Clinical Data Backgrounder

Tafinlar® (dabrafenib) and Mekinist® (trametinib) as a combination of oral targeted therapies for unresectable or metastatic melanoma with BRAF V600 E or K mutations

About Tafinlar® (dabrafenib) and Mekinist® (trametinib) in Combination Therapy

- GSK’s Tafinlar (dabrafenib) and Mekinist (trametinib) is the first approved combination of oral targeted therapies indicated for the treatment of adult patients with unresectable melanoma (melanoma that cannot be removed by surgery) or metastatic melanoma (melanoma which has spread to other parts of the body) with BRAF V600E or V600K mutations. These mutations must be detected by an FDA-approved test. Tafinlar is not indicated for treatment of patients with wild-type BRAF melanoma.

- The FDA approval of the combination is based on the demonstration of response rate and median duration of response in a Phase I/II study. Improvement in disease-related symptoms or overall survival has not been demonstrated for Tafinlar in combination with Mekinist.

- When taken in combination, the recommended dose for Tafinlar is 150mg taken orally, twice daily (300mg total per day) and the recommended dose for Mekinist is 2mg taken orally, once daily.

- More information about Tafinlar and Mekinist in combination is available online.

Clinical Evidence Supporting the Approval

Phase I/II Study Design

- The approval of dabrafenib for use in combination with trametinib is based on a Phase I/II study of patients with BRAF V600E or V600K mutation-positive melanoma.

- The safety of in dabrafenib (150mg twice daily) combination with trametinib (2mg once daily) was evaluated in 202 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma enrolled in the Phase I/II study.

- In the randomised portion of the study, 162 patients were randomised (1:1:1) to receive dabrafenib 150mg orally twice daily with trametinib 2mg orally once daily (N=54), or dabrafenib 150mg orally twice daily with trametinib 1mg orally once daily (N=54), or dabrafenib 150mg orally twice daily (N=54).

- The main efficacy endpoint was investigator-assessed overall response rate (ORR). Additional efficacy outcome measures were investigator-assessed duration of response, independent radiologic review committee (IRRC)-assessed ORR, and IRRC-assessed duration of response.

Study population

- The majority of patients were male (57%) and white (>99%). The median age across treatment arms was 53 years, and 66 per cent of patients had Eastern Cooperative Oncology Group (ECOG) performance status of zero. The ECOG performance status is a scale used to assess how the disease affects the daily living abilities of the patient, and to determine appropriate treatment and prognosis.

- Sixty-seven per cent of patients had M1c disease (their melanoma had spread to other organs and/or locations in the body), 54 per cent had a normal LDH at baseline and 8 per cent had a history of brain
metastases. Most patients (81%) had not received prior anti-cancer therapy for unresectable or metastatic disease. Patients with prior exposure to BRAF inhibitors or MEK inhibitors were ineligible. All patients had tumours containing BRAF V600E or V600K mutations as determined by local laboratory or centralised testing, 85 per cent with BRAF V600E mutations and 15 per cent with BRAF V600K mutations. Tumour samples from patients were tested retrospectively using the FDA-approved companion diagnostic test, THxID-BRAF assay. The median duration of follow-up was 14 months.

Efficacy results

### Phase II Study Efficacy Results

<table>
<thead>
<tr>
<th>Efficacy outcome measure</th>
<th>Dabrafenib (150mg) + Trametinib (2mg)</th>
<th>Dabrafenib (150mg)</th>
</tr>
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<tbody>
<tr>
<td>N=54</td>
<td>N=54</td>
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</table>

**Investigator-Assessed Results**

<table>
<thead>
<tr>
<th>Overall Response Rate</th>
<th>76 per cent (95% CI, 62, 87)</th>
<th>54 per cent (95% CI, 40, 67)</th>
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<tbody>
<tr>
<td>Median Duration of Response</td>
<td>10.5 months (95% CI, 7, 15)</td>
<td>5.6 months (95% CI, 5, 7)</td>
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</tbody>
</table>

**Independent Radiologic Review Committee-Assessed Results**

<table>
<thead>
<tr>
<th>Overall Response Rate</th>
<th>57 per cent (95% CI, 43, 71)</th>
<th>46 per cent (95% CI, 33, 60)</th>
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<tbody>
<tr>
<td>Median Duration of Response</td>
<td>7.6 months (95% CI, 7, NR)</td>
<td>7.6 months (95% CI, 6, NR)</td>
</tr>
</tbody>
</table>

### Key Terminology

**Overall Response Rate:**
The percentage of patients whose cancer shrinks or disappears after treatment.

**Median Duration of Response:**
The median length of time tumour reduction was maintained before the disease progressed.

### Safety Results

- Dabrafenib in combination with trametinib can cause serious side effects, some of which can be life threatening, including: new primary cutaneous malignancies (new skin cancers); tumour promotion in wild-type BRAF; trametinib in combination with dabrafenib can cause serious side effects, some of which can be life threatening, including: new primary cutaneous malignancies (new skin cancers); tumour promotion in wild-type BRAF melanoma; haemorrhagic events (symptomatic bleeding in a critical area or organ); venous thromboembolic events (blood clots); cardiomyopathy (heart problems, including heart failure); ocular (eye-related) toxicities; interstitial lung disease (ILD); serious febrile drug reactions (severe fevers); serious skin toxicity (rash); hyperglycaemia (blood sugar problems); haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency; and embryofoetal toxicity (potential harm to the unborn baby in pregnant women).

- The most frequently occurring adverse reactions at the recommended dose of trametinib 2mg once daily in combination with dabrafenib 150mg twice daily (all grades in more than 20% of patients) in the randomised part of Phase I/II study included: pyrexia (fever) (71%), chills (58%), fatigue (53%), rash (45%), nausea (44%), vomiting (40%), diarrhoea (36%), abdominal pain (33%), oedema peripheral (swelling of tissues, usually in the lower limbs) (31%), cough (29%), headache (29%), arthralgia (27%), night sweats (24%), decreased appetite (22%), constipation (22%) and myalgia (muscular pain) (22%). The most common (≥2%) Grade 3 or 4 adverse events observed in the combination group in this study were: renal failure (7%), pyrexia (5%), back pain (5%), haemorrhage (5%), fatigue (4%), chills (2%), nausea (2%), vomiting (2%), diarrhoea (2%), abdominal pain (2%), myalgia (2%) and urinary tract infection (2%).

### Mechanism of Action

- Dabrafenib, targeting BRAF, and trametinib, targeting MEK, work to inhibit two different parts of the MAPK pathway, which regulates the normal growth and death of cells, including skin cells. In BRAF-mutant melanoma, the over-expressed BRAF and MEK proteins disrupt the normal regulation...
of cell growth and death, leading to increased cancer cell production and survival. Dabrafenib and trametinib work to block abnormal signalling in the pathway, potentially stopping or slowing tumour cell growth. Use of trametinib and dabrafenib in combination resulted in greater growth inhibition of BRAF V600 mutation-positive melanoma cell lines in vitro and prolonged inhibition of tumour growth in BRAF V600 mutation-positive melanoma xenografts compared with either drug alone.

**Regulatory Status**

- In the United States, the combination of Tafinlar and Mekinist is now approved for the treatment of adult patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. These mutations must be detected by an FDA-approved test. Tafinlar is not indicated for treatment of patients with wild-type BRAF melanoma.
- Tafinlar and Mekinist are already approved as single-agent therapies in the U.S. Tafinlar is approved for unresectable or metastatic melanoma in adult patients with BRAF V600E mutation. Tafinlar is not indicated for treatment of patients with wild-type BRAF melanoma. Mekinist is approved for unresectable or metastatic melanoma in adult patients with BRAF V600E or V600K mutations. Mekinist as a single agent is not indicated for treatment of patients who have received prior BRAF-inhibitor therapy.
- The ongoing Phase III programme evaluating the combination of dabrafenib and trametinib in patients with BRAF mutation-positive metastatic melanoma is comprised of two trials:
  - COMBI-d (Combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib versus dabrafenib monotherapy), a Phase III trial which will evaluate whether combining the two agents is better than dabrafenib single-agent therapy in stopping or slowing the progression of metastatic melanoma (progression-free survival).
  - COMBI-v (Combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib versus vemurafenib monotherapy), a Phase III trial which will evaluate whether combining the two agents is better than single-agent therapy with vemurafenib, an approved BRAF inhibitor, in improving the overall survival of patients with metastatic melanoma (overall survival).

**About Metastatic Melanoma and Genetic Mutations**

- Melanoma is the most serious and deadly form of skin cancer. When melanoma spreads in the body, the disease is called metastatic melanoma. One in two patients worldwide with metastatic melanoma is expected to survive for a year after diagnosis, while the five-year survival rate was less than 15 per cent (2003-2009).
- Among patients with metastatic melanoma, approximately half have a BRAF mutation that can disrupt the normal regulation of cell growth and death and lead to increased cancer cell production. The most commonly observed BRAF mutations, V600E and V600K, account for approximately 85 per cent and 10 per cent of all BRAF mutations in metastatic melanoma, respectively.

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**Important Safety Information for Mekinist in combination with Tafinlar**

**WARNINGS AND PRECAUTIONS: Tafinlar and Mekinist combination**

**New Primary Malignancies (cutaneous and non-cutaneous)**

When Tafinlar was used in combination with Mekinist at the recommended dose, the incidence of basal cell carcinoma was increased. The incidence of basal cell carcinoma was 9% (5/55) in patients receiving the combination compared to 2% (1/53) in patients receiving Tafinlar as a single agent. Tafinlar results in an increased incidence of cutaneous squamous cell carcinoma (cuSCC), keratoacanthoma and melanoma. Cutaneous squamous cell carcinoma, including keratoacanthoma, occurred in 7% of patients receiving the combination and 19% of patients receiving Tafinlar as a single agent.
Tumour Promotion in Wild-Type BRAF Melanoma

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in wild-type BRAF cells that are exposed to BRAF inhibitors.

Haemorrhage

Treatment with the combination resulted in an increased incidence and severity of haemorrhagic events: 16% (9/55) of patients treated with the combination compared with 2% (1/53) of patients treated with Tafinlar as a single agent. Intracranial haemorrhage was fatal in two (4%) patients receiving the combination.

Venous Thromboembolic Events

Treatment with the combination resulted in an increased incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE): 7% (4/55) of patients treated with the combination compared with none of the 53 patients treated with Tafinlar as a single agent. Pulmonary embolism was fatal in one (2%) patient receiving the combination.

Cardiomyopathy

When Mekinist was used in combination with Tafinlar at the recommended dose, cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased left ventricular ejection fraction [LVEF]) occurred in 9% (5/55) of patients treated with the combination and in none of patients treated with Tafinlar as a single agent.

Ocular Toxicities

Retinal Vein Occlusion (RVO): across clinical trials of Mekinist the incidence of RVO was 0.2% (4/1,749). RVO may lead to macular oedema, decreased visual function, neovascularisation, and glaucoma.

Retinal Pigment Epithelial Detachment (RPED): in the randomised Phase II part of the Phase I/II open-label study 2% (1/55) of patients receiving Mekinist in combination with Tafinlar developed RPED.

Uveitis and Iritis: across clinical trials of the combination, uveitis occurred in 1% (2/202) of patients.

Interstitial lung disease (ILD)

In clinical trials of Mekinist (N = 329) as a single agent, ILD or pneumonitis occurred in 2% of patients.

Serious Febrile Drug Reactions

Serious febrile reactions and fever of any severity accompanied by hypotension, rigors or chills, dehydration or renal failure, can occur when Mekinist is used in combination with Tafinlar. The incidence and severity of pyrexia are increased when Mekinist is given with Tafinlar compared with Tafinlar alone. The incidence of fever (serious and non-serious) was 71% (39/55) in patients treated with the combination and 26% (14/53) in patients treated with Tafinlar as a single agent. Febrile reactions of any severity, accompanied by hypotension, rigors or chills, occurred in 25% (14/55) of patients treated with the combination compared with 2% (1/53) of patients treated with Tafinlar as a single agent.

Serious Skin Toxicity

In the randomised part of Phase I/II study, the incidence of any skin toxicity, the most common of which were rash, dermatitis acneiform rash, palmar-plantar erythrodysesthesia syndrome or erythema, was similar for patients receiving the combination (65% [36/55]) compared with patients receiving Tafinlar as a single agent (68% [36/53]). Across all clinical trials of the combination (N = 202), severe skin toxicity requiring hospitalisation occurred in 2.5% (5/202) of patients.

Hyperglycaemia

Hyperglycaemia can occur when Mekinist is used in combination with Tafinlar. The incidence of Grade 3 hyperglycaemia based on laboratory values was 5% (3/55) in patients treated with the combination compared with 2% (1/53) in patients treated with Tafinlar as a single agent.
Glucose-6-Phosphate Dehydrogenase Deficiency

Tafinlar, which contains a sulfonamide moiety, confers a potential risk of haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Embryofetal Toxicity

Tafinlar and Mekinist both can cause foetal harm when administered to a pregnant woman. Tafinlar can also render hormonal contraceptives ineffective.

Drug Interactions

Effects of Other Drugs on Dabrafenib

Drugs that Inhibit or Induce Drug-Metabolising Enzymes: dabrafenib is primarily metabolised by CYP2C8 and CYP3A4. Strong inhibitors or inducers of CYP3A4 or CYP2C8 may increase or decrease, respectively, concentrations of dabrafenib.

Drugs that Affect Gastric pH: Drugs that alter the pH of the upper GI tract (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) may alter the solubility of dabrafenib and reduce its bioavailability.

Effects of Dabrafenib on Other Drugs

Dabrafenib induces CYP3A4 and CYP2C9. Dabrafenib decreased systemic exposures of midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4/CYP1A2 substrate). Coadministration of dabrafenib with other substrates of these enzymes, including dexamethasone, or hormonal contraceptives, can result in decreased concentrations and loss of efficacy.

Combination of trametinib with dabrafenib

Co-administration of trametinib 2mg once daily and dabrafenib 150mg twice daily resulted in no clinically relevant pharmacokinetic drug interactions

Please see full Prescribing Information and Medication Guide for Tafinlar:

Please see full U.S. Prescribing Information and Patient Information Leaflet for Mekinist:


1 GSK. Mekinist Prescribing Information 2014.
2 GSK. Tafinlar Prescribing Information 2014.
   A. Page 2, Left column, Paragraph 1, Lines 4-16.
4 Cantwell-Dorris, ER, O'Leary, J., Sheils, OM. BRAFV600E: Implications for Carcinogenesis and Molecular Therapy. Mol Cancer Ther. March 2011.
   A. Page 386, Right column, Paragraph 2, Lines 13-17.
   A. Page 1, Paragraph 1, Line 1.
   A. Page 2, Table 1, “Melanoma Stage IV” Line.
   A. Page 1, Paragraph 1, Lines 7-8
   B. Page 1, Paragraph 3, Lines 3-4
   A. Page 1, Left column, Paragraph 1, Lines 5-12.

   A. Page 2326, Right Column, Paragraph 2, Lines 1-4.