Report on the Deliberation Results

March 8, 2018
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

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	December 5, 2016

Results of Deliberation

In its meeting held on March 2, 2018, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since an extremely limited number of patients participated in the Japanese clinical study of the product The applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until data from a certain number of patients have been accumulated to identify the characteristics of patients treated with the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

February 13, 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
Applicant	Novartis Pharma K.K.
Date of Application	December 5, 2016
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)
Application Classification	Prescription drug, (4) Drugs with a new indication
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 389 of 2016 [*28 yaku*], PSEHB/PED Notification No. 0927-1 dated September 27, 2016, from the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health 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 unresectable advanced or recurrent non-small cell lung cancer 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. Cutaneous squamous cell carcinoma, secondary malignancies other than cutaneous squamous cell carcinoma, eye disorders, pyrexia, hepatic dysfunction, cardiac disorders, and rhabdomyolysis should be further investigated in the post-marketing surveillance.

Indications

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

(Underline denotes additions.)

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)

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since an extremely limited number of patients participated in the Japanese clinical studies of the product, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until data from a certain number of patients have been accumulated to identify the characteristics of patients treated with the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

Attachment

Review Report (1)

December 22, 2017

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 December 5, 2016

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 Indications

1. Unresectable malignant melanoma with *BRAF* mutations
2. Unresectable advanced or recurrent *BRAF V600* mutation-positive non-small cell lung cancer

(Underline denotes additions.)

Proposed Dosage and Administration

Malignant melanoma

The usual adult dosage is 150 mg of dabrafenib administered orally twice daily under fasted conditions. 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.

(Underline denotes additions.)

[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 December 5, 2016

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 Indications

1. Unresectable malignant melanoma with *BRAF* mutations
2. Unresectable advanced or recurrent *BRAF V600* mutation-positive non-small cell lung cancer

(Underline denotes additions.)

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)

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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 mutations (amino acid substitution for valine at coden 600) have been found in approximately 2% of patients with non-small cell lung cancer (NSCLC) (*J Clin Oncol.* 2011;29:3574-9, *Clin Cancer Res.* 2013;19:4532-40). BRAF V600 mutation causes constitutive activation of the BRAF 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 growth.

Dabrafenib mesilate (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 (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 in March 2016 for the indication of "unresectable malignant melanoma with *BRAF* mutations."

1.2 Development history, etc.

The clinical development program of DAB and TRA for the treatment of NSCLC was initiated outside Japan. The applicant conducted a multi-regional phase II study (Study E2201) in patients with NSCLC with BRAF V600E mutation (the substitution of glutamic acid for valine at codon 600) starting in August 2011.

In the US and the EU, applications for combination therapy with DAB and TRA were submitted in September 2016 and in July 2016, respectively, with the results of Study E2201 as the pivotal data. DAB and TRA were approved in the US in June 2017 for the following indications: "TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test," and "MEKINIST is indicated, in combination with dabrafenib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test." The 2 drug products were also approved in the EU in March 2017 for the following indications: "Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation," and "Trametinib in combination with dabrafenib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation."

As of November 2017, DAB and TRA are approved in 38 countries or regions for the treatment of NSCLC.

In Japan, patient enrollment in Study E2201 was started in December 2013.

The applicant has submitted a partial change application for DAB and TRA to add the indication and the dosage and administration for the treatment of NSCLC, based on the results of Study E2201 as the pivotal data.

DAB and TRA were designated as orphan drugs in September 2016, with the intended indication of "unresectable advanced or recurrent *BRAF* mutation-positive non-small cell lung cancer" (Orphan Drug Designation No. 389 and 390 of 2016 [28 *yaku*]).

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

The present application is intended to add a new indication and a new dosage. No new "data relating to quality" were not submitted.

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

3.1 Primary pharmacodynamics

3.1.1 Growth-suppressive effect against malignant tumor-derived cell lines (CTD 4.2.1.1-1)

Using human NSCLC-derived cell lines with *BRAF* mutations, the growth suppressive effect of DAB or TRA alone or coadministered DAB and TRA ("DAB/TRA") was investigated using viable cell-derived adenosine triphosphate (ATP) level as the index. Table 1 shows the IC_{50} values of DAB and TRA against each cell line. The combination index[1)] of DAB/TRA against human NSCLC-derived MV522 cell line was 0.89 ± 0.12, showing the synergistic effect[2)] of coadministered DAB and TRA.

Table 1. Growth-suppressive effect of DAB and TRA against human NSCLC-derived cell lines with *BRAF* mutations

Cell line	*BRAF* mutation	IC_{50} (nmol/L)			
		DAB	TRA	DAB/TRA	
				DAB[*1]	TRA[*2]
MV522	V600E	4.3 ± 1.5	1.3 ± 0.5	2.3 ± 0.2	0.2 ± 0.0
NCI-H1395	G469A	>10,000, >10,000	>1000, >1000	>10,000, >10,000	>1000, >1000
NCI-H1755	G469A	>10,000, >10,000	43, 75	114, 173	11, 17

Mean ± standard deviation (SD) (individual values for n = 2); n = 2 or 4; *1 IC_{50} of DAB when DAB and TRA were added at a molar ratio of 10:1; *2 IC_{50} of TRA when DAB and TRA were added at a molar ratio of 10:1.

Using MV522 cell line, the inhibitory effect of DAB against phosphorylation of MEK, ERK, and ribosomal protein S6 (S6), which are signal molecules in the downstream of mitogen-activated protein kinase (MAPK) pathway, was investigated by Western blotting. DAB inhibited the phosphorylation of MEK, ERK, and S6 in a concentration-dependent manner.

Using MV522 cell line, the apoptosis induction and cell cycle-arrest of DAB or TRA alone or DAB/TRA were investigated by Western blotting, using the expression levels of truncated poly (ADP-ribose) polymerase (PARP), p27, and cyclin D1 as indices. Compared with DAB or TRA alone, DAB/TRA enhanced apoptosis induction and cell cycle-arrest.

1) Calculated based on the method of Chou & Talalay (*Adv Enzyme Regul.* 1984;22:27-55).
2) The interaction was defined as synergistic if the combination index was <0.9.

3.R Outline of the review conducted by PMDA

Based on the growth-suppressive effect of DAB/TRA against malignant tumors with BRAF V600 mutations confirmed in the initial approval (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), on the data submitted in the present application, and on the reviews presented in sections below, PMDA concluded that DAB/TRA is expected to be effective in the treatment of NSCLC with BRAF V600 mutations.

3.R.1 Efficacy against NSCLC with BRAF V600 mutations

The applicant's explanation about the efficacy of DAB/TRA against NSCLC with BRAF V600 mutations:

In transgenic mice that were engineered to express BRAF V600E mutant in response to doxycycline-induced activation of Clara cell secretory protein (*CCSP*) gene promotor, lung cancer formation was observed within 16 weeks after doxycycline administration (*Cancer Res.* 2007;67:4933-9). This and other findings suggest that BRAF V600E mutation plays an important role (driver mutation) for carcinogenesis (transformation) of NSCLC with said mutation. Regarding the mechanism of the carcinogenesis (transformation) induced by BRAF V600E, the BRAF mutation constitutively activates MARK pathway, thereby inducing enhanced cell growth (*Science.* 2013;339:1546-58, etc.).

Given the mechanism of carcinogenesis induced by BRAF V600E mutation and the findings that each of DAB and TRA alone suppresses the growth of human NSCLC-derived cell lines with BRAF V600E mutation and coadministered DAB and TRA exhibited a synergistic effect [see Section 3.1.1], DAB/TRA is expected to be effective in the treatment of NSCLC with BRAF V600 mutations.

PMDA accepted the explanation of the applicant.

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

Pharmacokinetics (PK) of DAB and TRA was investigated using mice. Transporters for the metabolites of DAB were studied using biomaterials of human and animal origin.

4.1 Distribution

4.1.1 DAB

DAB (30 mg/kg once daily or quaque die [QD]) was administered orally for 22 days to female mice subcutaneously transplanted with human melanoma-derived A375P F11 cell line, and tissue distribution of DAB and its metabolites (M4 [carboxy-dabrafenib], M7 [hydroxy-dabrafenib], and M8 [demethy-dabrafenib]) was investigated on Day 22. Among DAB and its metabolites, M4 was detected at the highest level in all tissues examined. DAB, M4, M7, and M8 were distributed at high concentrations in the liver, kidney, and tumor, whereas DAB, M4, and M8 were barely detected in the lung and brain.

DAB (150 mg/kg QD) was administered orally for 14 days to male and female mice, and tissue distribution of DAB and its metabolites (M4, M7, and M8) was investigated on Day 14. In all tissues tested, DAB concentration was higher in males than in females, whereas no clear sex difference was observed in the concentrations of M4, M7, and M8.

4.2 Metabolism

4.2.1 DAB

A single dose of ^{14}C-labeled DAB (^{14}C-DAB, 100 mg/kg) was administered orally to male and female mice and to bile duct-cannulated male mice to analyze metabolites in plasma, liver, urine, feces, and bile.

In male and female mice, the radioactive compound detected predominantly in plasma at 30 minutes post-dose was unchanged DAB (which accounted for 38.0% and 42.5% of plasma radioactivity in males and females, respectively) and M4 (68.7% and 78.9%, respectively) at 24 hours post-dose. Similarly, the radioactive compound detected predominantly in the liver was unchanged DAB at 30 minutes post-dose and M4 at 24 hours post-dose. Predominant radioactive compounds detected in feces up to 48 hours post-dose were M4 (which accounted for 24.6% of the administered radioactivity in males and 29.5% of the administered radioactivity in females) and M8 (24.3% and 17.9%, respectively). In urine collected up to 24 hours post-dose, M4 (1.63% and 1.64%, respectively) was predominantly detected, whereas unchanged DAB was not detected.

In bile duct-cannulated male mice, M4 (52.5% of the administered radioactivity) was predominantly detected in the bile during 48 hours post-dose (during 24 hours post-dose in 2 of 6 animals, during 72 hours post-dose in 1 animal), whereas unchanged DAB was not detected.

4.2.2 TRA

A single dose of ^{14}C-labeled TRA (^{14}C-TRA 0.3 mg/kg) was administered orally to male and female mice, and metabolites in plasma and feces were investigated. The radioactive compound detected predominantly in plasma was unchanged TRA. From 2 to 24 hours post-dose, unchanged TRA accounted for 73.1% to 90.3% of plasma radioactivity in males and 61.8% to 89.6% of plasma radioactivity in females. In the plasma of both males and females, M5 (deacetylation of trametinib) and M7 (oxygenation of M5) were detected as metabolites of TRA. In feces collected up to 120 hours post-dose, the unchanged TRA (percentage relative to the administered radioactivity, 63.3% in males and 47.6% in females) was predominantly detected, together with its metabolites M5 and M7.

4.3 Pharmacokinetic interactions

4.3.1 DAB

Results of the following studies showed that M7 and M8 are substrates for breast cancer resistance protein (BCRP) but not for either organic cation transporter (OCT)1 or organic anion transporter polypeptide (OATP)2B1, and that M4 is not a substrate for BCRP:

- BCRP-mediated transport of M4, M7, and M8 (5 μmol/L) was investigated using dog kidney-derived MDCKII cell line expressing human BCRP. The ratio of permeability coefficient in the direction of secretion to that in the direction of absorption (efflux ratio) of M4, M7, and M8 was 1.1, 1.3, and 1.3, respectively, in the presence of a BCRP inhibitor (GF120918 2 μmol/L) and 0.70, 13, and 6.6, respectively, in the absence of the inhibitor.

- OCT1-mediated transport of M7 (0.35 μmol/L) and M8 (0.06 μmol/L) was investigated using human liver cells. Intracellular uptake of M7 and M8 was not inhibited by an OCT1 inhibitor (imipramine 100 μmol/L).
- OATP2B1-mediated transport of M7 and M8 (1 μmol/L) was investigated using human fetal kidney-derived HEK-MSRII cell line expressing human OATP2B1. Intracellular uptake of M7 and M8 was not inhibited by an OATP2B1 inhibitor (montelukast 10 μmol/L).

4.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the discussions of the applicant regarding the distribution, metabolism, and pharmacokinetic interactions of DAB and TRA are acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application is intended to add a new indication and a new dosage. No new "data relating to toxicity" were not submitted.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

6.1.1 Analytical methods

To identify BRAF V600E mutation in Study E2201, genetic testing methods were selected arbitrarily at each study site. The marketing application for "Oncomine Dx Target Test Multi-CDx System" manufactured by Life Technologies Japan, Ltd. was submitted on May 29, 2017 as a companion diagnostic, etc. The companion diagnostic is intended to identify patients with NSCLC who may benefit from treatment with DAB/TRA.

6.2 Clinical pharmacology

PK of DAB in patients with cancer was investigated following the administration of DAB alone, DAB/TRA, and DAB/rabeprazole sodium (rabeprazole) or DAB/rifampicin. The effect of DAB on the PK of rosuvastatin potassium (rosuvastatin), etc., was also investigated.

PK of TRA in patients with cancer was investigated following the administration of DAB/TRA.

6.2.1 Drug-drug interactions

6.2.1.1 Drug-drug interactions between DAB and rabeprazole or rifampicin (CTD 5.3.3.4-1, Study A2103 [December 2013 to March 2016])

An open-label, uncontrolled study was conducted in 23 patients with advanced solid cancer with BRAF V600 mutations (17 patients included in PK analysis) to investigate the effect of rabeprazole (proton pump inhibitor) or rifampicin (inducer of CYP3A and CYP2C8) on the PK of DAB. The patients were to orally receive DAB (150 mg bis in die [BID]) from Day 1 to Day 29, rabeprazole (40 mg QD) on Day 16 to Day 19, and rifampicin (600 mg QD) from Day 20 to Day 29.

The geometric least-squares mean ratios [90% confidence interval (CI)] of C_{max} and AUC_{tau} of DAB following the administration of DAB/rabeprazole (Day 19) to those following the administration of

DAB alone (Day 15) were 0.88 [0.67, 1.15] and 1.03 [0.87, 1.23], respectively. The geometric least-squares mean ratios [90% CI] of C_{max} and AUC_{tau} of DAB following the administration of DAB/rifampicin (Day 29) to those following the administration of DAB alone (Day 15) were 0.73 [0.55, 0.97] and 0.66 [0.55, 0.78], respectively.

The applicant's explanation, based on the above results:
Since combination of a proton pump inhibitor, etc., with DAB is unlikely to cause pharmacokinetic interaction, it is unnecessary to draw attention to interaction between DAB and drugs affecting intragastric pH, such as proton pump inhibitors. On the other hand, combination of DAB with an inducer of CYP3A and CYP2C8 decreased the exposure to DAB, warranting precautions against combination of DAB with an inducer of CYP3A or CYP2C8.

6.2.1.2 Interaction between DAB and rosuvastatin or midazolam (CTD 5.3.3.4-2, Study A2104 [March 2015 to August 2016])

An open-label, uncontrolled study was conducted in 16 patients with advanced cancer with BRAF V600 mutations (16 patients included in PK analysis) to investigate the effect of DAB on the PK of rosuvastatin (substrate of OATP1B1 and OATP1B3) and midazolam (substrate of CYP3A). The patients were to orally receive rosuvastatin (10 mg) and midazolam (3 mg) on Days 1, 8, and 22, and DAB (150 mg BID) from Day 8 to Day 23. Since the results of the study on the effect of DAB on the PK of midazolam were similar to those evaluated in the initial approval of DAB, the description is omitted (see Review Report on Tafinlar Capsules 50 mg and Tafinlar Capsules 75 mg, dated January 21, 2016).

The geometric least-squares mean ratios [90% CI] of C_{max} and AUC_{inf} of rosuvastatin following the administration of DAB/rosuvastatin (Day 8) to those following the administration of rosuvastatin alone (Day 1) were 1.94 [1.65, 2.27] and 1.22 [1.07, 1.38], respectively. The geometric least-squares mean ratios [90% CI] of C_{max} and AUC_{inf} of rosuvastatin following the administration of DAB/rosuvastatin (Day 22) to those following the administration of rosuvastatin alone (Day 1) were 2.56 [2.18, 3.01] and 1.07 [0.93, 1.22], respectively.

Based on the above, the applicant explained that caution is necessary in combination of DAB with substrates of OATP1B1 or OATP1B3 because such combination therapy increased the exposure to the substrates of OATP1B1 and OATP1B3.

6.2.2 Relationship between exposure and efficacy or safety

6.2.2.1 Relationship between exposure and efficacy

The relationship between the response rate and average plasma concentration (C_{avg})[3)] of DAB and TRA during 6 weeks before the assessment of the response rate was investigated by logistic regression

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3) Estimates based on population pharmacokinetics (PPK) analysis (software, NONMEM Version 7.3.0) conducted using PK data of DAB (536 plasma concentration data from146 patients) and TRA (255 plasma concentration data from 71 patients) obtained from Cohorts A, B, and C of the multi-regional phase II study (Study E2201). The analysis was performed using the following models (a) and (b) for DAB and TRA, respectively:
(a) Two-compartment model with first-order absorption process and delayed absorption constructed using the PK data of patients with malignant melanoma (see Review Report on Tafinlar Capsules 50 mg and Tafinlar Capsules 75 mg, dated January 21, 2016).
(b) Two-compartment model with biphasic first order absorption process reconstructed by the pooled PK data of patients with malignant melanoma and patients of NSCLC, with the effect of between-study difference incorporated into CL/F and Vc/F.

analysis based on the results with Cohorts A and B in Study E2201. Results showed no clear relationship between the response rate and C_{avg} of DAB in Cohort A or B, or between the response rate and C_{avg} of TRA in Cohort B.

6.2.2.2 Relationship between exposure and safety

Data from previous studies suggested that the incidence of pyrexia increased with increase in the exposure to DAB and TRA in patients with malignant melanoma (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). Therefore, the relationship between the time to onset of pyrexia and the C_{max}[3)] of DAB and TRA before the onset of pyrexia was investigated by Cox proportional hazard regression analysis based on the results with Cohorts A, B, and C of Study E2201. Results showed no relationship between the time to onset of pyrexia and the C_{max} of DAB in Cohort A, B, or C, or C_{max} of TRA in Cohort B or C.

6.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the explanation of the applicant regarding the PK of DAB and TRA is acceptable.

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

The applicant submitted the efficacy and safety evaluation data, in the form of data from a multi-regional phase II study shown in Table 2. Also, the applicant submitted data from 2 foreign phase I studies shown in Table 2 as reference data.

Table 2. List of clinical studies on efficacy and safety

Data category	Region	Study	Phase	Study population	No. of patients	Dosage regimen	Main endpoints
Evaluation	Multi-regional	E2201	II	Cohorts A and B: Patients with NSCLC with BRAF V600E mutation who had a history of platinum-based chemotherapy Cohort C: Patients with NSCLC with BRAF V600E mutation who had no history of chemotherapy	Cohort A: 84 Cohort B: 59 Cohort C: 34	Cohort A: Oral dose of DAB 150 mg BID Cohorts B and C: Oral dose of DAB 150 mg BID and TRA 2 mg QD	Efficacy Safety
Reference	Foreign	A2103	I	Patients with advanced solid tumor with BRAF V600 mutations	23	Oral dose of DAB 150 mg BID on Day 1 to Day 29 and oral dose of rabeprazole 40 mg QD from Day 16 to Day 19, followed by oral dose of rifampicin 600 mg QD from Day 20 to Day 29	PK
		A2104	I	Patients with advanced cancer with BRAF V600 mutations	16	Oral dose of rosuvastatin 10 mg and midazolam 3 mg on Days 1, 8, and 22, and oral dose of DAB 150 mg BID from Day 8 to Day 23	PK

The outline of each clinical study was described below. Major adverse events other than death reported in each clinical study are described in Section "7.3 Adverse events, etc., observed in clinical studies," and PK-related results in Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Multi-regional clinical study

7.1.1.1 Multi-regional phase II study (CTD 5.3.5.2, Study E2201 [ongoing since August 2011 (data cut-off date: April 30, 2014 [Cohort A], October 7, 2015 [Cohort B], [redacted] [redacted], [redacted] [Cohort C])])

An open-label, uncontrolled study was conducted in 69 sites in 11 countries including Japan. The study enrolled patients with advanced or recurrent NSCLC with BRAF V600E mutation[4] without a history of chemotherapy or with a history of platinum-based chemotherapy (target sample size, 60 subjects in Cohort A,[5] 40 subjects in Cohort B, 25 subjects in Cohort C). The objective of the study in each cohort was as follows:

Cohort A: To investigate the efficacy and safety of DAB monotherapy in patients with a history of platinum-based chemotherapy

Cohort B: To investigate the efficacy and safety of DAB/TRA in patients with a history of platinum-based chemotherapy

4) Tested at laboratories certified by Clinical Laboratory Improvement Amendments (CLIA) of the US or their equivalents.

5) The target sample size was changed from 40 to 60 in order to assess the response rate at a higher precision (protocol amendment, ver. [redacted] [dated April 16, 2013]).

Cohort C: To investigate the efficacy and safety of DAB/TRA in patients without a history of chemotherapy

Patients were to orally receive DAB (150 mg BID) in Cohort A and DAB (150 mg BID) and TRA (2 mg QD) in Cohorts B and C until they showed disease progression or met any of the discontinuation criteria. Patients in Cohort A were allowed to receive DAB (150 mg BID) and TRA (2 mg QD) only if they showed disease progression and tolerance to DAB monotherapy.

All of 177 patients enrolled in the study (84 in Cohort A, 59 in Cohort B, and 34 in Cohort C) were included in the efficacy analysis population. All of these patients received the study drug and were included in the safety analysis population.

Patients without a history of chemotherapy ("treatment-naïve patients") were also allowed to be enrolled in Cohort A with the increase in the target sample size (protocol amendment, version [redacted] [dated April 16, 2013]) and as a result, 6 treatment-naïve patients were enrolled. However, the efficacy analysis population included only patients with a history of platinum-based chemotherapy according to the original protocol. The above 6 treatment-naïve patients were excluded from analysis, and 78 patients were included in the efficacy analysis. Cohort B included 2 treatment-naïve patients, who were evaluated for efficacy and safety in Cohort C. Consequently, 57 patients were evaluated for efficacy and safety in Cohort B and 36 patients in Cohort C.

As for efficacy, Table 3 shows the response rate[6)] assessed by the investigator based on Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1, the primary endpoint. Efficacy assessment was performed based on the method stipulated by the study protocol.[7)] In Cohorts A and B (40 each of patients initially enrolled), the response was observed in 15 and 27 patients, respectively, while 16 patients in Cohort C (25 patients initially enrolled). The results exceeded the pre-determined efficacy criterion in all cohorts.

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6) The threshold response rate in Cohorts A, B, and C was 10%, 30%, and 30%, respectively, for the following reasons:
Cohort A: Referring to the design of the clinical study of pemetrexed sodium hydrate, etc., in patients with advanced or recurrent NSCLC with a history of chemotherapy (*J Clin Oncol.* 2004;22:1589-97, etc.).
Cohort B: Expectation of the response rate exceeding the expected response rate (30%) in Cohort A.
Cohort C: Referring to the design of the clinical study on platinum-based chemotherapy in patients with advanced or recurrent NSCLC without a history of chemotherapy (*N Engl J Med.* 2006;355:2542-50, etc.)

7) The efficacy assessment method stipulated in the study protocol was as follows:
Cohort A: A 2-stage design was adopted. In stage 1, 20 patients were enrolled and, if response was observed in ≥3 patients, the study was to proceed to stage 2. In stage 2, patients were to be added up to a total of 40 and, if response was observed in ≥8 patients, the treatment was considered to be effective. This design corresponds to evaluation at a significance level of 3.8% (one-sided).
Cohort B: A 2-stage design was adopted. In stage 1, 20 patients were enrolled and, if response was observed in ≥6 patients, the study was to proceed to stage 2. In stage 2, patients were to be added up to a total of 40 and, if response was observed in ≥18 patients, the treatment was considered to be effective. This design corresponds to evaluation at a significance level of 3.2% (one-sided).
Cohort C: If response was observed in ≥12 of 25 patients based on the binominal test at significance level of 5% (one-sided), the treatment was considered to be effective.

Table 3. Best overall response and response rate (RECIST ver. 1.1, efficacy analysis population, assessed by investigator; data cut-off date: April 30, 2014 [Cohort A], October 7, 2015 [Cohort B], [redacted], [redacted] [Cohort C])

Best overall response	Number of patients (%)				
	Overall population			Japanese population[*1]	
	Cohort A (N = 78)	Cohort B (N = 57)	Cohort C (N = 36)	Cohort A (N = 2)	Cohort B (N = 1)
CR	0	2 (3.5)	2 (5.6)	0	0
PR	25 (32.1)	34 (59.6)	20 (55.6)	2 (100)	0
SD	19 (24.4)	9 (15.8)	5 (13.9)	0	0
PD	23 (29.5)	7 (12.3)	5 (13.9)	0	0
NE	11 (14.1)	5 (8.8)	4 (11.1)	0	1 (100)
Response (CR + PR) (Response rate [95% CI[*2]] [%])	25 (32.1 [21.9, 43.6])	36 (63.2 [49.3, 75.6])	22 (61.1 [43.5, 76.9])	2 (100 [15.8, 100.0])	0 (0 [0.0, 97.5])

*[1] No Japanese patients were enrolled in Cohort C; *[2] Clopper-Pearson method

As for safety, death occurred in 30 of 177 patients (16.9%) during the treatment period or within 30 days after the study treatment. The causes of death other than disease progression (13 patients in Cohort A, 6 patients in Cohort B, 3 patients in Cohort C) were euthanasia in 2 patients and intracranial haemorrhage and unknown cause in 1 patient each in Cohort A, retroperitoneal haemorrhage, lung infection, and subarachnoid haemorrhage in 1 patient each in Cohort B, and cardiac arrest in 1 patient in Cohort C. A causal relationship to the study drug could not be ruled out for intracranial haemorrhage in 1 patient in Cohort A.

7.2 Reference data

7.2.1 Clinical pharmacology

The applicant submitted the data of 2 clinical pharmacology studies in patients with advanced cancer with BRAF V600 mutations [see Section 6.2]. Death occurred in 1 patient in Study A2103 during the treatment period or within 28 days after the study treatment. The death was caused by disease progression, and its causal relationship to the study drug was ruled out.

7.2.1.1 Foreign phase I study (CTD 5.3.3.4-1, Study A2103 [December 2013 to March 2016])

7.2.1.2 Foreign phase I study (CTD 5.3.3.4-2, Study A2104 [March 2015 to August 2016])

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

On the basis of the following review, PMDA has concluded that a certain level of effectiveness of DAB/TRA is demonstrated in patients with advanced or recurrent NSCLC with BRAF V600E mutation.

7.R.1.1 Primary efficacy endpoint and efficacy evaluation

The applicant's explanation about the primary endpoint in Study E2201 and the efficacy of DAB/TRA in patients with advanced or recurrent NSCLC with BRAF V600E mutation:

Among patients with advanced or recurrent NSCLC with BRAF V600E mutation, patients showing response are expected to achieve improvement in clinical symptoms associated with disease progression (e.g., *J Thorac Oncol.* 2008;3:30-6, *JAMA.* 2003;290:2149-58), suggesting the clinical significance of the response. Therefore, the response rate was used as the primary endpoint in Study E2201.

As a result, the lower limit of 95% CI of the response rate (61.1% [43.5%, 76.9%]) in patients on DAB/TRA in Cohort C of Study E2201 exceeded the threshold response rate which was pre-determined based on the response rate in the standard first-line treatment for patients with advanced or recurrent NSCLC. Also, the lower limit of the 95% CI of the response rate (63.2% [49.3%, 75.6%]) in patients on DAB/TRA in Cohort B of Study E2201 exceeded the threshold response rate which was pre-determined based on the response rate in the standard second-line and subsequent treatments in patients with advanced or recurrent NSCLC and on the expected response rate in patients on DAB monotherapy in Cohort A [see Section 7.1.1.1]. Furthermore, the response rate [95% CI] in the first-line treatment and in the second-line and subsequent treatments, assessed by the independent diagnostic imaging center as a sensitivity analysis, was 61.1% [43.5%, 76.9%] and 63.2% [49.3%, 75.6%], respectively, supporting the response rate assessed by the investigator.

Taking account of the above results and the following findings, DAB/TRA is expected to be effective in patients with advanced or recurrent NSCLC with BRAF V600E mutation:

- In NSCLC with BRAF V600E mutation, the mutated BRAF gene is considered to be an important causative gene (driver mutation) for NSCLC [see Section 3.R.1].
- The response to DAB/TRA observed in Study E2201 was higher than the response to DAB monotherapy, and the response was considered to be clinically significant.

Because of the extremely limited number of patients with advanced or recurrent NSCLC with BRAF V600E mutation, only 3 Japanese patients were enrolled in Study E2201 (among them, 1 in Cohort B and 0 in Cohort C received DAB/TRA), and none of them showed a response to DAB/TRA. Nevertheless, the applicant explained that DAB/TRA is expected to be effective in Japanese patients with advanced or recurrent NSCLC with BRAF V600E mutation as well, for the following reasons:

- PKs of DAB and TRA following the administration of DAB/TRA did not show any clear difference between Japanese subjects and non-Japanese subjects (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).
- There is no clear difference in the efficacy of DAB/TRA against malignant melanoma with *BRAF* mutations between Japanese and non-Japanese patients (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).
- In NSCLC with BRAF V600E mutation, the mutation is considered to be the driver mutation [see Section 3.R.1]. In such a malignant tumor, whether or not an antineoplastic agent targets the driver mutation significantly affects the treatment effect. Also, there is no racial/ethnic difference in the efficacy of antineoplastic agents.

PMDA's view:

The true endpoint in patients with advanced or recurrent NSCLC with BRAF V600E mutation is overall survival (OS), but the relationship between response and OS is unclear. Therefore, the life-prolonging effect of DAB/TRA in these patients cannot be evaluated based on the results of the primary endpoint of Study E2201. However, the above explanation of the applicant on the efficacy of DAB/TRA is understandable. Taking account of the following findings as well, DAB/TRA showed a certain level of

efficacy in patients with advanced or recurrent NSCLC with BRAF V600E mutation, including Japanese patients, as judged from the response rate, etc., in Study E2201:

- Results obtained from Cohort A of Study E2201 showed that DAB monotherapy led to partial response (PR) in 2 Japanese patients with NSCLC with BRAF V600E mutation.
- There is no clear difference in the treatment algorithm for NSCLC, including advanced or recurrent NSCLC with BRAF V600E mutation, recommended in and outside Japan.

7.R.2 Safety [for adverse events, see Section "7.3 Adverse events, etc., observed in clinical studies"]

As a result of the following reviews, PMDA has concluded that adverse events requiring particular attention in administering DAB/TRA to patients with advanced or recurrent NSCLC with BRAF V600 mutations are the same as those for which caution was required at the approval of DAB and TRA in patients with unresectable malignant melanoma with *BRAF* 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 in treatment with DAB/TRA.

PMDA also concluded that although caution should be exercised against the risk of the above adverse events during treatment with DAB/TRA, DAB/TRA is well tolerated in patients with advanced or recurrent NSCLC with BRAF V600 mutations provided that appropriate measures, such as monitoring and management of adverse events and modification of the doses of DAB or TRA, are taken by physicians with adequate knowledge and experience of cancer chemotherapy.

7.R.2.1 Safety profile of DAB/TRA and difference between Japanese and non-Japanese patients

The applicant's explanation about the safety profile of DAB/TRA based on the safety information of DAB/TRA obtained from Study E2201:

Tables 4 shows the summary of safety data from Cohort B and Cohort C in Study E2201 and Table 5 shows adverse events reported by ≥15% of patients in either cohort.

Table 4. Summary of safety (Study E2201)

	Number of patients (%)	
	Cohort B (N = 57)	Cohort C (N = 36)
All adverse events	56 (98.2)	36 (100)
Grade ≥3 adverse events	40 (70.2)	21 (58.3)
Adverse events leading to death	4 (7.0)	1 (2.8)
Serious adverse events	35 (61.4)	21 (58.3)
Adverse events leading to treatment discontinuation	12 (21.1)	7 (19.4)
DAB	11 (19.3)	7 (19.4)
TRA	12 (21.1)	7 (19.4)
Adverse events leading to dose reduction	22 (38.6)	11 (30.6)
DAB	22 (38.6)	11 (30.6)
TRA	19 (33.3)	10 (27.8)
Adverse events leading to treatment interruption	37 (64.9)	25 (69.4)
DAB	37 (64.9)	24 (66.7)
TRA	33 (57.9)	22 (61.1)

Table 5. Adverse events reported by ≥15% of patients in either cohort (Study E2201)

System organ class Preferred term (MedDRA/J ver. 19.0)	Number of patients (%)			
	Cohort B (N = 57)		Cohort C (N = 36)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	56 (98.2)	40 (70.2)	36 (100)	21 (58.3)
General disorders and administration site conditions				
Pyrexia	28 (49.1)	1 (1.8)	23 (63.9)	4 (11.1)
Asthenia	20 (35.1)	2 (3.5)	4 (11.1)	1 (2.8)
Oedema peripheral	20 (35.1)	0	12 (33.3)	0
Chills	13 (22.8)	1 (1.8)	9 (25.0)	0
Chest pain	10 (17.5)	0	1 (2.8)	0
Fatigue	10 (17.5)	2 (3.5)	11 (30.6)	0
Gastrointestinal disorders				
Nausea	24 (42.1)	0	19 (52.8)	0
Vomiting	23 (40.4)	0	11 (30.6)	3 (8.3)
Diarrhoea	18 (31.6)	1 (1.8)	13 (36.1)	1 (2.8)
Constipation	10 (17.5)	0	5 (13.9)	0
Skin and subcutaneous tissue disorders				
Dry skin	19 (33.3)	1 (1.8)	11 (30.6)	0
Rash	13 (22.8)	0	7 (19.4)	1 (2.8)
Pruritus	9 (15.8)	0	4 (11.1)	1 (2.8)
Respiratory, thoracic and mediastinal disorders				
Cough	15 (26.3)	0	6 (16.7)	0
Dyspnoea	13 (22.8)	3 (5.3)	6 (16.7)	2 (5.6)
Musculoskeletal and connective tissue disorders				
Arthralgia	12 (21.1)	0	3 (8.3)	0
Investigations				
Blood alkaline phosphatase increased	10 (17.5)	0	1 (2.8)	0
Metabolism and nutrition disorders				
Decreased appetite	17 (29.8)	0	9 (25.0)	0
Hyponatraemia	9 (15.8)	7 (12.3)	4 (11.1)	1 (2.8)
Nervous system disorders				
Headache	8 (14.0)	0	7 (19.4)	0
Blood and lymphatic system disorders				
Neutropenia	12 (21.1)	6 (10.5)	1 (2.8)	1 (2.8)
Anaemia	11 (19.3)	3 (5.3)	4 (11.1)	1 (2.8)
Vascular disorders				
Hypotension	8 (14.0)	1 (1.8)	6 (16.7)	2 (5.6)

In Cohort B of Study E2201, serious adverse events reported by ≥3% patients were pyrexia in 9 patients (15.8%), ejection fraction decreased in 4 patients (7.0%), anaemia and nausea in 3 patients (5.3%) each, and back pain, confusional state, decreased appetite, haemoptysis, hypercalcaemia, hypotension, lung infection, renal failure, respiratory distress, squamous cell carcinoma of skin, tubulointerstitial nephritis, and vomiting in 2 patients (3.5%) each. Adverse events leading to treatment discontinuation reported by ≥3% of patients were ejection fraction decreased and respiratory distress in 2 patients (3.5%) each. Adverse events leading to dose reduction with an incidence of ≥3% were pyrexia in 8 patients (14.0%), diarrhoea in 3 patients (5.3%), and blood creatinine increased, chills, decreased appetite, nausea, neutropenia, tubulointerstitial nephritis, and vomiting in 2 patients (3.5%) each. Adverse events leading to treatment interruption reported by ≥3% patients were pyrexia in 14 patients (24.6%), vomiting in 8 patients (14.0%), chills and neutropenia in 6 patients (10.5%) each, ejection fraction decreased and nausea in 4 patients (7.0%) each, blood creatinine increased and renal failure in 3 patients (5.3%) each, and anaemia, asthenia, confusional state, decreased appetite, diarrhoea, fatigue, hypotension, lung infection, malaise, and tubulointerstitial nephritis in 2 patients (3.5%) each.

In Cohort C of Study E2201, serious adverse events with an incidence of ≥3% were alanine aminotransferase (ALT) increased and pyrexia in 4 patients (11.1%) each, aspartate aminotransferase (AST) increased and ejection fraction decreased in 3 patients (8.3%) each, and hypotension and vomiting in 2 patients (5.6%) each. The adverse events leading to treatment discontinuation reported by ≥3% patients were pyrexia in 2 patients (5.6%). Adverse events leading to dose reduction reported by ≥3% patients were pyrexia in 3 patients (8.3%) and abdominal pain, nausea, and vomiting in 2 patients (5.6%) each. Adverse events leading to treatment interruption reported by ≥3% of patients were pyrexia in 12 patients (33.3%), vomiting in 5 patients (13.9%), abdominal pain, ALT increased, and nausea in 3 patients (8.3%) each, and AST increased, diarrhoea, ejection fraction decreased, and malaise in 2 patients (5.6%) each.

The applicant's explanation about the difference in the safety profile of DAB/TRA between patients with advanced or recurrent NSCLC with BRAF V600 mutations and patients with unresectable malignant melanoma with *BRAF* mutations, the disease for which DAB/TRA has already been indicated: Regarding the adverse events observed in patients receiving DAB/TRA in Study E2201, their incidences were compared with those in patients with unresectable malignant melanoma with *BRAF* mutations in foreign phase III studies (Study MEK115306 [COMBI-D study], Study MEK116513 [COMBI-V study]) (Table 6).

Table 6. Summary of safety in patients with NSCLC and patients with malignant melanoma

	Number of patients (%)	
	Patients with NSCLC N = 93	Patients with malignant melanoma N = 559
All adverse events	92 (98.9)	548 (98.0)
Grade ≥3 adverse events	61 (65.6)	321 (57.4)
Adverse events leading to death	5 (5.4)	10 (1.8)
Serious adverse events	56 (60.2)	259 (46.3)
Adverse events leading to treatment discontinuation	19 (20.4)	88 (15.7)
DAB	18 (19.4)	76 (13.6)
TRA	19 (20.4)	76 (13.6)
Adverse events leading to treatment interruption	62 (66.7)	335 (59.9)
DAB	61 (65.6)	330 (59.0)
TRA	55 (59.1)	280 (50.1)
Adverse events leading to dose reduction	33 (35.5)	189 (33.8)
DAB	33 (35.5)	172 (30.8)
TRA	29 (31.2)	127 (22.7)

All-grade adverse events with an incidence ≥10% higher in patients with NSCLC than in patients with malignant melanoma were oedema peripheral (32 patients with NSCLC [34.4%], 102 patients with malignant melanoma [18.2%]), dry skin (30 patients [32.3%], 63 patients [11.3%]), decreased appetite (26 patients [28.0%], 75 patients [13.4%]), dyspnoea (19 patients [20.4%], 47 patients [8.4%]), hypotension (14 patients [15.1%], 27 patients [4.8%]), and hyponatraemia (13 patients [14.0%], 22 patients [3.9%]). The Grade ≥3 adverse event with an incidence ≥5% higher in patient with NSCLC than in patients with malignant melanoma was hyponatraemia (8 patients [8.6%], 20 patients [3.6%]). Serious adverse events with an incidence ≥3% higher in patient with NSCLC than in patients with malignant melanoma were ALT increased (5 patients [5.4%], 9 patients [1.6%]) and AST increased (4 patients [4.3%], 4 patients [0.7%]). Adverse events leading to treatment interruption with an incidence ≥3% higher in patients with NSCLC than in patients with malignant melanoma were vomiting (13 patients [14.0%], 32 patients [5.7%]) and neutropenia (7 patients [7.5%], 25 patients [4.5%]). Adverse events leading to dose reduction with an incidence ≥3% higher in patients with NSCLC than in patients with malignant melanoma were diarrhoea (4 patients [4.3%], 7 patients [1.3%]), nausea (4 patients [4.3%], 7 patients [1.3%]), and vomiting (4 patients [4.3%], 5 patients [0.9%]). There were no adverse events leading to treatment discontinuation with an incidence ≥3% higher in patients with NSCLC than in patients with malignant melanoma.

Thus, although there were some adverse events that were observed in patients with NSCLC but not in patients with malignant tumor or that were observed at a higher incidence in patients with NSCLC than in patients with malignant melanoma, all were known adverse events, suggesting that there is no difference in the safety of DAB/TRA between patients with NSCLC and patients with malignant melanoma.

Also, the applicant explained the difference of the safety of DAB/TRA between Japanese patients and non-Japanese patients based on the safety information obtained from Study E2201, as follows:
The safety in Study E2201 was compared between 3 Japanese patients receiving DAB/TRA (2 patients in Cohort A who were allowed to receive DAB/TRA after DAB monotherapy and 1 in Cohort B) and 92 non-Japanese patients assigned to Cohort B or C.

All-grade adverse events reported by ≥2 Japanese patients were nausea and decreased appetite, both of which were observed in 2 of 3 patients (66.7%), while in non-Japanese patients, they were observed in 42 of 92 patients (45.7%) and in 26 of 92 patients (28.3%), respectively. Grade ≥3 adverse events observed in Japanese patients were decreased appetite, hyponatraemia, and subarachnoid haemorrhage in 1 of 3 patients (33.3%) each, while in non-Japanese patients, they were observed in 0 of 92 patients (0%), 7 of 92 patients (7.6%), and 0 of 92 patients (0%), respectively. The adverse event reported only by Japanese patients and not in non-Japanese patients was Grade 5 subarachnoid haemorrhage, and its causal relationship to DAB/TRA was ruled out.

PMDA's view:
There were adverse events with a higher incidence in patients with NSCLC with BRAF V600 mutations than in patients with malignant melanoma with *BRAF* mutation, the disease for which DAB/TRA has already been indicated. However, taking into account that they are known adverse events associated with the use of DAB or TRA and that there was no clear difference in the incidence of Grade ≥3 adverse events between the two patient populations, DAB/TRA is well tolerated in patients with NSCLC with BRAF V600 mutations provided that appropriate measures, such as monitoring and management of adverse events and modification of the doses of DAB or TRA, are taken by physicians with adequate knowledge and experience of cancer chemotherapy. In Study E2201, both all-grade neutropenia and Grade ≥3 neutropenia were observed with ≥5% higher incidence in Cohort B (previously treated) than in Cohort C (previously untreated), whereas no clear difference was observed in the incidences of serious adverse events. Based on these findings, there is no clear difference in the safety of DAB/TRA between patients with and without previous treatment.

PMDA also concluded that although there is only limited use experience in Japanese patients, there are no adverse events requiring particular caution in Japanese patients, judging from the information currently available.

7.R.3 Clinical positioning and indications

The proposed indication for DAB and TRA was "unresectable advanced or recurrent *BRAF V600* mutation-positive non-small cell lung cancer." Also, the Precautions for Indications section contained 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 laboratory. An approved *in vitro* diagnostic should be used for the test.
- The physician should thoroughly understand the description in the "Clinical Studies" section and become fully aware of the efficacy and safety of dabrafenib (or trametinib) before identifying patients eligible for treatment with dabrafenib (or trametinib).
- The efficacy and safety of dabrafenib (or trametinib) as adjuvant chemotherapy have not been established.

Upon examining Sections "7.R.1 Efficacy" and "7.R.2 Safety," and upon reviews in the following sections, PMDA concluded that the indication of DAB and TRA should be "unresectable advanced or recurrent non-small cell lung cancer with *BRAF* mutations," that the Clinical Studies section of the

package insert should state that patients with BRAF V600E mutation were investigated in Study E2201, and that the Precautions for Indications section should contain the above statements.

7.R.3.1 Clinical positioning of DAB/TRA and indications

Clinical practice guidelines available in and outside Japan (e.g., Clinical practice guideline for lung cancer based on evidence-based medicine [EBM], 2016, edited by the Japan Lung Cancer Society and the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology [NCCN guidelines]) and leading clinical oncology textbooks were consulted for the use of DAB/TRA for treatment of unresectable advanced or recurrent NSCLC with *BRAF* mutations. The following recommendation was found:

[Clinical practice guidelines]

- NCCN Guidelines, Non-Small Cell Lung Cancer (v.6.2017)
  - Combination therapy with dabrafenib/trametinib is recommended for patients with unresectable advanced or recurrent NSCLC with BRAF V600E mutations.

The applicant's explanation about the eligible patient population and indication of DAB/TRA:

On the basis of the results obtained in Cohort B and Cohort C of Study E2201, DAB/TRA is positioned as a treatment option for patients with unresectable advanced or recurrent NSCLC with BRAF V600E mutations, regardless of the history of chemotherapy.

There are few reports on patients with NSCLC harboring non-V600E BRAF mutations (*J Clin Oncol.* 29:3574-9). Therefore, the target population for enrollment in Study E2201 were limited to patients with NSCLC with BRAF V600E mutations. However, taking account of the finding that DAB suppressed the growth of tumors with V600E and non-V600E BRAF mutations (see Review Report on Tafinlar Capsules 50 mg and Tafinlar Capsules 75 mg, dated January 21, 2016), DAB/TRA is expected to be effective in patients with NSCLC harboring non-V600E BRAF mutations as well, judging from the mechanism of action of DAB.

Therapy with DAB/TRA for the proposed indication should be limited to patients with NSCLC with BRAF V600 mutations confirmed by a companion diagnostic "Oncomine Dx Target Test Multi-CDx System" manufactured by Life Technologies Japan, Ltd.

On the above basis, "unresectable advanced or recurrent *BRAF V600* mutation-positive non-small cell lung cancer" was selected as the indication of DAB and TRA. Moreover, the Clinical Studies section of the package insert will state that patients with NSCLC with BRAF V600E mutations were investigated in Study E2201, and the Precautions for Indications section will contain the following precautions:

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

- The efficacy and safety of dabrafenib (or trametinib) in adjuvant chemotherapy have not been established.

PMDA's view:
The applicant's explanation is basically acceptable. However, given that DAB/TRA is administered to patients with NSCLC by physicians with adequate knowledge and experience of cancer chemotherapy and that "Oncomine Dx Target Test Multi-CDx System" is used as a companion diagnostic to identify patients eligible for treatment with DAB/TRA, the indication statement for NSCLC should be "unresectable advanced or recurrent non-small cell lung cancer with *BRAF* mutations" in line with the approved indication of malignant melanoma.

7.R.4 Dosage and administration

The proposed dosage and administration for DAB and TRA for the treatment of NSCLC were as shown in the following table. The Precautions for Dosage and Administration section for the treatment of NSCLC included the descriptions shown in the following table.

	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 when 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 or 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 or at least 2 hours after a meal to avoid food effect. • If adverse drug reactions are adequately 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 and 2-mg tablet formulations has not been demonstrated, 0.5-mg tablets should not be used when 2 mg is administered.

Upon examining Sections "7.R.1 Efficacy" and "7.R.2 Safety," and upon reviews in the following sections, PMDA concluded that the proposed statements for the Dosage and Administration section for DAB and TRA and the Precautions for Indication section are acceptable.

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 advanced or recurrent NSCLC with BRAF V600 mutations:
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 in Study E2201 were "oral administration of DAB 150 mg BID and TRA 2 mg QD." The study demonstrated the

clinical benefit of DAB/TRA in patients with unresectable advanced or recurrent NSCLC with BRAF V600 mutations.

Further, (a) DAB monotherapy, (b) TRA monotherapy, and (c) DAB or TRA in combination with other antineoplastic agents are not recommended, for the following reasons.

(a) In Study E2201, DAB/TRA achieved a higher response rate than DAB alone, showing no clear tendency toward an increase in the incidence of serious adverse events.
(b) There is only extremely limited experience of TRA monotherapy in patients with NSCLC (*Ann Oncol.* 2015;26:894-901).
(c) There are no results of clinical studies available on the use of DAB or TRA in combination with other antineoplastic agents.

On the above basis, the applicant selected the above-mentioned dosage and administration of DAB and TRA.

PMDA accepted the explanation of the applicant.

7.R.4.2 Dose adjustment

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

In Study E2201, the criteria for dose adjustment in case of adverse drug reactions were the same as those used in the COMBI-D study and the COMBI-V study in patients with unresectable malignant melanoma with *BRAF* mutations, the approved indication of DAB. DAB was shown to be effective and safe when administered in compliance with the criteria. Based on the above, the Precautions for Dosage and Administration section will include the same criteria for dose adjustment as those for the treatment of patients with unresectable malignant melanoma with *BRAF* mutations, the approved indication.

The criteria for TRA dose adjustment will be the same as those for the treatment of patients with unresectable malignant melanoma with *BRAF* mutations, the approved indication of TRA. However, the following proviso will be added to the criteria for reasons described below: "After TRA dose reduction due to an adverse drug reaction, dose re-escalation following the same steps as dose reduction may be considered if the adverse drug reaction is adequately managed by an appropriate measure."

- A rule for dose re-escalation of TRA was specified in foreign phase III studies in patients with unresectable malignant melanoma with *BRAF* mutations (Studies MEK115306 and MEK116513), the approved indication of TRA. However, this rule is not described in the current package insert because it was not included in the Company Core Data Sheet (CCDS) of TRA at time of the initial approval. On the other hand, this rule is described in the latest CCDS and the same rule was specified in the protocol of Study E2201. Therefore, this rule is described in the proposed package insert of TRA.

PMDA accepted the explanation of the applicant.

7.R.5 Post-marketing investigations

The applicant's explanation about the plan for the post-marketing surveillance:
In order to evaluate the safety, etc., of DAB/TRA in post-marketing clinical use, the applicant plans to conduct a post-marketing surveillance covering all patients with unresectable advanced or recurrent NSCLC with BRAF V600 mutations who are treated with DAB/TRA.

The same items[8)] as those identified as the safety specifications for the approved indication are selected as the safety specifications in the post-marketing surveillance for the new indication. This is because no clear difference was observed between the safety profile of DAB/TRA evaluated in Study E2201 and the safety profile of DAB/TRA evaluated for the approved indication [see Section 7.R.2.1]. In addition, haemorrhage was included in the safety specifications, taking account of its incidences in Japanese and foreign clinical studies conducted so far and in post-marketing clinical use of DAB/TRA.

The target sample size was 50 patients, taking account of the incidence of events, selected as the safety specifications, in patients receiving DAB/TRA in Study E2201.

The follow-up period was 1 year, because the data from Study E2201 showed that most of the events selected as the safety specifications occurred in patients receiving DAB/TRA within 1 year after the start of treatment with DAB/TRA.

PMDA's view:
A post-marketing surveillance covering all patients treated with DAB/TRA should be conducted for a certain period in the post-marketing setting, thereby to collect safety information in a prompt and unbiased manner and to communicate safety information thus obtained to healthcare professionals without delay, for the following reasons: (a) Only limited information is available on the safety of DAB/TRA in patients with advanced or recurrent NSCLC with BRAF V600 mutations and (b) results of the ongoing post-marketing surveillance on the approved indication are as yet unavailable.

Factors other than the use of DAB and TRA may have been involved in the clinically significant haemorrhagic events reported in Japanese and foreign clinical studies and in the post-marketing clinical setting after the initial approval of DAB and TRA in Japan. At present, therefore, there is little need to include haemorrhage in the safety specifications. It will suffice only to include the same events as those specified in the post-marketing surveillance for the approved indication. The target sample size and the follow-up period proposed by the applicant are appropriate.

7.3 Adverse events, etc., reported in clinical studies

Among the data of clinical studies submitted for safety evaluation, death is described in Sections "7.1 Evaluation data" and "7.2 Reference data." Main adverse events other than death were as shown in sections below.

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8) Cutaneous squamous cell carcinoma, secondary malignancies other than cutaneous squamous cell carcinoma, eye disorder, pyrexia, hepatic dysfunction, cardiac disorder, and rhabdomyolysis

7.3.1 Multi-regional phase II study (Study E2201)

7.3.1.1 Cohort A

7.3.1.1.1 DAB monotherapy

Adverse events occurred in 83 of 84 patients (98.8%). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 77 of 84 patients (91.7%). Table 7 shows adverse events reported by ≥20% of patients.

Table 7. Adverse events reported by ≥20% of patients

System organ class Preferred term (MedDRA/J ver. 18.1)	n (%) N = 84 All Grades	 Grade ≥3
All adverse events	83 (98.8)	41 (48.8)
General disorders and administration site conditions		
Pyrexia	31 (36.9)	2 (2.4)
Asthenia	26 (31.0)	5 (6.0)
Fatigue	25 (29.8)	1 (1.2)
Skin and subcutaneous tissue disorders		
Hyperkeratosis	25 (29.8)	1 (1.2)
Dry skin	21 (25.0)	0
Palmar-plantar erythrodysaesthesia syndrome	19 (22.6)	2 (2.4)
Alopecia	18 (21.4)	0
Gastrointestinal disorders		
Nausea	24 (28.6)	1 (1.2)
Vomiting	18 (21.4)	1 (1.2)
Respiratory, thoracic and mediastinal disorders		
Cough	24 (28.6)	0
Dyspnoea	17 (20.2)	3 (3.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Skin papilloma	23 (27.4)	0
Metabolism and nutrition disorders		
Decreased appetite	24 (28.6)	1 (1.2)

Serious adverse events occurred in 36 of 84 patients (42.9%). Serious adverse events reported by ≥3 patients were squamous cell carcinoma of skin in 8 patients (9.5%), pyrexia in 5 patients (6.0%), and basal cell carcinoma in 4 patients (4.8%). A causal relationship to the study drug could not be ruled out for squamous cell carcinoma of skin in 8 patients, pyrexia in 3 patients, and basal cell carcinoma in 3 patients.

Adverse events leading to discontinuation of study treatment occurred in 6 of 84 patients (7.1%). They were blister, chills, general physical health deterioration, haemorrhage intracranial, malaise, and palmar-plantar erythrodysaesthesia syndrome in 1 patient (1.2%) each. A causal relationship to the study drug was not ruled out for blister, chills, haemorrhage intracranial, malaise, and palmar-plantar erythrodysaesthesia syndrome in 1 patient each.

7.3.1.1.2 DAB/TRA combination therapy

Adverse events occurred in 15 of 16 patients (93.8%). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 13 of 16 patients (81.3%). Table 8 shows adverse events reported by ≥3 patients.

Table 8. Adverse events reported by ≥3 patients

System organ class Preferred term (MedDRA/J ver. 18.1)	n (%) N = 16 All Grades	Grade ≥3
All adverse events	15 (93.8)	8 (50.0)
Gastrointestinal disorders		
Nausea	8 (50.0)	0
Vomiting	6 (37.5)	0
Constipation	3 (18.8)	1 (6.3)
General disorders and administration site conditions		
Pyrexia	5 (31.3)	0
Metabolism and nutrition disorders		
Decreased appetite	5 (31.3)	1 (6.3)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	3 (18.8)	1 (6.3)
Respiratory, thoracic and mediastinal disorders		
Cough	4 (25.0)	1 (6.3)

Serious adverse events occurred in 3 of 16 patients (18.8%). They were abdominal pain, ascites, blood creatinine increased, constipation, gastritis viral, haematemesis, hyperkalaemia, macular hole, macular oedema, and tachycardia in 1 patient (6.3%) each. A causal relationship to the study drug could not be ruled out for macular hole and macular oedema in 1 patient each.

Adverse events leading to discontinuation of study treatment occurred in 2 of 16 patients (12.5%). They were ascites, blood creatinine increased, macular hole, and macular oedema in 1 patient (6.3%) each. A causal relationship to the study drug could not be ruled out for macular hole and macular oedema in 1 patient each.

7.3.1.2 Cohort B

Adverse events occurred in 56 of 57 patients (98.2%). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 51 of 57 patients (89.5%). Table 9 shows adverse events reported by ≥20% of patients.

Table 9. Adverse events reported by ≥20% of patients

System organ class Preferred term (MedDRA/J ver. 19.0)	n (%) N = 57 All Grades	 Grade ≥3
All adverse events	56 (98.2)	40 (70.2)
General disorders and administration site conditions		
Pyrexia	28 (49.1)	1 (1.8)
Asthenia	20 (35.1)	2 (3.5)
Oedema peripheral	20 (35.1)	0
Chills	13 (22.8)	1 (1.8)
Gastrointestinal disorders		
Nausea	24 (42.1)	0
Vomiting	23 (40.4)	0
Diarrhoea	18 (31.6)	1 (1.8)
Skin and subcutaneous tissue disorders		
Dry skin	19 (33.3)	1 (1.8)
Rash	13 (22.8)	0
Respiratory, thoracic and mediastinal disorders		
Cough	15 (26.3)	0
Dyspnoea	13 (22.8)	3 (5.3)
Musculoskeletal and connective tissue disorders		
Arthralgia	12 (21.1)	0
Metabolism and nutrition disorders		
Decreased appetite	17 (29.8)	0
Blood and lymphatic system disorders		
Neutropenia	12 (21.1)	6 (10.5)

Serious adverse events occurred in 35 of 57 patients (61.4%). Serious adverse events reported by ≥3 patients were pyrexia in 9 patients (15.8%), ejection fraction decreased in 4 patients (7.0%), and anaemia and nausea in 3 patients (5.3%) each. A causal relationship to the study drug could not be ruled out for pyrexia in 8 patients, ejection fraction decreased in 4 patients, anaemia in 2 patients, and nausea in 1 patient.

Adverse events leading to discontinuation of study treatment occurred in 12 of 57 patients (21.1%). Adverse events leading to discontinuation of study treatment reported by ≥2 patients were ejection fraction decreased and respiratory distress in 2 patients (3.5%) each. A causal relationship to the study could not be ruled out for all events.

7.3.1.3 Cohort C

Adverse events were observed in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 32 of 36 patients (88.9%). Table 10 shows adverse events reported by ≥20% of patients.

Table 10. Adverse events reported by ≥20% of patients

System organ class Preferred term (MedDRA/J ver. 19.0)	n (%) N = 36 All Grades	Grade ≥3
All adverse events	36 (100)	21 (58.3)
General disorders and administration site conditions		
Pyrexia	23 (63.9)	4 (11.1)
Oedema peripheral	12 (33.3)	0
Fatigue	11 (30.6)	0
Chills	9 (25.0)	0
Skin and subcutaneous tissue disorders		
Dry skin	11 (30.6)	0
Gastrointestinal disorders		
Nausea	19 (52.8)	0
Diarrhoea	13 (36.1)	1 (2.8)
Vomiting	11 (30.6)	3 (8.3)
Metabolism and nutrition disorders		
Decreased appetite	9 (25.0)	0

Serious adverse events occurred in 21 of 36 patients (58.3%). Serious adverse events reported by ≥3 patients were ALT increased and pyrexia in 4 patients (11.1%) each, and AST increased and ejection fraction decreased in 3 patients (8.3%) each. A causal relationship to the study drug could not be ruled out for pyrexia in 4 patients, ALT increased and ejection fraction decreased in 3 patients each, and AST increased in 2 patients.

Adverse events leading to discontinuation of study treatment occurred in 7 of 36 patients (19.4%). The adverse event leading to discontinuation of study treatment reported by ≥2 patients was pyrexia in 2 patients (5.6%). A causal relationship to the study drug could not be ruled out for pyrexia in 1 patient.

7.3.2 Foreign phase I study (Study A2103)

Adverse events occurred in 18 of 23 patients (78.3%) receiving DAB alone, in 5 of 17 patients (29.4%) receiving DAB plus rabeprazole, and in 3 of 16 patients (18.8%) receiving DAB plus rifampicin. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 13 of 23 patients (56.5%) receiving DAB alone, in 3 of 17 patients (17.6%) receiving DAB plus rabeprazole, and in 1 of 16 patients (6.3%) receiving DAB plus rifampicin. Adverse events reported by ≥10% of patients were analyzed for each treatment group. Adverse events in patients receiving DAB alone were vomiting, fatigue, and arthralgia in 4 patients (17.4%) each, and nausea, pyrexia, palmar-plantar erythrodysaesthesia syndrome, and decreased appetite in 3 patients (13.0%) each, and adverse events in patients receiving DAB plus rabeprazole were dry skin in 2 patients (11.8%).

Serious adverse events occurred in 1 of 23 patients (4.3%) receiving DAB alone, in 2 of 17 patients (11.8%) receiving DAB plus rabeprazole, and in 1 of 16 patients (6.3%) receiving DAB plus rifampicin. Serious adverse events reported were analyzed by treatment group. Adverse events in patients receiving DAB alone were large intestine perforation and urinary tract infection in 1 patient (4.3%). Adverse events in patients receiving DAB plus rabeprazole were small intestinal obstruction and cholangitis in 1 patient (5.9%) each. An adverse event in patients receiving DAB plus rifampicin was cognitive disorder in 1 patient (6.3%). A causal relationship between the study drug and all of these events was ruled out.

Adverse events leading to discontinuation of study treatment occurred in 4 of 23 patients (17.4%) receiving DAB alone and in 2 of 16 patients (12.5%) receiving DAB plus rifampicin. Adverse events in patients receiving DAB alone were fatigue in 2 patients (8.7%), hyperlipasaemia, arthralgia, and urinary tract infection in 1 patient (4.3%) each. Adverse events in patients receiving DAB plus rifampicin were cognitive disorder and vomiting in 1 patient (6.3%) each. A causal relationship to the study drug could not be ruled out for fatigue (2 patients), and hyperlipasaemia (1 patient), and arthralgia (1 patient) noted in patients receiving DAB alone, and for vomiting (1 patient) noted in patients receiving DAB plus rifampicin.

7.3.3 Foreign phase I study (Study A2104)

Adverse events occurred in 5 of 16 patients (31.3%) not receiving concomitant DAB and in 12 of 16 patients (75.0%) concomitantly receiving DAB and other drugs. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 4 of 16 patients (25.0%) not receiving concomitant DAB and in 11 of 16 patients (68.8%) concomitantly receiving DAB and other drugs. Adverse events reported by ≥2 patients were somnolence in 3 patients (18.8%) not receiving concomitant DAB; and somnolence and pyrexia in 4 patients (25.0%) each, headache and fatigue in 3 patients (18.8%) each, and hyperkeratosis in 2 patients (12.5%) concomitantly receiving DAB and other drugs.

Serious adverse events occurred in 2 of 16 patients (12.5%) concomitantly receiving DAB and other drugs. They were presyncope, pyrexia, hyponatraemia, and hypotension in 1 patient (6.3%) each. A causal relationship to the study drug could not be ruled out for presyncope, pyrexia, and hypotension (1 patient each).

Adverse events leading to discontinuation of study treatment occurred in 2 of 16 patients (12.5%) concomitantly receiving DAB and other drugs. They were presyncope, pyrexia, and hypotension in 1 patient (6.3%) each. A causal relationship between the study drug and these events was not ruled out.

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 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.

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

The new drug application data (CTD 5.3.5.2-1 and CTD 5.3.5.2-2) 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.

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 treatment of unresectable advanced or recurrent NSCLC with *BRAF* mutations, and that DAB/TRA has acceptable safety in view of its benefits. DAB/TRA combination therapy has clinical significance because it offers a new treatment option for patients with unresectable advanced or recurrent NSCLC with *BRAF* mutations. Further investigations are necessary to fully evaluate the efficacy, etc., of DAB/TRA.

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

Review Report (2)

February 13, 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	December 5, 2016
[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	December 5, 2016

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 concluded that DAB/TRA has a certain level of efficacy in patients with advanced or recurrent NSCLC with BRAF V600E mutation, based on the following results with Cohorts B and C in the multi-regional phase II study (Study E2201) in the above patient group:

- In Cohort B comprising patients with a history of platinum-based chemotherapy, the response rate [95% CI], the primary endpoint, was 63.2% [49.3%, 75.6%], with the lower limit of 95% CI of the response rate exceeding the threshold response rate (30%).
- In Cohort C comprising patients without a history of chemotherapy, the response rate [95% CI], the primary endpoint, was 61.1% [43.5%, 76.9%], with the lower limit of 95% CI of the response rate exceeding the threshold response rate (30%).

The above conclusions of the 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" of the Review Report (1), PMDA has concluded that adverse events requiring special caution in the use of DAB/TRA in patients with advanced or recurrent NSCLC with BRAF V600E mutation are the same as those identified at the initial approval for the treatment of unresectable malignant melanoma with *BRAF* mutations (secondary malignancies, cardiac disorders, hepatic dysfunction, pyrexia, eye disorders, and rhabdomyolysis), and that particular attention should be paid to the risk of developing these adverse events during treatment with DAB/TRA.

PMDA has also concluded that although attention should be paid to the risk of developing the above adverse events during treatment with DAB/TRA, DAB/TRA is well tolerated in patients with advanced or recurrent NSCLC with BRAF V600E mutation provided that appropriate measures, such as monitoring and management of adverse events and modification of the doses of DAB or TRA, are taken by physicians with adequate knowledge and experience of cancer chemotherapy.

The above conclusions of the 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 indications" in the Review Report (1), PMDA has concluded that both DAB and TRA should be indicated for "unresectable advanced or recurrent non-small cell lung cancer with *BRAF* mutations." The "Clinical Studies" section of the package insert should include the description that the target population for enrollment in Study E2201 were patients with BRAF V600E mutation, 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 laboratory. An approved *in vitro* diagnostic should be used for the test.
- The physician should thoroughly understand the description in the "Clinical Studies" section and become fully aware of the efficacy and safety of dabrafenib (or trametinib) before identifying patients eligible for treatment with dabrafenib (or trametinib).
- The efficacy and safety of dabrafenib (or trametinib) in adjuvant chemotherapy have not been established.

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

Based on the above, PMDA instructed the applicant to specify the indication as above. The applicant agreed to the instruction.

A marketing application was submitted for "Oncomine Dx Target Test Multi-CDx System" (Life Technologies Japan, Ltd.) as a companion diagnostic used to identify patients with NSCLC who are

eligible for treatment with DAB/TRA. Ultimately its brand name was changed to "Oncomine Dx Target Test CDx System."

1.4 Dosage and administration

As a result of its review in Section "7.R.4 Dosage and administration" in the Review Report (1), PMDA has concluded that the Dosage and Administration section and the Precautions for Dosage and Administrationpati section for DAB and TRA should be specified as described in the following table.

	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 when 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 or 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 or 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 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 the 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. The applicant agreed to the instruction.

1.5 Risk management plan (draft)

In order to evaluate the safety, etc., of DAB/TRA in post-marketing clinical use, the applicant plans to conduct a post-marketing surveillance covering all patients with unresectable advanced or recurrent NSCLC with BRAF V600 mutations who are treated with DAB/TRA, with the planned sample size of 50 patients and the follow-up period of 1 year.

As a result of its review in Section "7.R.5 Post-marketing investigations" of the Review Report (1), PMDA concluded that it is essential to conduct a surveillance covering all patients treated with DAB/TRA during a certain period after the market launch, thereby to collect safety information promptly and in an unbiased manner, and to provide safety information thus obtained to healthcare professionals without delay. Also, PMDA concluded that the surveillance plan should be designed as follows:

- Safety specifications for the surveillance should include survey items selected in the post-marketing surveillance for the approved indication, namely, cutaneous squamous cell carcinoma, secondary malignancies other than cutaneous squamous cell carcinoma, eye disorders, pyrexia, hepatic dysfunction, cardiac disorders, and rhabdomyolysis.
- The target sample size and the follow-up period planned by the applicant are appropriate.

The above conclusion of PMDA was supported by the expert advisors. The following comments were also raised:

- Since DAB/TRA is expected to be administered for ≥1 year, it may be a good idea to select a longer follow-up period.

PMDA's view:

In patients who were treated with DAB/TRA in Study E2201, most of the events identified as safety specifications were observed within 1 year after the start of treatment with DAB/TRA. It is therefore appropriate to select the 1-year follow-up period in the surveillance. However, by taking into account the above comment from the expert adviser, PMDA concluded that, in case that any safety concerns arise in the course of the pharmacovigilance activities, additional pharmacovigilance activities should be considered promptly.

Based on the above discussions, PMDA instructed the applicant to review the surveillance plan.

The applicant's response:

The safety specifications for the surveillance will include cutaneous squamous cell carcinoma, secondary malignancies other than cutaneous squamous cell carcinoma, eye disorders, pyrexia, hepatic dysfunction, cardiac disorders, and rhabdomyolysis.

PMDA accepted the response of the applicant.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) should include the safety and efficacy specifications presented in Tables 11 and 13 and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 12, 14, and 15.

Table 11. 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 malignancies 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 dysfunction
Efficacy specifications (matters related to the present partial change application)		
Not applicable		

Table 12. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan for DAB (draft)

Additional pharmacovigilance activities	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)	• Prepare and distribute materials for healthcare professionals • Prepare and supply materials for patients

Underlined parts: Activities to be conducted for the added indication

Table 13. 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 impairment • Decreased fertility • Effect on embryofetal development	• Safety in patients with hepatic dysfunction
Efficacy specifications (matters related to the present partial change application)		
Not applicable		

Table 14. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan for TRA (draft)

Additional pharmacovigilance activities	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)	• Prepare and distribute materials for healthcare professionals. • Prepare and supply materials for patients.

Underlined parts: Activities to be conducted for the added indication

Table 15. Outline of post-marketing surveillance plan (draft)

Objective	To investigate the safety etc., of dabrafenib/trametinib in clinical use
Survey method	All-case surveillance
Population	All patients with unresectable advanced or recurrent NSCLC with *BRAF* mutations who are treated with dabrafenib/trametinib
Follow-up period	1 year
Planned sample size	50 patients treated with dabrafenib/trametinib
Main survey items	Safety specification: Cutaneous squamous cell carcinoma, secondary malignancies other than cutaneous squamous cell carcinoma, eye disorder, pyrexia, hepatic dysfunction, cardiac disorder, and rhabdomyolysis Other key survey items: Patient characteristics, use status of dabrafenib and trametinib, concomitant medications and therapies, adverse events (including changes in laboratory values)

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the products may be approved after modifying the indication as well as the dosage and administration as shown below, with the following conditions of approval, on the premise that (1) the applicant ensures that healthcare professionals become 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 responding appropriately to emergencies. Since dabrafenib and trametinib for the indication proposed in the present application are designated as orphan drugs, the re-examination period is 10 years.

Tafinlar Capsules 50 mg and Tafinlar Capsules 75 mg

Indications (Underline denotes additions.)

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 additions.)

Malignant melanoma

The usual adult dosage is 150 mg of dabrafenib administered orally twice daily under fasted conditions. 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

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since an extremely limited number of patients participated in the Japanese clinical study of the product, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until data from a certain number of patients have been accumulated to identify the characteristics of patients treated with the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

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 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 (Underline denotes additions.)

1. Dabrafenib should be administered to patients who are confirmed to have *BRAF* mutations through tests performed by a well-experienced pathologist or 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 become 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 chemotherapy have not been established.

Precautions for Dosage and Administration (No change)

1. The efficacy and safety of dabrafenib in combination 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 or 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 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 treatment interruption, dose reduction, and discontinuation

NCI-CTCAE[1)] Grade	Action
Intolerable Grade 2, or Grade 3	Interrupt therapy. 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 managed by appropriate measures, dose re-escalation following the same steps as dose reduction may be considered.

Mekinist Tablets 0.5 mg and Mekinist Tablets 2 mg

Indications (Underlines denotes additions.)

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

Dosage and Administration (No change)

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.

Conditions of approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since an extremely limited number of patients participated in the Japanese clinical studies of the product, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until data from a certain number of patients have been accumulated to identify the characteristics of patients treated with the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

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 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 (Underlines denotes additions.)
1. Trametinib should be administered to patients who are confirmed to have *BRAF* mutations through tests performed by a well-experienced pathologist or 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 become 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 chemotherapy have not been established.

Precautions for Dosage and Administration (Underline denotes additions.)
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 or at least 2 hours after a meal to avoid food effect.
2. If an adverse drug reaction occurs during trametinib treatment, treatment should be interrupted, discontinued, or continued at a reduced dose 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 treatment interruption, dose reduction, and discontinuation

NCI-CTCAE[1)] Grade	Action
Intolerable Grade 2, or Grade 3	Interrupt therapy. 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 managed 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 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

^{14}C-DAB	^{14}C-labeled DAB
^{14}C-TRA	^{14}C-labeled TRA
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BCRP	breast cancer resistance protein
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
CCDS	Company Core Data Sheet
CCSP	Clara cell secretory protein
CI	confidence interval
COMBI-D study	Study MEK115306
COMBI-V study	Study MEK116513
CR	complete response
C_{avg}	average plasma concentration
DAB	Dabrafenib mesilate
DAB/TRA	Combination therapy with dabrafenib and trametinib
ERK	extracellular signal-regulated kinase
efflux ratio	Ratio of permeability coefficient in the direction of secretion to that in the direction of absorption
Japanese clinical practice guideline	Clinical practice guideline for lung cancer based on evidence-based medicine (EBM), 2016, edited by the Japan Lung Cancer Society
MAPK	mitogen-activated protein kinase
MEK	mitogen-activated protein kinase/ extracellular signal-regulated kinase kinase
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer
NSCLC	non-small cell lung cancer
OATP	organic anion transporter polypeptide
OCT	organic cation transporter
OS	overall survival
PARP	poly (ADP-ribose) polymerase
PD	progressive disease
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
Partial change application	Application for partial changes to approved information
QD	quaque die
RECIST	Response Evaluation Criteria in Solid Tumors
Rabeprazole	Rabeprazole sodium
Rosuvastatin	Rosuvastatin potassium
S6	ribosomal protein S6
SD	stable disease
TRA	Trametinib dimethyl sulfoxide
Vc/F	apparent volume of distribution of the central compartment