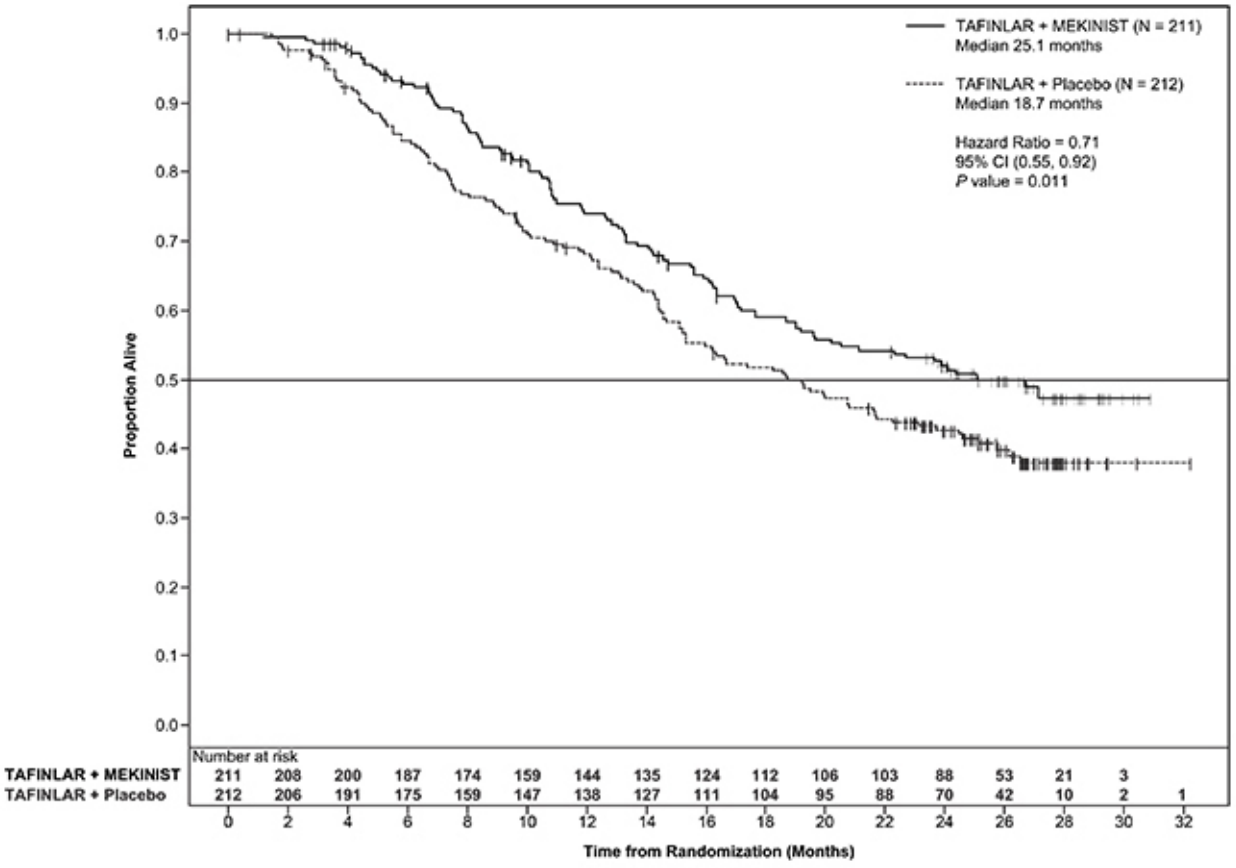
The COMBI-d study demonstrated statistically significant improvements in PFS and OS. Table 17 and Figure 2 summarize the efficacy results.

Table 17. Efficacy Results in the COMBI-d Study

Endpoint	MEQSEL plus Dabrafenib N = 211	Placebo plus Dabrafenib N = 212
Progression-Free Survival[a]		
Number of events (%)	102 (48%)	109 (51%)
Median, months (95% CI)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)
HR (95% CI)	0.75 (0.57, 0.99)	
P-value[b]	0.035	
Overall Survival		
Number of deaths (%)	99 (47%)	123 (58%)
Median, months (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.1)
HR (95% CI)	0.71 (0.55, 0.92)	
P-value[b]	0.01	
Overall Response Rate[a]		
ORR (95% CI)	66% (60%, 73%)	51% (44%, 58%)
P-value	< 0.001	
Complete response	10%	8%
Partial response	56%	42%
Median DoR, months (95% CI)	9.2 (7.4, NR)	10.2 (7.5, NR)

Abbreviations: CI, confidence interval; DoR, duration of response; HR, hazard ratio; NR, not reached; ORR, overall response rate.
[a] PFS and ORR were assessed by investigator.
[b] Based on stratified log-rank test.

Figure 2. Kaplan-Meier Curves of Overall Survival in the COMBI-d Study



COMBI-MB Study

The activity of MEQSEL with dabrafenib for the treatment of BRAF V600E or V600K mutation-positive melanoma, metastatic to the brain, was evaluated in a non-randomized, open-label, multi-center, multi-cohort trial (the COMBI-MB study; NCT02039947). Eligible patients were required to have at least one measurable intracranial lesion and to have no leptomeningeal disease, parenchymal brain metastasis greater than 4 cm in diameter, ocular melanoma, or primary mucosal melanoma. Patients received MEQSEL 2 mg orally once daily and dabrafenib 150 mg orally twice daily until disease progression or unacceptable toxicity. The major efficacy outcome measure was intracranial response rate, defined as the percentage of patients with a confirmed intracranial response per RECIST v1.1, modified to allow up to five intracranial target lesions at least 5 mm in diameter, as assessed by independent review.

The COMBI-MB study enrolled 121 patients with a BRAF V600E (85%) or V600K (15%) mutation. The median age was 54 years (range: 23 to 84), 58% were male, 100% were White, 8% were from the United States, 65% had normal LDH at baseline, and 97% had an ECOG performance status of 0 or 1. Intracranial metastases were asymptomatic in 87% and symptomatic in 13% of patients, 22% received prior local therapy for brain metastases, and 87% also had extracranial metastases.

The intracranial response rate was 50% (95% CI: 40, 60), with a complete response rate of 4.1% and a partial response rate of 46%. The median duration of intracranial response was 6.4 months (range: 1 to 31). Of the patients with an intracranial response, 9% had stable or progressive disease as their best overall response.

13.2 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma

The efficacy of MEQSEL administered with dabrafenib was evaluated in an international, multi-center, randomized, double-blind, placebo-controlled trial (COMBI-AD; NCT01682083) that enrolled patients with Stage III melanoma with BRAF V600E or V600K mutations. Enrollment required complete resection of melanoma with complete lymphadenectomy within 12 weeks prior to randomization. The trial excluded patients with mucosal or ocular melanoma, unresectable in-transit metastases, distant metastatic disease, or prior systemic anti-cancer treatment, including radiotherapy. Patients were randomized (1:1) to receive MEQSEL 2 mg once daily in combination with dabrafenib 150 mg twice daily or two placebos for up to 1 year. Randomization was stratified by BRAF mutation status (V600E or V600K). The major efficacy outcome measure was relapse-free survival (RFS), defined as the time from randomization to disease recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause, whichever occurred first as assessed by the investigator. Patients underwent imaging for tumor recurrence every 3 months for the first two years and every 6 months thereafter.

In COMBI-AD, a total of 870 patients were randomized: 438 to the MEQSEL in combination with dabrafenib and 432 to placebo. Median age was 51 years (range: 18 to 89), 55% were male, 99% were White, and 91% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIa (18%), Stage IIIb (41%), Stage IIIc (40%), stage unknown (1%); BRAF V600E mutation (91%), BRAF V600K mutation (9%); macroscopic lymph nodes (65%); and tumor ulceration (41%).

The median duration of follow-up at the time of the primary analysis was 2.8 years.

COMBI-AD showed a statistically significant improvement in RFS in patients randomized to MEQSEL in combination with dabrafenib compared to those randomized to placebo. Efficacy results are presented in Table 18 and Figure 3.

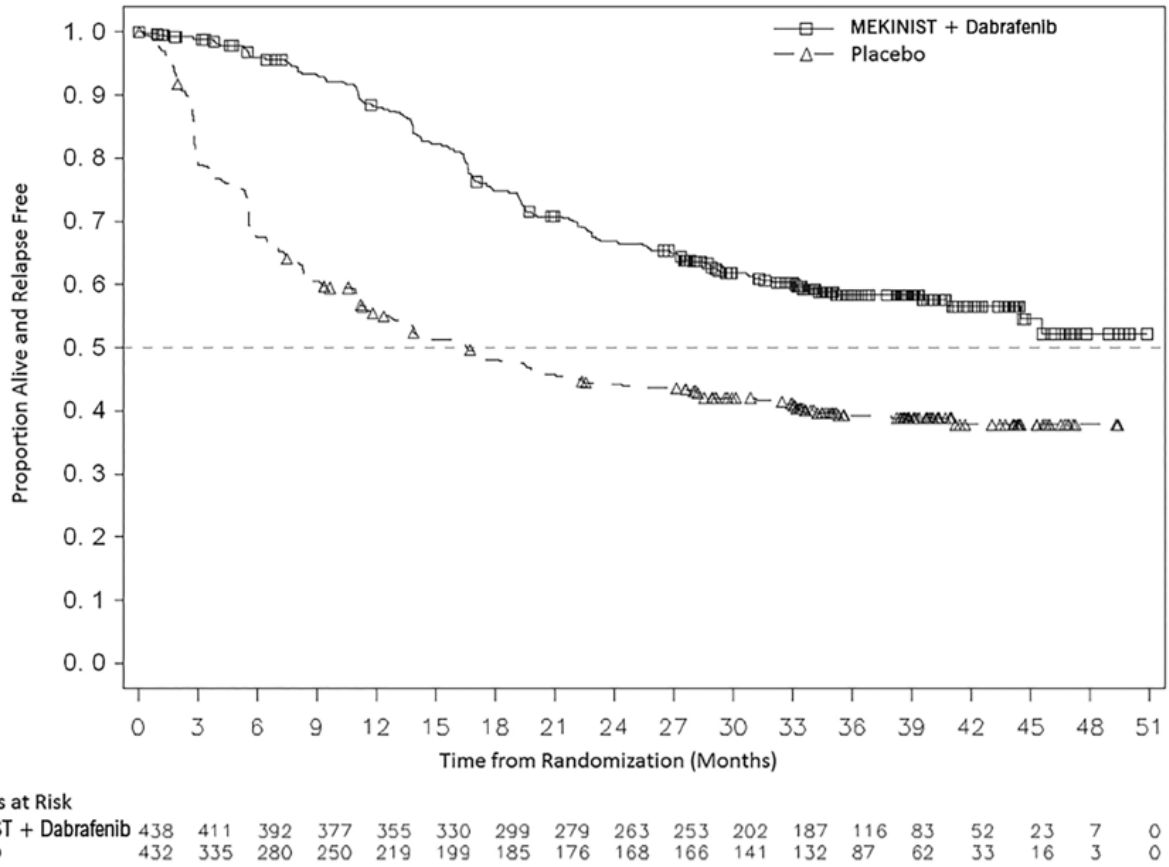
Table 18. Efficacy Results in COMBI-AD in the Adjuvant Treatment of Melanoma

Investigator-Assessed Endpoint	**MEQSEL plus Dabrafenib N = 438**	**Placebo N = 432**
Relapse-Free Survival		
Number of events (%)	166 (38)	248 (57)

Median, months (95% CI)	NE (44.5, NE)	16.6 (12.7, 22.1)
HR (95% CI)[a]	0.47 (0.39, 0.58)	
P-value[b]	< 0.0001	

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable.
[a] Pike estimator obtained from the stratified log-rank test.
[b] Log-rank test stratified by disease stage (IIIA vs. IIIB vs. IIIC) and BRAF V600 mutation type (V600E vs. V600K).

Figure 3. Kaplan-Meier Curves for Investigator-Assessed Relapse-Free Survival in COMBI-AD in the Adjuvant Treatment of Melanoma



The median duration of follow-up at the time of the final overall survival analysis was 8.0 years. 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. Median overall survival was not estimable in both arms.

13.3 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer

The safety and efficacy of dabrafenib alone or administered with MEQSEL were evaluated in a multi-center, three-cohort, non-randomized, activity-estimating, open-label trial (Study BRF113928; NCT01336634). Key eligibility criteria were locally confirmed BRAF V600E mutation-positive metastatic NSCLC, no prior exposure to BRAF or MEK inhibitor, and absence of EGFR mutation or ALK rearrangement (unless patients had progression on prior tyrosine kinase inhibitor therapy). Patients enrolled in Cohorts A and B were required to have received at least one previous platinum-based chemotherapy regimen for NSCLC with demonstrated disease progression but no more than three prior systemic regimens. Patients in Cohort C could not have received prior systemic therapy for metastatic NSCLC. Patients in Cohort A received dabrafenib 150 mg twice daily. Patients in Cohorts B and C received MEQSEL 2 mg once daily and dabrafenib 150 mg twice daily. The major efficacy outcome measure was overall response rate (ORR) per RECIST v1.1 as assessed by independent review committee (IRC) and duration of response (DoR).

There were a total of 171 patients enrolled which included 78 patients enrolled in Cohort A, 57 patients enrolled in Cohort B, and 36 patients enrolled in Cohort C. The characteristics of the study population were: a median age of 66 years; 48% male; 81% White, 14% Asian, 3% Black, and 2% Hispanic; 60% former smokers, 32% never smokers, and 8% current smokers; 27% had ECOG performance status (PS) of 0, 63% had ECOG PS of 1, and 11% had ECOG PS of 2; 99% had metastatic disease of which 6% had brain metastasis at baseline and 14% had liver metastasis at baseline; 11% had systemic anti-cancer therapy in the adjuvant setting and 58% of the 135 previously treated patients had only one line of prior systemic therapy for metastatic disease; 98% had non-squamous histology.

Efficacy results are summarized in Table 19.

Table 19. Efficacy Results Based on Independent Review in Study BRF113928

Treatment	**Dabrafenib**	**MEQSEL plus Dabrafenib**	
Population	**Previously Treated N = 78**	**Previously Treated N = 57**	**Treatment Naïve N = 36**
Overall Response Rate[a]			
ORR (95% CI)	27% (18%, 38%)	61% (48%, 74%)	61% (44%, 77%)
Complete response	1%	5%	8%
Partial response	26%	56%	53%
Duration of Response[a]	n = 21	n = 35	n = 22
Median DoR, months (95% CI)	18.0 (4.2, 40.1)	9.0 (5.8, 26.2)	15.2 (7.8, 23.5)

Abbreviations: CI, confidence interval; DoR, duration of response; ORR, overall response rate.
[a]Represents final analysis results (cutoff date of 24 Feb 2021) for the primary analysis responder cohorts.

In a subgroup analysis of patients with retrospectively centrally confirmed BRAF V600E mutation-positive NSCLC, the ORR results were similar to those presented in Table 19.

13.4 Lack of Clinical Activity in Metastatic Melanoma Following BRAF-Inhibitor Therapy

The clinical activity of MEQSEL as a single agent was evaluated in a single-arm, multi-center, international trial in 40 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma who had received prior treatment with a BRAF inhibitor. All patients received MEQSEL at a dose of 2 mg orally once daily until disease progression or unacceptable toxicity.

The median age was 58 years, 63% were male, all were White, 98% had baseline ECOG PS of 0 or 1, and the distribution of BRAF V600 mutations was V600E (83%), V600K (10%), and the remaining patients had multiple V600 mutations (5%), or unknown mutational status (2%). No patient achieved a confirmed partial or complete response as determined by the clinical investigators.

13.5 BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors

The safety and efficacy of MEQSEL in combination with dabrafenib for the treatment of BRAF V600E mutation-positive unresectable or metastatic solid tumors were evaluated in Trials BRF117019, NCI-MATCH, and CTMT212X2101, and supported by results in COMBI-d, COMBI-v *[see Clinical Studies (13.2)]*, and BRF113928 *[see Clinical Studies (13.4)]*. In adult studies, patients received MEQSEL 2 mg once daily and dabrafenib 150 mg twice daily. The major efficacy outcome measures were ORR per RECIST v1.1, RANO [HGG] or modified RANO [LGG] criteria and duration of response (DoR).

BRF117019 Study and NCI-MATCH Study

Study BRF117019 (NCT02034110) *[see Clinical Studies (13.5)]* is a multi-cohort, multi-center, non-randomized, open-label trial in adult patients with selected tumors with the BRAF V600E mutation, including high-grade glioma (HGG) (n = 45), biliary tract cancer (BTC) (n = 43), low-grade glioma (LGG) (n = 13), adenocarcinoma of small intestine (ASI) (n = 3), gastrointestinal stromal tumor (GIST) (n = 1). Patients were enrolled based on

local assessments of BRAF V600E mutation status; a central laboratory confirmed the BRAF V600E mutation in 93 of 105 patients.

Arm H (EAY131-H) of the NCI-MATCH study (NCT02465060) is a single-arm, open-label study that enrolled patients with a BRAF V600E mutation. Patients with melanoma, thyroid cancer, or CRC were excluded. BRAF V600E mutation status for enrollment was determined either by central or local laboratory test. The study included adult patients with solid tumors including gastrointestinal tumors (n = 14), lung tumors (n = 7), gynecologic or peritoneal tumors (n = 6), CNS tumors (n = 4), and ameloblastoma of mandible (n = 1).

Among the 131 patients enrolled in BRF117019 and NCI-MATCH with the tumor types shown in Table 20, the baseline characteristics were: median age of 51 years with 20% age 65 or older; 56% female; 85% White, 9% Asian, 3% Black, 3% other; and 37% ECOG PS of 0, 56% ECOG PS of 1, and 6% ECOG PS of 2. Of the 131 patients, 90% received prior systemic therapy.

Efficacy results in patients with solid tumors are summarized in Table 20.

Table 20. Efficacy Results Based on Independent Review in Study BRF117019 and NCI-MATCH Arm H

Tumor Type[a]	**N**	**Objective Response Rate**		**Duration of Response**
		%	**95% CI**	**Range (months)**
Biliary tract cancer[b]	48	46	(31, 61)	1.8[d], 40[d]
High-grade glioma[c]	48	33	(20, 48)	3.9, 44
Glioblastoma	32	25	(12, 43)	3.9, 27
Anaplastic pleomorphic xanthoastrocytoma	6	67	(22, 96)	6, 43
Anaplastic astrocytoma	5	20	(0.5, 72)	15
Astroblastoma	2	100	(16, 100)	15, 23[d]
Undifferentiated	1	PR	(2.5, 100)	6
Anaplastic ganglioglioma	1	0	NA	NA
Anaplastic oligodendroglioma	1	0	NA	NA
Low-grade glioma	14	50	(23, 77)	6, 29[d]
Astrocytoma	4	50	(7, 93)	7, 23
Ganglioglioma	4	50	(7, 93)	6, 13
Pleomorphic xanthoastrocytoma	2	50	(1.3, 99)	6
Pilocytic astrocytoma	2	0	NA	NA
Choroid plexus papilloma	1	PR	(2.5, 100)	29[d]
Gangliocytoma/ganglioglioma	1	PR	(2.5, 100)	18[d]
Low-grade serous ovarian carcinoma	5	80	(28, 100)	12, 42[d]
Adenocarcinoma small intestine	4	50	(7, 93)	7, 8
Adenocarcinoma pancreas	3	0	NA	NA
Mixed ductal/adenoneuroendocrine carcinoma	2	0	NA	NA
Neuroendocrine carcinoma of colon	2	0	NA	NA
Ameloblastoma of mandible	1	PR	(2.5, 100)	30
Combined small cell-squamous carcinoma of lung	1	PR	(2.5, 100)	5
Mucinous-papillary serous adenocarcinoma of peritoneum	1	PR	(2.5, 100)	8
Adenocarcinoma of anus	1	0	NA	NA

Tumor Type[a]	N	Objective Response Rate		Duration of Response
		%	95% CI	Range (months)
Gastrointestinal stromal tumor	1	0	NA	NA

Abbreviations: NA, not applicable; PR, partial response.
[a] Excludes NSCLC (n = 6) and ATC (n = 36).
[b] Median DoR 9.8 months (95% CI: 5.3, 20.4).
[c] Median DoR 13.6 months (95% CI: 5.5, 26.7).
[d] Denotes a right-censored DoR.

CTMT212X2101 (X2101) Study

Study X2101 (NCT02124772) was a multi-center, open-label, multi-cohort study in pediatric patients with refractory or recurrent solid tumors. Part C was a dose escalation of MEQSEL in combination with dabrafenib in patients with a BRAF V600E mutation. Part D was a cohort expansion phase of MEQSEL in combination with dabrafenib in patients with LGG with a BRAF V600E mutation. The major efficacy outcome measure was ORR as assessed by independent review committee per RANO criteria.

The efficacy of MEQSEL in combination with dabrafenib was evaluated in 48 pediatric patients, including 34 patients with LGG and 2 patients with HGG.

For patients with BRAF V600E mutation-positive LGG and HGG in Parts C and D, the median age was 10 years (range: 1 to 17); 50% were male, 75% White, 8% Asian, 3% Black; and 58% had Karnofsky/Lansky performance status of 100. Prior anti-cancer treatments included surgery (83%), external beam radiotherapy (2.8%), and systemic therapy (92%). The ORR was 25% (95% CI: 12%, 42%). For the 9 patients who responded, DoR was ≥ 6 months for 78% of patients and ≥ 24 months for 44% of patients.

CDRB436G2201 (G2201) Study – High-Grade Glioma Cohort

Study G2201 (NCT02684058) was a multi-center, randomized, open-label, Phase II study of dabrafenib and trametinib in chemotherapy-naïve pediatric patients with BRAF V600E mutant low-grade glioma (LGG) and patients with relapsed or progressive BRAF V600E mutant HGG. Patients with HGG were enrolled in a single-arm cohort. The major efficacy outcome measure for the HGG cohort was ORR as assessed by independent review committee per RANO 2010 criteria.

The efficacy of MEQSEL in combination with dabrafenib was evaluated in 41 pediatric patients with relapsed or progressive HGG.

For patients with BRAF V600E mutant HGG enrolled in the HGG cohort, the median age was 13 years (range: 2 to 17); 56% were female, 61% White, 27% Asian, 2.4% Black, and 37% had Karnofsky/Lansky performance status of 100. Prior anti-cancer treatments included surgery (98%), radiotherapy (90%), and chemotherapy (81%). The ORR was 56% (95% CI: 40, 72). The median DoR was not reached (95% CI: 9.2, NE). For the 23 patients who responded in the HGG cohort, DoR was ≥ 6 months for 78% of patients, ≥ 12 months for 48% of patients, and ≥ 24 months for 22% of patients.

14 HOW SUPPLIED/STORAGE AND HANDLING

MEQSEL tablets:

0.5 mg tablets: Yellow, modified oval, biconvex, film-coated tablets, approximately 5.0 x 9.0 mm, with the company logo debossed on one face and “TT” on the opposing face.

2 mg tablets: Pink, round, biconvex, film-coated tablets, approximately 7.6 mm, with the company logo debossed on one face and “LL” on the opposing face.

Store in a refrigerator (2° to 8°C).

Protect from moisture and light. Store in the original container. Keep the bottle tightly closed. Do not remove the desiccant.

Storage information might differ in some countries.

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

15 PRODUCT REGISTRATION HOLDER

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Malaysia Package Insert

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™ = trademark

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