Review Report

May 11, 2018
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Mekinist Tablets 0.5 mg Mekinist Tablets 2 mg
Non-proprietary Name	Trametinib Dimethyl Sulfoxide (JAN*)
Applicant	Novartis Pharma K.K.
Date of Application	November 17, 2017
Dosage Form/Strength	Tablets, each containing 0.5635 or 2.254 mg of Trametinib Dimethyl Sulfoxide (equivalent to 50 or 75 mg of trametinib, respectively)
Application Classification	Prescription drugs, (4) Drugs with new indications and (6) Drugs with new dosages
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 317 of 2013 [*25 yaku*], PFSB/ELD Notification No. 0422-1 dated April 22, 2015, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with malignant melanoma with *BRAF* mutations, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following conditions.

Indications

1. ~~Unresectable~~ Malignant melanoma with *BRAF* mutations
2. Unresectable advanced or recurrent non-small cell lung cancer with *BRAF* mutations

(Strikethrough denotes deletion. Double-underline denotes additions made after submission of the present application [as of March 23, 2018].)

Dosage and Administration

The usual adult dosage is 2 mg of trametinib administered orally once daily under fasted conditions when used in combination with dabrafenib. In the adjuvant treatment setting patients should be treated with trametinib in combination with dabrafenib for up to 12 months. The dose may be adjusted according to the patient's condition.

(Underline denotes addition.)

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.

* *Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

March 29, 2018

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

[1] Brand Name Tafinlar Capsules 50 mg
Tafinlar Capsules 75 mg

Non-proprietary Name Dabrafenib Mesilate

Applicant Novartis Pharma K.K.

Date of Application November 17, 2017

Dosage Form/Strength Capsules, each containing 59.25 or 88.88 mg of Dabrafenib Mesilate (equivalent to 50 or 75 mg of dabrafenib, respectively)

Proposed Indication ~~Unresectable~~ Malignant melanoma with *BRAF* mutations
(Strikethrough denotes deletion.)

Proposed Dosage and Administration
The usual adult dosage is 150 mg of dabrafenib administered orally twice daily under fasted conditions. <u>In adjuvant chemotherapy, dabrafenib is given in combination with trametinib.</u> The dose may be adjusted according to the patient's condition.
(Underline denotes addition.)

[2] Brand Name Mekinist Tablets 0.5 mg
Mekinist Tablets 2 mg

Non-proprietary Name Trametinib Dimethyl Sulfoxide

Applicant Novartis Pharma K.K.

Date of Application November 17, 2017

Dosage Form/Strength Tablets, each containing 0.5635 or 2.254 mg of Trametinib Dimethyl Sulfoxide (equivalent to 0.5 or 2 mg of trametinib, respectively)

Proposed Indication ~~Unresectable~~ Malignant melanoma with *BRAF* mutations
(Strikethrough denotes deletion.)

Proposed Dosage and Administration
The usual adult dosage is 2 mg of trametinib administered orally once daily under fasted conditions when used in combination with

dabrafenib. The dose may be adjusted according to the patient's condition.

(No change)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the product submitted for registration

BRAF V600 mutation (amino acid substitution for valine at codon 600) has been found in approximately 50% of patients with malignant melanoma (*Nature*. 2002;417:949-54). BRAF V600 mutation causes constitutive activation of the pathway, which leads to activation of extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase/extracellular signal-regulated kinase kinase (MEK), resulting in abnormal cell proliferation.

Dabrafenib mesilate (dabrafenib or DAB) is a low molecular weight compound discovered by GlaxoSmithKline (UK), and is considered to suppress the growth of tumors with BRAF V600 mutations by inhibiting the kinase activity of BRAF.

Trametinib dimethyl sulfoxide (trametinib or TRA) is a low molecular weight compound discovered by Japan Tobacco Inc. and is considered to suppress the growth of tumors with BRAF V600 mutations by inhibiting the kinase activity of MEK1 and MEK2.

In Japan, DAB and TRA were approved for the treatment of "Unresectable malignant melanoma with *BRAF* mutations" in March 2016 and approved for the treatment of "Unresectable advanced or recurrent non-small cell lung cancer (NSCLC) with *BRAF* mutations" in March 2018. The latter approval was granted after the submission of the present application for partial change in the approved application (partial change application).

1.2 Development history, etc.

The clinical development of combination therapy with DAB and TRA as the adjuvant treatment of malignant melanoma was undertaken by GlaxoSmithKline (UK), and a multi-regional phase III study (Study F2301 [Study DRB436F2301]) involving patients with malignant melanoma with BRAF V600 mutations following complete resection was initiated in January 2013.

Applications for DAB and TRA to be used in combination for the adjuvant treatment of malignant melanoma were submitted in the US in October 2017 and in the EU in [redacted] 2017, with the results of Study F2301 as the pivotal data. The applications are currently under review.

As of February 2018, DAB and TRA are not approved for the adjuvant treatment of malignant melanoma in any countries or regions.

In Japan, patient enrollment in Study F2301 was initiated in [redacted].

Recently, partial change applications for DAB and TRA have been submitted to add the indication and the dosage and administration for the adjuvant treatment of malignant melanoma, based on the results of Study F2301 as the pivotal data.

DAB and TRA were designated as orphan drugs in April 2015 with the intended indication of "malignant melanoma with BRAF V600 mutations" (Orphan Drug Designation No. 318 and 317 of 2013 [*25 yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Since the present application is intended to add a new indication and new dosage, no new data relating to quality were submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although the present application is intended to add a new indication and a new dosage, no new study data were submitted on the ground that non-clinical pharmacology data had been reviewed at the initial approval.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application is intended to add a new indication and a new dosage, no new study data were submitted on the ground that non-clinical pharmacokinetics data had been reviewed at the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is intended to add a new indication and new dosage, no new data relating to toxicity were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

Although the present application is intended to add a new indication and a new dosage, no new study data were submitted on the ground that data on biopharmaceutic studies and associated analytical methods had been reviewed at the initial approval. New data on clinical pharmacology were submitted, and PMDA concluded that the applicant's explanation based on the data is consistent with the data evaluated at the initial approval.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of the data from a multi-regional phase III study (see Table 1).

Table 1. Clinical study to evaluate efficacy and safety

Data category	Region	Study identifier	Phase	Study population	No. of subjects	Dosage regimen	Main endpoints
Evaluation	Multi -regional	F2301	III	Patients with high-risk malignant melanoma with BRAF V600 mutations following surgical resection	870 (a) 438 (b) 432	(a) Oral dose of DAB 150 mg BID and TRA 2 mg QD (b) Oral dose of DAB placebo BID and TRA placebo QD	Efficacy Safety

The outline of the clinical study is described below. Major adverse events other than death reported in the clinical study are described in Section "7.2 Adverse events, etc., reported in clinical study."

7.1 Evaluation data

7.1.1 Multi-regional study

7.1.1.1 Multi-regional phase III study (CTD 5.3.5.1.1, Study F2301; ongoing since January 2013 [data cut-off as of June 30, 2017])

A double-blind, randomized, comparative study was conducted in 169 sites in 25 countries including Japan to evaluate the efficacy and safety of DAB and TRA combination therapy (DAB/TRA) versus two matching placebos in patients with high-risk[1)] malignant melanoma with BRAF V600 mutation[2)] following surgical resection.[3)]

The DAB/TRA group received DAB 150 mg bis in die (BID) and TRA 2 mg quaque die (QD) orally, and the placebo group received DAB placebo BID and TRA placebo QD orally. The treatment was continued for up to 12 months unless the patient had disease recurrence or met any of the criteria for study discontinuation.

All of 870 patients enrolled in the study and randomized (438 in the DAB/TRA group, 432 in the placebo group) were included in the intention-to-treat (ITT) population, which was used for the efficacy analysis. Among the patients included in the ITT population, 867 patients (435 in the DAB/TRA group, 432 in the placebo group) were included in the safety analysis set, and the remaining 3 patients were excluded from analysis because they did not receive the study drug.

The primary endpoint of this study was relapse-free survival (RFS)[4)] assessed by the investigator, and it was planned to perform the analysis when 467 events were observed. However, because of a delay in event data collection behind schedule, the protocol was revised to conduct the analysis at the time point when approximately 410 events were expected to have been collected (protocol, ver. 7 [May 31, 2017]).

Efficacy data were analyzed. The results of RFS and Kaplan-Meier curves are shown in Table 2 and Figure 1, respectively.

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1) (a) Stage IIIA (metastatic lymph node >1 mm), (b) stage IIIB, and (c) stage IIIC were defined as "high-risk" (of recurrence).
2) Patients with malignant melanoma determined to be BRAF V600E or V600K mutation-positive using bioMérieux's THxID BRAF Assay (approved in Japan) at the central laboratory.
3) Patients who underwent complete resection of melanoma
4) Defined as the time from randomization to (a) loco-regional, distant metastasis, or secondary malignant melanoma or (b) death, whichever occurred earlier.

Table 2. Results of RFS (assessed by the investigator, ITT population, data cut-off as of June 30, 2017)

	DAB/TRA	Placebo
N	438	432
Number of events (%)	166 (37.2)	248 (57.2)
Median [95% CI] (months)	NE [44.5, NE]	16.6 [12.7, 22.1]
Hazard ratio [95% CI][*1]	0.47 [0.39, 0.58]	
P value (two-sided)[*2]	1.53×10^{-14}	

[*1] Pike estimator; [*2] Stratified log-rank test with disease stage (IIIA, IIIB, IIIC) and BRAF mutation type (V600E, V600K) as the stratification factors at the significance level (two-sided) of 0.05

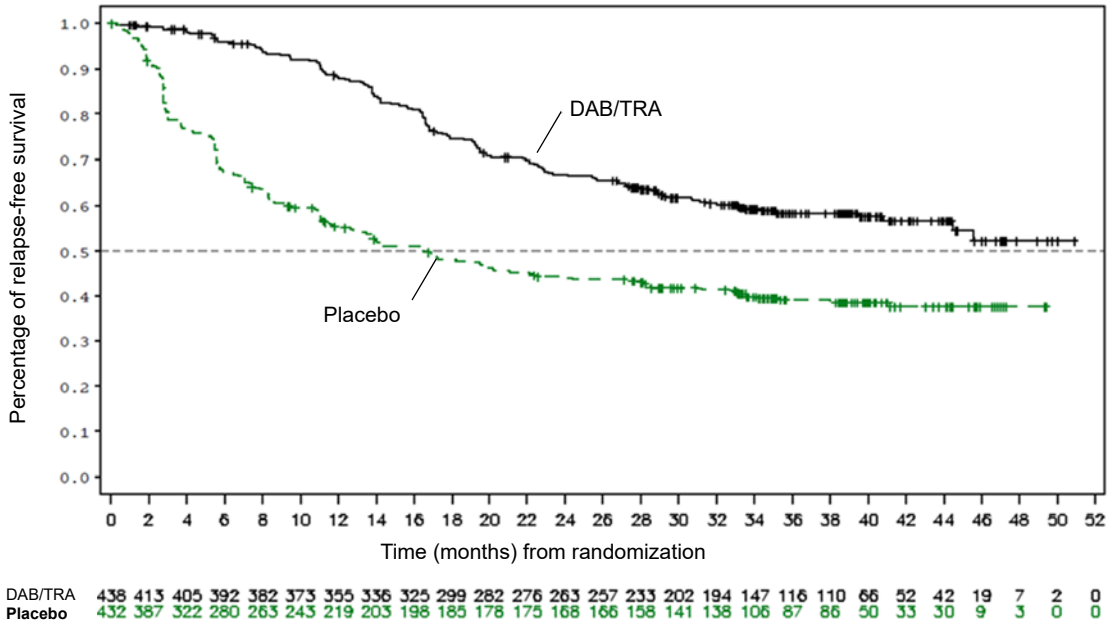

Figure 1. Kaplan-Meier curves (assessed by the investigator, ITT population, data cut-off as of June 30, 2017)

According to safety analysis, death occurred in 4 of 435 patients (0.9%) in the DAB/TRA group and in 1 of 432 patients (0.2%) in the placebo group during the study treatment or within 30 days after the study treatment. Four patients died due to disease progression (3 in the DAB/TRA group and 1 in the placebo group). The cause of death in 1 patient in the DAB/TRA group was pneumonia, and the event was considered unrelated to the study drug.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

On the basis of the following review, PMDA has concluded that the efficacy of DAB/TRA in patients with malignant melanoma with BRAF V600 mutations following complete resection has been demonstrated by the data submitted.

7.R.1.1 Selection of control group

The applicant's explanation:

At the time when Study F2301 was being planned, no treatment options for the target population of Study F2301 were recommended as standard therapy by the National Comprehensive Cancer Network

Clinical Practice Guidelines in Oncology for Melanoma (NCCN Guidelines) (v.3. 2012) and other guidelines. Therefore, placebo was used as the control in Study F2301.

PMDA accepted the explanation of the applicant.

7.R.1.2 Efficacy endpoints

The applicant's explanation about the appropriateness of using RFS as the primary endpoint of Study F2301:

For RFS used as the primary endpoint of Study F2301, (a) loco-regional, distant metastasis, or secondary malignant melanoma and (b) death, were defined as events. New primary cancer other than malignant melanoma (including squamous cell carcinoma and keratoacanthoma) was not included in RFS events because squamous cell carcinoma and keratoacanthoma are easily resectable.

In patients with malignant melanoma with BRAF V600 mutations following complete resection, prolongation of RFS, i.e., prolongation of time to events such as (a) and (b) above leads to the maintenance of the physical function and the quality of life of the patient, thus resulting in clinically significant outcomes. Selecting RFS as the primary endpoint was appropriate.

PMDA's view:

The objective of treatment administered to patients with malignant melanoma with BRAF V600 mutations following complete resection is life prolongation. Therefore, overall survival (OS) should have been selected as the primary endpoint of Study F2301. However, the applicant's above explanation (prolonged RFS has a certain clinical significance in this patient population) is understandable. The efficacy of DAB/TRA can be evaluated based on RFS as the primary endpoint of Study F2301, along with the results of OS in this study.

7.R.1.3 Efficacy evaluation

Study F2301 demonstrated the superiority of DAB/TRA to placebo in terms of investigator-assessed RFS, the primary endpoint [see Section 7.1.1.1]. The interim analysis of OS (one of the secondary endpoints) was performed at the time of the analysis of RFS. The interim analysis results and Kaplan-Meier curves are shown in Table 3 and Figure 2, respectively. A statistical test on OS at the two-sided significance level of 0.05 was to be performed if a statistical significant difference in the primary endpoint (RFS) was observed between treatments. The type I error rate for the interim analysis was adjusted using O'Brien-Fleming type α spending function based on the method of Lan and DeMets.

Table 3. Results of interim analysis of OS (ITT population, data cut-off as of June 30, 2017)

	DAB/TRA	Placebo
N	438	432
Number of events (%)	60 (13.7)	93 (21.5)
Median [95% CI] (months)	NE [NE, NE]	NE [NE, NE]
Hazard ratio [95% CI][*1]	0.57 [0.42, 0.79]	
P value (two-sided)[*2]	6.0×10^{-4}	

[*1] Pike estimator; [*2] Stratified log-rank test with disease stage (IIIA, IIIB, IIIC) and BRAF mutation type (V600E, V600K) as stratification factors at the significance level (two-sided) 1.9×10^{-5}

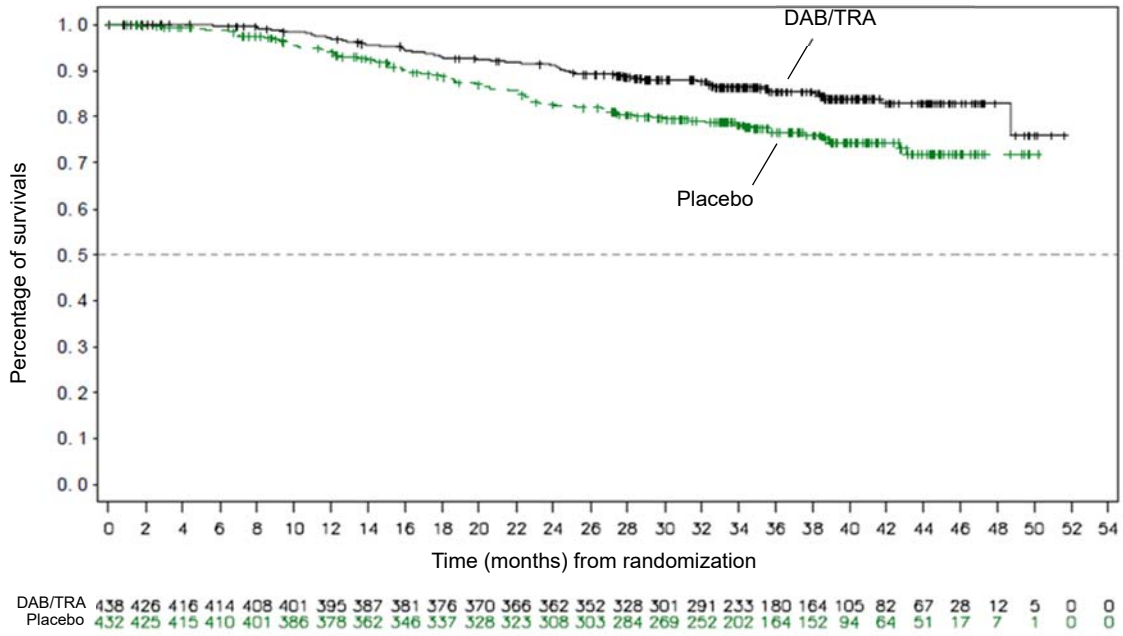

Figure 2. Kaplan-Meier curves at the time point of OS analysis
(ITT population, data cut-off as of June 30, 2017)

Results of RFS in 5 Japanese patients (3 in the DAB/TRA group, 2 in the placebo group) (data cut-off as of June 30, 2017) were as follows:

- In the DAB/TRA group, recurrence occurred in 1 patient at 26.8 months and 1 patient was censored at 33.4 months and another at 33.1 months.
- In the placebo group, recurrence occurred in 1 patient at 8.6 months and the remaining 1 patient was censored at 13.9 months.

PMDA's view:

The data submitted have demonstrated the efficacy of DAB/TRA in patients with malignant melanoma with BRAF V600 mutations following complete resection. This conclusion is based on the following:

- Study F2301 demonstrated the superiority of DAB/TRA to placebo in terms of investigator-assessed RFS, the primary endpoint. Also, the study results suggested a tendency of prolonged OS (one of the secondary endpoints) in the DAB/TRA group compared with the placebo group.
- Because of a small number of Japanese patients participating in Study F2301 and the limited number of events reported in the study, it is difficult to evaluate the efficacy of DAB/TRA in Japanese patients. However, the efficacy of DAB/TRA in Japanese patients can be supported by the above results and the following findings:
  - ➢ No clear difference was observed in the pharmacokinetics (PK) of DAB or TRA between Japanese and non-Japanese patients.
  - ➢ There is no clear difference in the efficacy of DAB/TRA between Japanese and non-Japanese patients with the approved indication of unresectable malignant melanoma with BRAF V600 mutations (see "Review Report on Tafinlar Capsules 50 mg and Tafinlar Capsules 75 mg, dated

January 21, 2016" and "Review Report on Mekinist Tablets 0.5 mg and Mekinist Tablets 2 mg, dated January 21, 2016").

7.R.2 Safety [for adverse events, see Section "7.2 Adverse events, etc., reported in clinical study"]

As a result of the following reviews, PMDA has concluded that adverse events requiring particular attention during adjuvant treatment with DAB/TRA for patients with malignant melanoma with BRAF V600 mutations are the same as the adverse events identified as those requiring attention at the previous approval of DAB and TRA combination therapy indicated for the treatment of patients with unresectable malignant melanoma with BRAF V600 mutations (secondary malignancies, cardiac disorders, hepatic dysfunction, pyrexia, eye disorders, and rhabdomyolysis) (see "Review Report on Tafinlar Capsules 50 mg and Tafinlar Capsules 75 mg, dated January 21, 2016" and "Review Report on Mekinist Tablets 0.5 mg and Mekinist Tablets 2 mg, dated January 21, 2016"). Attention should be paid to the risk of these adverse events during treatment with DAB/TRA.

PMDA has also concluded that although caution should be exercised against the risk of the above adverse events during treatment with DAB/TRA, combination therapy with DAB and TRA is well-tolerated in patients with malignant melanoma with BRAF V600 mutations following complete resection as well, provided that appropriate measures, such as monitoring and management of adverse events and adjustment of the doses of DAB or TRA, are taken by physicians with sufficient knowledge and experience of cancer chemotherapy.

7.R.2.1 Safety profile and difference between Japanese and non-Japanese populations

The applicant's explanation about the safety profile of DAB/TRA based on the safety information obtained from Study F2301:

Table 4 shows the summary of safety in Study F2301.

Table 4. Summary of safety (Study F2301)

	n (%)	
	DAB/TRA N = 435	Placebo N = 432
All adverse events	422 (97.0)	380 (88.0)
Grade ≥3 adverse events	181 (41.6)	61 (14.1)
Adverse events leading to death	1 (0.2)	0
Serious adverse events	155 (35.6)	44 (10.2)
Adverse events leading to treatment discontinuation	114 (26.2)	12 (2.8)
DAB	109 (25.1)	12 (2.8)
TRA	104 (23.9)	12 (2.8)
Adverse events leading to treatment interruption	289 (66.4)	65 (15.0)
DAB	285 (65.5)	62 (14.4)
TRA	237 (54.5)	59 (13.7)
Adverse events leading to dose reduction	167 (38.4)	11 (2.5)
DAB	152 (34.9)	7 (1.6)
TRA	102 (23.4)	7 (1.6)

In Study F2301, all-Grade adverse events with a ≥10% higher incidence in the DAB/TRA group than in the placebo group were pyrexia (273 patients [62.8%] in the DAB/TRA group vs. 47 patients [10.9%] in the placebo group), fatigue (204 patients [46.9%] vs. 122 patients [28.2%]), nausea (172

patients [39.5%] vs. 88 patients [20.4%]), headache (170 patients [39.1%] vs. 102 patients (23.6%)), chills (161 patients [37.0%] vs. 19 patients [4.4%]), diarrhoea (144 patients [33.1%] vs. 65 patients [15.0%]), vomiting (122 patients [28.0%] vs. 43 patients [10.0%]), arthralgia (120 patients [27.6%] vs. 61 patients [14.1%]), rash (106 patients [24.4%] vs. 47 patients [10.9%]), alanine aminotransferase (ALT) increased (67 patients [15.4%] vs. 6 patients [1.4%]), aspartate aminotransferase (AST) increased (63 patients [14.5%] vs. 7 patients [1.6%]), and dermatitis acneiform (54 patients [12.4%] vs. 10 patients [2.3%]). Grade ≥3 adverse event with a ≥3% higher incidence in the DAB/TRA group than in the placebo group were hypertension (25 patients [5.7%] vs. 8 patients [1.9%]), pyrexia (23 patients [5.3%] vs. 2 patients [0.5%]), fatigue (19 patients [4.4%] vs. 1 patient [0.2%]), neutropenia (18 patients [4.1%] vs. 0 patients), AST increased (16 patients [3.7%] vs. 1 patient [0.2%]), and ALT increased (16 patients [3.7%] vs. 1 patient [0.2%]). Serious adverse events with a ≥2% higher incidence in the DAB/TRA group than in the placebo group were pyrexia (67 patients [15.4%] vs. 4 patients [0.9%]) and chills (13 patients [3.0%] vs. 0 patients). Adverse events leading to treatment discontinuation with a ≥3% higher incidence in the DAB/TRA group than in the placebo group were pyrexia (38 patients [8.7%] vs. 0 patients) and chills (16 patients [3.7%] vs. 0 patients). Adverse events leading to dose reduction with a ≥3% higher incidence in the DAB/TRA group than in the placebo group were pyrexia (81 patients [18.6%] vs. 1 patient [0.2%]) and chills (17 patients [3.9%] vs. 0 patients). Adverse events leading to treatment interruption with a ≥3% higher incidence in the DAB/TRA group than in the placebo group were pyrexia (194 patients [44.6%] vs. 14 patients [3.2%]), chills (65 patients [14.9%] vs. 0 patients), fatigue (27 patients [6.2%] vs. 1 patient [0.2%]), headache (25 patients [5.7%] vs. 4 patients [0.9%]), vomiting (23 patients [5.3%] vs. 5 patients [1.2%]), nausea (22 patients [5.1%] vs. 4 patients [0.9%]), influenza like illness (20 patients [4.6%] vs. 1 patient [0.2%]), arthralgia (16 patients [3.7%] vs. 2 patients [0.5%]), AST increased (16 patients [3.7%] vs. 0 patients), ALT increased (16 patients [3.7%] vs. 0 patients), rash (14 patients [3.2%] vs. 1 patient [0.2%]), myalgia (13 patients [3.0%] vs. 0 patients), and neutropenia (13 patients [3.0%] vs. 0 patients). There were no adverse events leading to death with a ≥1% higher incidence in the DAB/TRA group than in the placebo group.

The applicant's explanation about the difference in the safety profile of DAB/TRA between patients with malignant melanoma with BRAF V600 mutations following complete resection and patients with approved indications, i.e., patients with unresectable malignant melanoma with BRAF V600 mutations or patients with unresectable advanced or recurrent non-small cell lung cancer (NSCLC) with BRAF V600 mutations:

Table 5 shows the comparison of safety data from different patient populations. The incidences of adverse events observed in the DAB/TRA group of Study F2301 were compared with those observed in the pooled analysis of data from the DAB/TRA group in foreign phase III studies (COMBI-D study [Study MEK115306] and COMBI-V study [Study MEK116513]) in patients with unresectable malignant melanoma and with those observed in the multi-regional phase II study (Cohorts B and C in Study E2201 [Study DRB436E2201]) in patients with NSCLC with BRAF V600 mutations.

Table 5. Summary of safety in patients with malignant melanoma following complete resection, patients with unresectable malignant melanoma, and patients with advanced or recurrent NSCLC

	n (%)		
	Patients with malignant melanoma following complete resection N = 435	Patients with unresectable malignant melanoma N = 559	Patients with unresectable advanced or recurrent NSCLC N = 93
All adverse events	422 (97.0)	548 (98.0)	92 (98.9)
Grade ≥3 adverse events	181 (41.6)	321 (57.4)	61 (65.6)
Adverse events leading to death	1 (0.2)	10 (1.8)	6 (6.5)
Serious adverse events	155 (35.6)	257 (46.0)	56 (60.2)
Adverse events leading to treatment discontinuation	114 (26.2)	88 (15.7)	19 (20.4)
DAB	109 (25.1)	76 (13.6)	18 (19.4)
TRA	104 (23.9)	76 (13.6)	19 (20.4)
Adverse events leading to treatment interruption	289 (66.4)	334 (59.7)	62 (66.7)
DAB	285 (65.5)	329 (58.9)	61 (65.6)
TRA	237 (54.5)	279 (49.9)	55 (59.1)
Adverse events leading to dose reduction	167 (38.4)	189 (33.8)	33 (35.5)
DAB	152 (34.9)	172 (30.8)	33 (35.5)
TRA	102 (23.4)	127 (22.7)	29 (31.2)

The all-Grade adverse events with a ≥10% higher incidence in patients with malignant melanoma following complete resection than in both patients with unresectable malignant melanoma and patients with NSCLC were fatigue (46.9% of patients with malignant melanoma following complete resection, 34.5% of patients with unresectable malignant melanoma, 22.6% of patients with unresectable advanced or recurrent NSCLC). There were no Grade ≥3 adverse events with a ≥5% higher incidence, adverse events leading to death with a ≥1% higher incidence, or serious adverse events with a ≥3% higher incidence in patients with malignant melanoma following complete resection. Adverse event leading to treatment discontinuation with a ≥3% higher incidence was pyrexia (8.7%, 3.6%, 2.2%). Adverse events leading to treatment interruption with a ≥3% higher incidence were pyrexia (44.6%, 34.2%, 28.0%), chills (14.9%, 10.0%, 7.5%), and headache (5.7%, 2.7%, 0%). Adverse event leading to dose reduction with a ≥3% higher incidence was pyrexia (18.6%, 15.0%, 11.8%).

Thus, there were no safety concerns specific to patients with malignant melanoma following complete resection compared to patients with unresectable malignant melanoma or patients with unresectable advanced or recurrent NSCLC.

The applicant's explanation about the difference in the safety of DAB/TRA combination between Japanese and non-Japanese patients, based on the safety information obtained in Study F2301:
All-Grade adverse events reported by ≥2 Japanese patients were pyrexia (3 Japanese patients [100%] vs. 270 non-Japanese patients [62.5%]), headache (3 patients [100%] vs. 167 patients [38.7%]), AST increased (2 patients [66.7%] vs. 61 patients [14.1%]), epistaxis (2 patients [66.7%] vs. 39 patients [9.0%]), and oropharyngeal pain (2 patients [66.7%] vs. 37 patients [8.6%]). Grade ≥3 adverse events reported by Japanese patients were pyrexia (1 patient [33.3%] vs. 22 patients [5.1%]) and neutropenia (1 patient [33.3%] vs. 17 patients [3.9%]). Adverse events reported by Japanese patients only were Grade ≤2 blood triglycerides increased and polyarthritis in 1 patient (33.3%) each. Neither serious adverse events nor adverse events leading to death occurred in Japanese patients.

Because only 3 Japanese patients participated in Study F2301, there are limitations to discussing the difference in safety between Japanese and non-Japanese patients based on the results of the study. However, adverse events observed in multiple Japanese patients were also observed in multiple non-Japanese patients, and there were no adverse events requiring particular attention in Japanese patients.

PMDA's view:
There were adverse events reported more frequently in the DAB/TRA group than in the placebo group in Study F2301. Also, there were adverse events reported more frequently in patients with malignant melanoma with BRAF V600 mutations following complete resection compared with patients with approved indications, i.e., patients with unresectable malignant melanoma or with unresectable advanced or recurrent NSCLC. However, most of them were Grade ≤2 adverse events or those known to occur during treatment with DAB/TRA, and considered manageable with treatment interruption or dose reduction. Therefore, DAB/TRA is well-tolerated in patients with malignant melanoma with BRAF V600 mutations following complete resection as well, provided that appropriate measures, such as monitoring and management of adverse events and the adjustment of the doses of DAB or TRA, are taken by physicians with sufficient knowledge and experience of cancer chemotherapy.

Although there is only limited experience with the use of DAB/TRA in Japanese patients with malignant melanoma following complete resection, currently available data indicate that there are no adverse events requiring particular attention in Japanese patients.

7.R.3 Clinical positioning and indication

The proposed indication for DAB and TRA was "malignant melanoma with *BRAF* mutations" in place of the approved indication for "unresectable malignant melanoma with *BRAF* mutations." Also, the Precautions for Indications section included the following descriptions:

- Dabrafenib (or trametinib) should be administered to patients who are confirmed to have *BRAF* mutations through tests performed by a well experienced pathologist or testing laboratory. An approved *in vitro* diagnostic, etc. should be used for the test.
- The physician should thoroughly understand the description in the "Clinical Studies" section and be fully aware of the efficacy and safety of dabrafenib (or trametinib) before identifying patients eligible for treatment with dabrafenib (or trametinib).

On the basis of reviews presented in Sections "7.R.1 Efficacy" and "7.R.2 Safety," and of reviews in the subsections below, PMDA has concluded that the proposed indication of DAB and TRA and the proposed descriptions in the Precautions for Indications section are acceptable.

7.R.3.1 Clinical positioning and target patients of DAB/TRA treatment

Japanese and foreign clinical practice guidelines and leading clinical oncology textbooks show the following descriptions on DAB/TRA for the adjuvant treatment of patients with malignant melanoma with BRAF V600 mutations.

Clinical practice guidelines

- NCCN Guideline (v2. 2018):
  DAB/TRA is strongly recommended as one of options for the adjuvant treatment of patients with stage III malignant melanoma with BRAF V600 mutations with sentinel lymph node metastasis of >1 mm.
- US National Cancer Institute Physician Data Query (NCI PDQ) (accessed as of February 2, 2018):
  Study F2301 demonstrated the efficacy of DAB/TRA as an adjuvant therapy for stage III malignant melanoma with BRAF V600 mutations.

PMDA asked the applicant to explain the target patient population for DAB/TRA and the indication so as to further define patients with malignant melanoma with BRAF V600 mutations following complete resection.

The applicant's response:
Based on the results of Study F2301, DAB/TRA is recommended as an adjuvant therapy for the patient population investigated in the study, namely patients with high-risk malignant melanoma determined to be BRAF V600 mutation-positive using BioMérieux's THxID BRAF Assay.

Although it is presumable that adjuvant therapy may be administered to some patients with malignant melanoma in disease stages ineligible for enrollment in Study F2301, DAB/TRA should not be recommended to treat those patients because there are currently no clinical data that have demonstrated the clinical usefulness of DAB/TRA as an adjuvant therapy for such patients. However, given that DAB and TRA are used by physicians with sufficient knowledge and experience of cancer chemotherapy, it is not necessary to provide advice about the disease stage treatable with DAB/TRA in the Indications section. Instead, information on the disease stage of patients investigated in Study F2301 will be provided in the Clinical Studies section of the package insert, and the relevant precautionary statement will be included in the Precautions for Indications section.

On the above basis, the proposed indication for DAB and TRA was "malignant melanoma with *BRAF* mutations" in place of the approved indication "unresectable malignant melanoma with *BRAF* mutations." The Precautions for Indications section included the following descriptions:

- Dabrafenib (or trametinib) should be administered to patients who are confirmed to have *BRAF* mutations through tests performed by a well experienced pathologist or testing laboratory. An approved *in vitro* diagnostic, etc. should be used for the test.
- The physician should thoroughly understand the description in the "Clinical Studies" section and be fully aware of the efficacy and safety of dabrafenib (or trametinib) before identifying patients eligible for treatment with dabrafenib (or trametinib).

PMDA accepted the explanation of the applicant.

7.R.4 Dosage and administration

The proposed dosage and administration for DAB in combination with TRA for the treatment of malignant melanoma with BRAF V600 mutations are shown in the table below (underline denoting

additions to the dosage and administration statements approved for the treatment of malignant melanoma). The Precautions for Dosage and Administration statements for malignant melanoma with *BRAF* mutations included the descriptions shown in the table below.

	Dosage and Administration	Precautions for Dosage and Administration
DAB	The usual adult dosage is 150 mg of dabrafenib administered orally twice daily under fasted conditions. In adjuvant chemotherapy, dabrafenib is used in combination with trametinib. The dose may be adjusted according to the patient's condition.	• Postprandial administration of dabrafenib has been reported to result in decreased C_{max} and AUC. Dabrafenib should be taken at least 1 hour before and at least 2 hours after a meal to avoid food effect. • If adverse drug reactions are manageable by treatment interruption, dose reduction, discontinuation, or any other appropriate measures, dose re-escalation following the same steps as dose reduction may be considered.
TRA	The usual adult dosage is 2 mg of trametinib administered orally once daily under fasted conditions when used in combination with dabrafenib. The dose may be adjusted according to the patient's condition.	• Postprandial administration of trametinib has been reported to result in decreased C_{max} and AUC. Trametinib should be taken at least 1 hour before and at least 2 hours after a meal to avoid food effect. • If adverse drug reactions are manageable by treatment interruption, dose reduction, discontinuation, or any other appropriate measures, dose re-escalation following the same steps as dose reduction may be considered. • Since the bioequivalence of the 0.5-mg tablet and 2-mg tablet formulations has not been demonstrated, 0.5-mg tablets should not be used when 2 mg is administered.

Based on the considerations in Sections "7.R.1 Efficacy" and "7.R.2 Safety" and on reviews in sections below, PMDA has concluded that the Dosage and Administration and the Precautions for Indication sections for both DAB and TRA should be specified as shown in the table below (underline denoting additions to the Dosage and Administration statements approved for the treatment of malignant melanoma).

	Dosage and Administration	Precautions for Dosage and Administration
DAB	The usual adult dosage is 150 mg of dabrafenib administered orally twice daily under fasted conditions. In the adjuvant treatment setting, patients should be treated with dabrafenib in combination with trametinib for up to 12 months. The dose may be adjusted according to the patient's condition.	• Postprandial administration of dabrafenib has been reported to result in decreased C_{max} and AUC. Dabrafenib should be taken at least 1 hour before and at least 2 hours after a meal to avoid food effect. • If adverse drug reactions are manageable by treatment interruption, dose reduction, discontinuation, or any other appropriate measures, dose re-escalation following the same steps as dose reduction may be considered.
TRA	The usual adult dosage is 2 mg of trametinib administered orally once daily under fasted conditions when used in combination with dabrafenib. In the adjuvant treatment setting, patients should be treated with trametinib in combination with dabrafenib for up to 12 months. The dose may be adjusted according to the patient's condition.	• Postprandial administration of trametinib has been reported to result in decreased C_{max} and AUC. Trametinib should be taken at least 1 hour before and 2 hours after a meal to avoid food effect. • If adverse drug reactions are manageable by treatment interruption, dose reduction, discontinuation, or any other appropriate measures, dose re-escalation following the same steps as dose reduction may be considered. • Since the bioequivalence of the 0.5-mg tablet and 2-mg tablet formulations has not been demonstrated, 0.5-mg tablets should not be used when 2 mg is administered.

7.R.4.1 Dosage and administration of DAB and TRA

The applicant's explanation about the rationale for the proposed dosage and administration of DAB and TRA in patients with malignant melanoma with BRAF V600 mutations following complete resection:

On the basis of studies including foreign phase I studies in patients with advanced solid tumor (Studies BRF112680 and MEK111054) and the foreign phase I/II study in patients with unresectable malignant melanoma with BRAF V600 mutations (Study BRF113220) (see "Review Report on Tafinlar Capsules

50 mg and Tafinlar Capsules 75 mg, dated January 21, 2016" and "Review Report on Mekinist Tablets 0.5 mg and Mekinist Tablets 2 mg, dated January 21, 2016"), the dosage regimen of DAB and TRA used in Study F2301 was "Oral dose of DAB 150 mg BID and TRA 2 mg QD." The study demonstrated the clinical usefulness of DAB/TRA in patients with malignant melanoma with BRAF V600 mutations following complete resection.

On the other hand, the coadministration of DAB or TRA with other antineoplastic agents is not recommended because there are no clinical study data on the coadministration of DAB or TRA with other antineoplastic agents.

In Study F2301, treatment with DAB/TRA was to be continued for up to 12 months. Therefore, PMDA asked the applicant to explain whether the duration of treatment with DAB/TRA should be defined in the Dosage and Administration sections for DAB and TRA.

The applicant's response:
When Study F2301 was being planned, the combination treatment was given for 12 months in clinical studies for the adjuvant treatment of patients with malignant melanoma (e.g., Study E1684[5)]). For this and other reasons, a maximum duration of 12 months was selected for treatment with DAB/TRA. Although there are no data from clinical studies investigating >12-month treatment with DAB/TRA in patients with malignant melanoma in the adjuvant setting, limiting the treatment duration to a maximum of 12 months is unnecessary for the dosage and administration of DAB/TRA, for the following reasons:

- In the foreign phase III study (COMBI-D study) in patients with unresectable malignant melanoma with BRAF V600 mutations, patients receiving DAB/TRA for >12 months did not show any new safety concern compared with the safety profile in those receiving DAB/TRA for ≤12 months.
- The Clinical Studies section of the package insert will provide information to the effect that patients were treated with DAB/TRA for up to 12 months in Study F2301.

PMDA's view:
PMDA accepted the applicant's explanation about the proposed dosage and administration, i.e., oral dose of DAB 150 mg BID and TRA 2 mg QD. On the other hand, the duration of treatment with DAB/TRA should be clearly specified in the Dosage and Administration section, for the following reasons: (1) There are no clinical study data supporting the clinical usefulness of >12-month treatment with DAB/TRA, and (2) the radical surgery has a probability of cure in the target patient population of Study F2301 and therefore it should be avoided to continue the injudicious use of DAB/TRA in patients who have completed the 12-month adjuvant therapy.

5) A phase III study conducted to evaluate the efficacy and safety of high-dose versus low-dose interferon α-2b in patients with stage IIB or III malignant melanoma (*J Clin Oncol.* 2000;18:2444-58).

Based on the above, PMDA concluded that the dosage and administration of DAB and TRA should be specified as shown below.

DAB

The usual adult dosage is 150 mg of dabrafenib administered orally twice daily under fasted conditions. In the adjuvant treatment setting, patients should be treated with dabrafenib in combination with trametinib for up to 12 months. The dose may be adjusted according to the patient's condition.

TRA

The usual adult dosage is 2 mg of trametinib administered orally once daily under fasted conditions when used in combination with dabrafenib. In the adjuvant treatment setting, patients should be treated with trametinib in combination with dabrafenib for up to 12 months. The dose may be adjusted according to the patient's condition.

7.R.4.2 DAB and TRA dose adjustment

The applicant's explanation about DAB and TRA dose adjustment:

The protocol of Study F2301 specified the criteria for dose adjustment in case of adverse drug reactions. The criteria were the same as those used in foreign phase III studies (COMBI-D and COMBI-V studies) in patients with unresectable malignant melanoma with BRAF V600 mutations for which DAB/TRA has already been indicated. DAB/TRA was shown to be effective and safe when administered in accordance with the criteria. Based on the above, the Precautions for Dosage and Administration section of the package inserts of DAB and TRA will include the same criteria for dose adjustment as those for the treatment of unresectable malignant melanoma, the approved indication of DAB and TRA.

PMDA accepted the applicant's explanation.

7.R.5 Post-marketing investigations

The applicant's explanation:

There are no newly identified safety specifications, and it is therefore currently unnecessary to conduct a new post-marketing surveillance on the adjuvant treatment of patients with malignant melanoma immediately after the approval of the new indication. This decision is based on the following findings:

- There was no clear difference in the safety profile between treatment with DAB/TRA in Study F2301 and treatment with DAB/TRA for the approved indication [see Section 7.R.2.1].
- There were no safety concerns specific to Japanese patients in Study F2301 [see Section 7.R.2.1].

PMDA accepted the applicant's explanation.

7.2 Adverse events, etc., reported in the clinical study

Among the clinical study data submitted for safety evaluation, death is described in Section "7.1 Evaluation data," and main adverse events other than death are shown in the subsection below.

7.2.1 Multi-regional phase III study (Study F2301)

Adverse events were observed in 422 of 435 patients (97.0%) in the DAB/TRA group and 380 of 432 patients (88.0%) in the placebo group. Adverse events which were considered possibly causally related to the study drug were observed in 398 of 435 patients (91.5%) in the DAB/TRA group and 272 of 432 patients (63.0%) in the placebo group. Table 6 shows adverse events with an incidence of ≥15% in either group.

Table 6. Adverse events with an incidence of ≥15% in either group

System Organ Class Preferred Term (MedDRA ver. 19.1)	n (%)			
	DAB/TRA N = 435		Placebo N = 432	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	422 (97.0)	181 (41.6)	380 (88.0)	61 (14.1)
General disorders and administration site conditions				
Pyrexia	273 (62.8)	23 (5.3)	47 (10.9)	2 (0.5)
Fatigue	204 (46.9)	19 (4.4)	122 (28.2)	1 (0.2)
Chills	161 (37.0)	6 (1.4)	19 (4.4)	0
Influenza like illness	67 (15.4)	2 (0.5)	29 (6.7)	0
Skin and subcutaneous tissue disorders				
Rash	106 (24.4)	0	47 (10.9)	1 (0.2)
Gastrointestinal disorders				
Nausea	172 (39.5)	4 (0.9)	88 (20.4)	0
Diarrhoea	144 (33.1)	4 (0.9)	65 (15.0)	1 (0.2)
Vomiting	122 (28.0)	4 (0.9)	43 (10.0)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	120 (27.6)	4 (0.9)	61 (14.1)	0
Myalgia	70 (16.1)	1 (0.2)	40 (9.3)	0
Nervous system disorders				
Headache	170 (39.1)	6 (1.4)	102 (23.6)	0
Respiratory, thoracic and mediastinal disorders				
Cough	73 (16.8)	0	33 (7.6)	0
Investigations				
Alanine aminotransferase increased	67 (15.4)	16 (3.7)	6 (1.4)	1 (0.2)

Serious adverse events were observed in 155 of 435 patients (35.6%) in the DAB/TRA group and 44 of 432 patients (10.2%) in the placebo group. Serious adverse events reported by ≥10 patients in either group were pyrexia in 67 patients (15.4%) and chills and ejection fraction decreased in 13 patients (3.0%) each in the DAB/TRA group. The possibility of a causal relationship between the study drug and the following events could not be ruled out: pyrexia (66 patients), chills (13 patients), and ejection fraction decreased (13 patients).

Adverse events leading to discontinuation of the study drug were observed in 114 of 435 patients (26.2%) in the DAB/TRA group and 12 of 432 patients (2.8%) in the placebo group. Adverse events leading to treatment discontinuation reported by ≥10 patients in either group were pyrexia in 38 patients (8.7%) and chills in 16 patients (3.7%) in the DAB/TRA group. The possibility of a causal relationship between the study drug and the following events could not be ruled out: pyrexia (38 patients) and chills (16 patients).

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that DAB/TRA has efficacy in the adjuvant treatment of malignant melanoma with *BRAF* mutations, and that DAB/TRA has acceptable safety in view of its benefits. DAB/TRA is clinically meaningful because it offers a new option for the adjuvant treatment of malignant melanoma with *BRAF* mutations. The indications, dosage and administration, etc. should be further evaluated.

PMDA has concluded that DAB and TRA may be approved if the combination therapy is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

May 10, 2018

Product Submitted for Approval

[1]	**Brand Name**	Tafinlar Capsules 50 mg Tafinlar Capsules 75 mg
	Non-proprietary Name	Dabrafenib Mesilate
	Applicant	Novartis Pharma K.K.
	Date of Application	November 17, 2017
[2]	**Brand Name**	Mekinist Tablets 0.5 mg Mekinist Tablets 2 mg
	Non-proprietary Name	Trametinib Dimethyl Sulfoxide
	Applicant	Novartis Pharma K.K.
	Date of Application	November 17, 2017

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of its review in Section "7.R.1 Efficacy" of the Review Report (1), PMDA has concluded that the submitted data have demonstrated the efficacy of DAB/TRA in the target patient population of Study F2301. This conclusion is based on the data supporting the superiority of DAB/TRA to placebo in terms of the investigator-assessed RFS,[6)] the primary endpoint, in the multi-regional phase III study (Study F2301) conducted to evaluate the efficacy and safety of DAB/TRA versus placebo in patients with high-risk[7)] malignant melanoma with BRAF V600 mutations[8)] after surgical resection.[9)]

6) Defined as the period from the day of randomization until (a) loco-regional, distal metastasis, or secondary malignant melanoma or (b) death, whichever occurred earlier.
7) (a) Stage IIIA (metastatic lymph node >1 mm), (b) stage IIIB, and (iii) stage IIIC were defined as "risk of recurrence" (of recurrence).
8) Patients with malignant melanoma determined to be BRAF V600E or V600K mutation-positive using bioMérieux's THxID BRAF Assay (approved in Japan) at the central laboratory.
9) Patients who underwent complete resection of melanoma

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of its review in Section "7.R.2 Safety" in the Review Report (1), PMDA has concluded that adverse events requiring particular attention during adjuvant treatment with DAB/TRA for patients with malignant melanoma with BRAF V600 mutations are the same as adverse events identified as those requiring particular caution at the initial approval of the indication for unresectable malignant melanoma with BRAF V600 mutations (secondary malignancies, cardiac disorders, hepatic dysfunction, pyrexia, eye disorders, and rhabdomyolysis), and that caution should be exercised against the risk of these adverse events during treatment with DAB/TRA.

PMDA has also concluded that although attention should be paid to the risk of the above adverse events during adjuvant treatment with DAB/TRA, DAB/TRA is well tolerated in patients with malignant melanoma with BRAF V600 mutations following complete resection as well, provided that appropriate measures, such as the monitoring and management of adverse events and the adjustment of the doses of DAB or TRA, are taken by physicians with sufficient knowledge and experience of cancer chemotherapy.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indications

As a result of its review in Section "7.R.3 Clinical positioning and indication" of the Review Report (1), PMDA has concluded that it is acceptable to change the approved indication of DAB and TRA for malignant melanoma from "unresectable malignant melanoma with *BRAF* mutations" to "malignant melanoma with *BRAF* mutations." The Clinical Studies section of the package insert should include the information on the disease stage, etc., of patients investigated in Study F2301, and the Precautions for Indications section should include the following precautionary statements.

Precautions for Indications

- Dabrafenib (or trametinib) should be administered to patients who are confirmed to have *BRAF* mutations through tests performed by a well experienced pathologist or testing laboratory. An approved *in vitro* diagnostic, etc. should be used for the test.
- The physician should thoroughly understand the description in the "Clinical Studies" section and fully aware of the efficacy and safety of dabrafenib (or trametinib) before identifying patients eligible for treatment with dabrafenib (or trametinib).

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to modify the indication as above, and the applicant agreed to the instruction. Also, the applicant responded that the term "adjuvant chemotherapy" in the Precaution for Indications section for NSCLC would be changed to "adjuvant therapy" for consistency.

1.4 Dosage and administration

As a result of its review in Section "7.R.4 Dosage and administration" of the Review Report (1), PMDA concluded that the Dosage and Administration and the Precautions for Dosage and Administration statements for DAB and TRA should be modified as described in the table below (underline denoting additions to the approved dosage and administration for malignant melanoma).

	Dosage and Administration	Precautions for Dosage and Administration
DAB	The usual adult dosage is 150 mg of dabrafenib administered orally twice daily under fasted conditions. In the adjuvant treatment setting, patients should be treated with dabrafenib in combination with trametinib for up to 12 months. The dose may be adjusted according to the patient's condition.	• Postprandial administration of dabrafenib has been reported to result in decreased C_{max} and AUC. Dabrafenib should be taken at least 1 hour before and at least 2 hours after a meal to avoid food effect. • If adverse drug reactions are manageable by treatment interruption, dose reduction, discontinuation, or any other appropriate measures, dose re-escalation following the same steps as dose reduction may be considered.
TRA	The usual adult dosage is 2 mg of trametinib administered orally once daily under fasted conditions when used in combination with dabrafenib. In the adjuvant treatment setting, patients should be treated with trametinib in combination with dabrafenib for up to 12 months. The dose may be adjusted according to the patient's condition.	• Postprandial administration of trametinib has been reported to result in decreased C_{max} and AUC. Trametinib should be taken at least 1 hour before and at least 2 hours after a meal to avoid food effect. • If adverse drug reactions are manageable by treatment interruption, dose reduction, discontinuation, or any other appropriate measures, dose re-escalation following the same steps as dose reduction may be considered. • Since the bioequivalence of the 0.5-mg tablet and 2-mg tablet formulations has not been demonstrated, 0.5-mg tablets should not be used when 2 mg is administered.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to specify the Dosage and Administration and Precautions for Dosage and Administration sections as above, and the applicant agreed to the instruction.

1.5 Risk management plan (draft)

As a result of its review in Section "7.R.5 Post-marketing investigations" of the Review Report (1), PMDA has concluded that there is little need to immediately conduct a post-marketing surveillance on the adjuvant treatment with DAB/TRA for patients with malignant melanoma, and that it will suffice to collect safety information through usual pharmacovigilance activities.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

In view of the discussion above, PMDA has concluded that the current draft risk management plan should include the safety and efficacy specifications presented in Tables 7 and 9 and that the applicant should conduct additional pharmacovigilance activities, efficacy surveillance and studies, and additional risk minimization activities presented in Tables 8 and 10.

Table 7. Safety and efficacy specifications in the risk management plan for DAB (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Cutaneous squamous cell carcinoma • Secondary malignant marignancies other than cutaneous squamous cell carcinoma • Eye disorders • Pyrexia • Hepatic dysfunction • Cardiac disorders	• Testicular toxicity • QT/QTc interval prolongation • Pancreatitis • Cerebrovascular disorders (cerebral haemorrhage, cerebrovascular accident, etc.) • Deep vein thrombosis and pulmonary embolism	• Safety in patients with hepatic impairment
Efficacy specifications		
• Efficacy in patients with unresectable malignant melanoma with BRAF mutations in routine clinical practice		

No change made by the present partial change application.

Table 8. Summary of additional pharmacovigilance activities, efficacy surveillance and studies, and risk minimization activities included under the risk management plan for DAB (draft)

Additional pharmacovigilance activities	Efficacy surveillance and studies	Additional risk minimization activities
• Specified use-results survey in patients with unresectable malignant melanoma with *BRAF* mutations (all-case surveillance) • Specified use-results survey in patients with unresectable advanced or recurrent NSCLC with *BRAF* mutations (all-case surveillance) • Post-marketing clinical study (extension of Study F2301)	• Specified use-results survey in patients with unresectable malignant melanoma with *BRAF* mutations (all-case surveillance)	• Prepare and distribute materials for healthcare professionals. • Prepare and supply materials for patients.

Underlined parts: Activities to be conducted for the added indication

Table 9. Safety and efficacy specifications in the risk management plan for TRA (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Cardiac disorders • Eye disorders • Hepatic dysfunction • Rhabdomyolysis • Pyrexia	• Deep vein thrombosis and pulmonary embolism • Interstitial lung disease • Cerebrovascular disorders (cerebral haemorrhage, cerebrovascular accident, etc.) • Renal dysfunction • Decreased fertility • Effect on embryofetal development	• Safety in patients with hepatic impairment
Efficacy specifications		
• Efficacy in patients with unresectable malignant melanoma with *BRAF* mutations in routine clinical practice		

No change made by the present partial change application.

Table 10. Summary of additional pharmacovigilance activities, efficacy surveillance and studies, and risk minimization activities included under the risk management plan for TRA (draft)

Additional pharmacovigilance activities	Efficacy surveillance and studies	Additional risk minimization activities
• Specified use-results survey in patients with unresectable malignant melanoma with *BRAF* mutations (all-case surveillance) • Specified use-results survey in patients with unresectable advanced or recurrent NSCLC with *BRAF* mutations (all-case surveillance) • Post-marketing clinical study (extension of Study F2301)	• Specified use-results survey in patients with unresectable malignant melanoma with *BRAF* mutations (all-case surveillance)	• Prepare and distribute materials for healthcare professionals. • Prepare and supply materials for patients.

Underlined parts: Activities to be conducted for the added indication

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication as well as the dosage and administration as shown below, with the following condition of approval, on the premise that (1) the applicant ensures that healthcare professionals are fully aware of precautions provided in the package insert and are appropriately informed of the proper use of DAB and TRA in the post-marketing setting, and (2) the proper use of DAB and TRA is ensured under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions capable of dealing with emergencies appropriately. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until March 27, 2026 for both).

Tafinlar Capsules 50 mg, Tafinlar Capsules 75 mg

Indications (Strikethrough denotes deletion. Double-underline denotes additions made after submission of the present application [as of March 23, 2018].)

1. ~~Unresectable~~ Malignant melanoma with *BRAF* mutations
2. Unresectable advanced or recurrent non-small cell lung cancer with *BRAF* mutations

Dosage and Administration (Single underline denotes new additions. Double-underline denotes additions made after submission of the present application [as of March 23, 2018].)

Malignant melanoma

The usual adult dosage is 150 mg of dabrafenib administered orally twice daily under fasted conditions. In the adjuvant treatment setting, patients should be treated with dabrafenib in combination with trametinib for up to 12 months. The dose may be adjusted according to the patient's condition.

Non-small cell lung cancer

The usual adult dosage is 150 mg of dabrafenib administered orally twice daily under fasted conditions when used in combination with trametinib. The dose may be adjusted according to the patient's condition.

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Warnings (No change)

Dabrafenib should be administered only to patients, who are considered to be eligible for treatment with dabrafenib, under the supervision of a physician with sufficient knowledge and experience in cancer chemotherapy at a medical institution capable of appropriately responding to emergencies. Before initiating treatment with dabrafenib, the attending physician should fully explain the efficacy and risks of dabrafenib to the patient or his/her family, and should obtain informed consent from the patient or his/her family.

Contraindications (No change)

1. Patients with a history of hypersensitivity to any ingredient of dabrafenib
2. Pregnant women or women who may possibly be pregnant

Precautions for Indications (Single underline denotes new additions. Strikethrough denotes deletions. Double-underline denotes additions made after submission of the present application [as of March 23, 2018].)

1. Dabrafenib should be administered to patients who are confirmed to have *BRAF* mutation through tests performed by a well experienced pathologist or testing laboratory. An approved *in vitro* diagnostic, etc. should be used for the test.
2. The physician should thoroughly understand the description in the "Clinical Studies" section and be fully aware of the efficacy and safety of dabrafenib before identifying patients eligible for treatment with dabrafenib.
3. The efficacy and safety of dabrafenib as adjuvant ~~chemo~~therapy have not been established for the treatment of non-small cell lung cancer.

Precautions for Dosage and Administration (No change)

1. The efficacy and safety of dabrafenib in concomitant use with antineoplastic agents other than trametinib have not been established.
2. Postprandial administration of dabrafenib has been reported to result in decreased C_{max} and AUC. Dabrafenib should be taken at least 1 hour before and at least 2 hours after a meal to avoid food effect.
3. If an adverse drug reaction occurs during dabrafenib treatment, treatment should be interrupted, discontinued, or continued at a reduced dose by referring to the following criteria. Cutaneous squamous cell carcinoma (squamous cell carcinoma of the skin) or new primary malignant melanoma should be managed by surgical resection or other appropriate actions, and then dabrafenib may be continued without treatment interruption or dose reduction.

Criteria for interruption, dose reduction, and discontinuation

NCI-CTCAE[1)] Grade	Action
Intolerable Grade 2, or Grade 3	Interruption If improved to Grade ≤1, then resume therapy at the next lower dose level.
Grade 4	In principle, therapy should be discontinued. If deemed desirable for the patient, therapy may be resumed at the next lower dose level after improvement to Grade ≤1.

1) Grade assessed by NCI-CTCAE v4.0

Guide for dose adjustment

Dose level[2)]	Dabrafenib dose
Recommended dose	150 mg twice daily
First dose reduction	100 mg twice daily
Second dose reduction	75 mg twice daily
Third dose reduction	50 mg twice daily
Fourth dose reduction	Discontinue

2) If adverse drug reactions are manageable by appropriate measures, dose re-escalation following the same steps as dose reduction may be considered.

Mekinist Tablets 0.5 mg, Mekinist Tablets 2 mg

Indications (Strikethrough denotes deletion. Double-underline denotes additions made after submission of the present application [as of March 23, 2018].)

1. ~~Unresectable~~ Malignant melanoma with *BRAF* mutations
2. Unresectable advanced or recurrent non-small cell lung cancer with *BRAF* mutations

Dosage and administration (Underline denotes addition.)

The usual adult dosage is 2 mg of trametinib administered orally once daily under fasted conditions when used in combination with dabrafenib. In the adjuvant treatment setting, patients should be treated with trametinib in combination with dabrafenib for up to 12 months. The dose may be adjusted according to the patient's condition.

Conditions of approval

The applicant is required to develop and appropriately implement a risk management plan.

Warnings (No change)

Trametinib should be administered only to patients, who are confirmed to be eligible for treatment with trametinib, under the supervision of a physician with sufficient knowledge and experience in cancer chemotherapy at a medical institution capable of appropriately responding to emergencies. Before initiating treatment with trametinib, the attending physician should fully explain the efficacy and risks of trametinib to the patient or his/her family, and should obtain informed consent from the patient or his/her family.

Contraindications (No change)

Patients with a history of hypersensitivity to any ingredient of trametinib

Precautions for Indications (Single-underline denotes new additions. Strikethrough denotes deletions. Double-underline denotes additions made after submission of the present application [as of March 23, 2018].)

1. Trametinib should be administered to patients who are confirmed to have *BRAF* mutations through tests performed by a well experienced pathologist or testing laboratory. An approved *in vitro* diagnostic, etc. should be used for the test.
2. The physician should thoroughly understand the description in the "Clinical Studies" section and be fully aware of the efficacy and safety of trametinib before identifying patients eligible for treatment with trametinib.
3. The efficacy and safety of trametinib as adjuvant ~~chemo~~therapy have not been established for the treatment of non-small cell lung cancer.

Precautions for Dosage and Administration (Double-underline denotes additions made after submission of the present application [as of March 23, 2018].)

1. Postprandial administration of trametinib has been reported to result in decreased C_{max} and AUC. Trametinib should be taken at least 1 hour before and at least 2 hours after a meal to avoid food effect.
2. If an adverse drug reaction occurs during the trametinib treatment, treatment should be interrupted, discontinued, or continued at a reduced dose by referring to the following criteria. Cutaneous squamous cell carcinoma (squamous cell carcinoma of the skin) or new primary malignant melanoma should be managed by surgical resection or other appropriate actions, and then trametinib may be continued without treatment interruption or dose reduction.

Criteria for interruption, dose reduction, and discontinuation

NCI-CTCAE[1)] Grade	Action
Intolerable Grade 2, or Grade 3	Interruption If improved to Grade ≤1, then resume therapy at the next lower dose level.
Grade 4	In principle, therapy should be discontinued. If deemed desirable for the patient, therapy may be resumed at the next lower dose level after improvement to Grade ≤1.

1) Grade assessed by NCI-CTCAE v4.0

Guide for dose adjustment

Dose level[2)]	Trametinib dose
Recommended dose	2 mg once daily
First dose reduction	1.5 mg once daily
Second dose reduction	1 mg once daily
Third dose reduction	Discontinue

2) If adverse drug reactions are manageable by appropriate measures, dose re-escalation following the same steps as dose reduction may be considered.

3. Since the bioequivalence of the 0.5-mg tablet and 2-mg tablet formulations has not been demonstrated, 0.5-mg tablets should not be used when 2 mg is administered.

Appendix

List of Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	bis in die
BRAF gene	v-Raf murine sarcoma viral oncogene homolog B1 gene
BRAF V600 mutation	BRAF mutation that results in a substitution of valine amino acid to other amino acids at codon 600
BRAF V600E mutation	BRAF mutation that results in a substitution of valine amino acid to glutamic acid at codon 600
BRAF V600K mutation	BRAF mutation that results in a substitution of valine amino acid to lysine at codon 600
CI	confidence interval
COMBI-D study	Study MEK115306
COMBI-V study	Study MEK116513
DAB	Dabrafenib mesilate
DAB/TRA	Combination therapy with dabrafenib and trametinib
ERK	extracellular signal-regulated kinase
ITT	intention-to-treat
Japanese clinical practice guidelines	Evidence-based Clinical Practice Guidelines for Management of Skin Cancer, ver. 2, edited by the Japanese Skin Cancer Society
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase/extracellular signal-regulated kinase kinase
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Melanoma
NCI PDQ	National Cancer Institute Physician Data Query
NE	not estimated
NSCLC	non-small cell lung cancer
OS	overall survival
Partial change application	Application for partial changes in the approved application
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
QD	quaque die
RFS	relapse-free survival
Study E2201	Study DRB436E2201
Study F2301	Study DRB436F2301
TRA	Trametinib dimethyl sulfoxide