Report on the Deliberation Results

February 24, 2016
Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Tafinlar Capsules 50 mg Tafinlar Capsules 75 mg
[Non-proprietary name]	Dabrafenib Mesilate (JAN*)
[Applicant]	Novartis Pharma K.K.
[Date of application]	April 27, 2015

[Results of deliberation]
In the meeting held on February 1, 2016, the Second Committee on New Drugs concluded that 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. The drug substance and the drug product are both classified as powerful drugs. The drug product is not classified as a biological product or a specified biological product.

[Conditions for approval]
The applicant is required to:

1. Develop and appropriately implement a risk management plan; and

2. Conduct a drug use-results survey in all patients treated with the product after market launch 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, since an extremely limited number of patients participated in the Japanese clinical study of the product.

**Japanese Accepted Name (modified INN)*

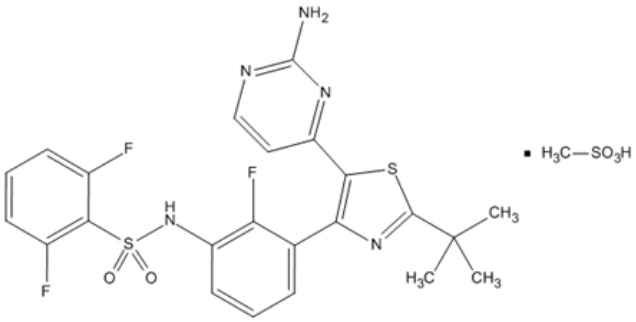
Review Report

January 21, 2016
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Tafinlar Capsules 50 mg Tafinlar Capsules 75 mg
[Non-proprietary name]	Dabrafenib Mesilate
[Applicant]	Novartis Pharma K.K.
[Date of application]	April 27, 2015
[Dosage form/Strength]	Capsules, each containing 59.25 or 88.88 mg of Dabrafenib Mesilate (equivalent to 50 or 75 mg of dabrafenib, respectively).
[Application classification]	Prescription drugs, (1) Drugs with a new active ingredient

[Chemical structure]



Molecular formula: $C_{23}H_{20}F_3N_5O_2S_2 \bullet CH_4O_3S$
Molecular weight: 615.67
Chemical name:
N-{3-[5-(2-Aminopyrimidin-4-yl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide monomethanesulfonate

[Items warranting special mention]
Orphan drug (Designation No. 318 of 2013 [*25 yaku*], Notification No. 0422-1 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated April 22, 2015)

[Reviewing office] Office of New Drug V

Review Results

January 21, 2016

[Brand name]	Tafinlar Capsules 50 mg Tafinlar Capsules 75 mg
[Non-proprietary name]	Dabrafenib Mesilate
[Applicant]	Novartis Pharma K.K.
[Date of application]	April 27, 2015

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of patients with unresectable malignant melanoma with *BRAF* mutations has been demonstrated, and that its safety is acceptable in view of its observed benefits. Further investigations should be necessary on secondary malignant tumor, cardiac disorders, hepatic dysfunction, pyrexia, and eye disorders in the post-marketing surveillance.

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

[Indication] Unresectable malignant melanoma with *BRAF* mutations

[Dosage and administration] 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.

[Conditions for approval] The applicant is required to:

1. Develop and appropriately implement a risk management plan; and
2. Conduct a drug use-results survey covering all patients treated with the product after market launch 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, since an extremely limited number of patients participated in the Japanese clinical studies of the product.

Review Report (1)

November 13, 2015

I. Product Submitted for Registration

[Brand name]	Tafinlar Capsules 50 mg Tafinlar Capsules 75 mg
[Non-proprietary name]	Dabrafenib Mesilate
[Applicant]	Novartis Pharma K.K.
[Date of application]	April 27, 2015
[Dosage form/Strength]	Capsules, each containing 59.25 or 88.88 mg of Dabrafenib Mesilate (equivalent to 50 or 75 mg of dabrafenib, respectively).
[Proposed indication]	Malignant melanoma with *BRAF* V600 mutations
[Proposed dosage and administration]	The usual adult dosage is 150 mg of dabrafenib administered orally twice daily.

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

1.(1) Outline of the product submitted for registration

The protein encoded by v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) gene is a serine/threonine kinase, and it is reported that BRAF with mutations in the amino acid at codon 600, valine, (BRAF V600 mutations) has been found in approximately 50% of patients with malignant melanoma (*Nature*. 2002;417:949-954). BRAF with V600 mutations is considered to be constitutively activated, resulting in activation of the downstream extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase/ERK kinase (MEK), leading to abnormal cell growth.

Dabrafenib mesilate (hereinafter referred to as dabrafenib) is a low molecular weight compound discovered by GlaxoSmithKline (UK) and is considered to suppress tumor growth by inhibiting serine/threonine kinase B-raf (BRAF) V600 mutation.

1.(2) Development history etc.

A phase I clinical study (Study BRF112680) of dabrafenib monotherapy in patients with advanced BRAF V600 mutation-positive solid tumors was initiated by GlaxoSmithKline (UK) in May 2009. Subsequently, a phase III study (Study BRF113683) was initiated to compare dabrafenib monotherapy and dacarbazine monotherapy in patients with unresectable malignant melanoma with BRAF V600 mutations in February 2011.

Also, a phase I/II study (Study BRF113220) of a combination therapy of dabrafenib and trametinib dimethyl sulfoxide (TRA) (dabrafenib/TRA) in patients with advanced solid cancer or unresectable malignant melanoma with BRAF V600 mutations was initiated by GlaxoSmithKline (UK) in March 2010. Subsequently, 2 phase III studies were initiated in patients with unresectable malignant melanoma with BRAF V600 mutations: Study MEK115306 comparing dabrafenib/TRA combination therapy and dabrafenib monotherapy in May 2012 and Study MEK116513 comparing dabrafenib/TRA combination therapy and vemurafenib monotherapy in June 2012.

An application for dabrafenib monotherapy was submitted in the US and EU in July 2012 with the results of Study BRF113683 as the pivotal data, and approved in the US in May 2013 for the following indication: “TAFINLAR is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.” The application was

approved in the EU in August 2013 for the following indication: "Dabrafenib is indicated in monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation".

An application for dabrafenib/TRA was submitted in the US in July 2013 with the results of Study BRF113220 as the pivotal data, and approved in January 2014 for the following indication: "TAFINLAR, in combination with trametinib, is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test. This indication is based on the demonstration of durable response rate. Improvement in disease-related symptoms or overall survival has not been demonstrated for TAFINLAR in combination with trametinib." In the EU, an application for dabrafenib/TRA was submitted in February 2013 simultaneously with the application for TRA monotherapy, with the results of Study BRF113220 as the pivotal data, and additional data obtained from Study MEK115306 were submitted in January 2014 during the review. However, because of the opinion from the Committee for Medicinal Products for Human Use to the effect that clinical usefulness of the product could not be established, the application for the dabrafenib/TRA combination was withdrawn in March 2014. Subsequently, with the results of Study MEK116513 made available, an application for dabrafenib/TRA was submitted in April 2015 and was approved in August 2015 after the indication was changed to "Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation."

As of September 2015, dabrafenib is approved in 52 countries or regions for the indication of malignant melanoma.

In Japan, a phase I study (Study BRF116056) of dabrafenib monotherapy in patients with advanced BRAF V600 mutation-positive solid tumors was initiated by the applicant in May 2012. Also, a phase I/II study (Study MEK116885) of dabrafenib/TRA in patients with advanced solid cancer or unresectable malignant melanoma, both with BRAF V600 mutations, was initiated in August 2013.

Recently, an application for dabrafenib has been submitted with the results of Studies BRF113683, MEK115306, MEK116513, and MEK116885 as the pivotal data.

Dabrafenib was designated as an orphan drug in April 2015 with the expected indication of "malignant melanoma with $BRAF^{V600}$ mutations" (Designation No. 318 of 2013 [25 *yaku*]).

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a white to light yellowish white powder. The general properties of the drug substance including description, solubility, hygroscopicity, melting point, dissociation constant, pH, partition coefficient, and particle size were determined. The drug substance is an anhydrate which does not show crystalline polymorphism. Each solvates of [redacted] and dabrafenib mesilate with 3 different solvents ([redacted], [redacted], and [redacted]) form crystals. However, since [redacted] is used in the synthesizing process of dabrafenib mesilate, and [redacted], [redacted], and [redacted] are not used in the [redacted] process, only anhydrate is produced in the actual production.

The chemical structure of the drug substance has been elucidated by elemental analysis, mass spectrometry, ultraviolet and visible spectrophotometry (UV-VIS), infrared spectrophotometry (IR), nuclear magnetic resonance spectrometry (^{1}H-NMR, ^{13}C-NMR), and single crystal X-ray diffractometry.

2.A.(1).2) Manufacturing process

The drug substance is synthesized using [redacted], [redacted], and [redacted] as starting materials.

Mainly the following were investigated using a quality-by-design (QbD) approach.

- [redacted], and [redacted] were identified as critical quality attributes (CQAs).
- Identification of critical process parameters (CPPs) and the acceptance range of manufacturing process parameters based on the quality risk assessment and on the experimental design
- Establishing strategies to control CQAs
- Investigation of [redacted]

*1: [redacted]
*2: [redacted]
*3: [redacted]
*4: [redacted]
*5: [redacted]

[redacted], and [redacted] are defined as critical process steps, and [redacted] are controlled as critical intermediates in order to constantly ensure the quality of the drug substance.

*1: [redacted]
*2: [redacted]

2.A.(1).3) Control of drug substance

The proposed specifications for the drug substance consist of content, description, identification (IR or Raman spectroscopy), purity (related substances [high-performance liquid chromatography (HPLC)], and residual solvents [gas chromatography]), water content, residue on ignition, [redacted], and assay (HPLC).

2.A.(1).4) Stability of drug substance

Stability studies of the drug substance were conducted as shown in the following table. The photostability test results showed that the drug substance was photostable.

Stability studies of drug substance

Study	Primary batch	Temperature	Humidity	Storage configuration	Storage period
Long-term	3 commercial scale batches	30°C	65%RH	Polyethylene bag	48 months
Accelerated	3 commercial scale batches	40°C	75%RH		6 months

On the basis of the study results above, a retest period of [redacted] months has been proposed for the drug substance when stored at room temperature in a polyethylene bag.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product, and formulation development

The drug product is immediate-release hard capsules containing 59.25 or 88.88 mg of the drug substance (50 or 75 mg of dabrafenib, respectively). The drug product contains microcrystalline cellulose, magnesium stearate, and light anhydrous silicic acid as excipients.

2.A.(2).2) Manufacturing process

The drug product is manufactured through [redacted], capsule filling, and packaging/labeling processes.

Mainly the following were investigated using a QbD approach.

- Identification of [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] as CQAs
- Identification of CPPs and the acceptance range of manufacturing process parameters based on the quality risk assessment
- Establishing strategies to control CQAs

[redacted] is defined as the critical process step, and process control parameters and control limits are defined for [redacted] and [redacted].

2.A.(2).3) Control of drug product

The proposed specifications for the drug product consist of content, description, identification (UV/VIS), uniformity of dosage unit (mass variation), dissolution (UV/VIS), and assay (HPLC).

2.A.(2).4) Stability of drug product

Stability studies of the drug product were conducted as shown in the following table. The photostability test results showed that the drug product was photostable.

Stability tests of drug product

Study	Primary batch	Temperature	Humidity	Storage configuration	Storage period
Long-term	3 commercial scale batches	30°C	75%RH	Polyethylene bottle/polypropylene cap with aluminum-laminated film (with desiccant)	24 months
Accelerated	3 commercial scale batches	40°C	75%RH		6 months

On the basis of the above tests, the shelf life of 36 months has been proposed for the drug product when stored at room temperature together with the desiccant in the polyethylene bottle stoppered with a polypropylene cap with aluminum-laminated film, according to the "Guideline on the Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3 2003). The long-term testing will be continued up to [redacted] months.

2.B Outline of the review by PMDA

On the basis of the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

3. Non-clinical data

In non-clinical studies, dabrafenib mesilate (hereinafter referred to as dabrafenib) and its free base (dabrafenib [free base]) were used. The dose and concentration of dabrafenib are expressed as free-base equivalent.

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Inhibitory effects on phosphorylation of kinases such as v-raf murine sarcoma viral oncogene product homolog B1 (BRAF) (Reports UH2008/00147/01, UH2010/00028/02, 2011N111729_00, 2012N139510_00, 2012N1533146_00, and 2008/00132/02)

The protein encoded by v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) gene is a serine/threonine kinase, and extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK)/ERK kinase (MEK) are located in the downstream of BRAF. The inhibitory effects of dabrafenib on phosphorylation of wild type BRAF, mutated types of BRAF (V600E, V600K, and V600D with amino acid in codon 600 mutated from valine (V) to glutamic acid (E), lysine (K), and aspartic acid (D), respectively), and the carboxyl terminal of constitutively activated CRAF (recombinant protein) was determined based on adenosinetriphosphatase (ATPase) activity of MEK (left

half in the following table). Also, the inhibitory effects of dabrafenib on phosphorylation of 287 different kinases other than RAF was assessed and, in 14 of them, phosphorylation was ≥75% inhibited by dabrafenib or dabrafenib (free base) at 300 nmol/L. Detail of the inhibition of phosphorylation of these kinases by dabrafenib (free base) was measured by time-resolved fluorescence/fluorescence resonance energy transfer or by fluorescence polarization of fluorescence-labeled kinases (right half of the following table). The IC_{50} values of <100 nmol/L against kinases were as shown in the following table.

Inhibitory effects of dabrafenib on phosphorylation of kinases

RAF kinase	n	IC_{50} (nmol/L)	Non-RAF kinases	n	IC_{50} (nmol/L)
Wild type BRAF	4	3.2 ± 0.7	ALK5	1	17
BRAF V600E	3	0.8 ± 0.07	BRK	1	79
	2	0.70, 0.60	CK1*2	1	41
BRAF V600K	2	0.51, 0.50	LIMK1	1	15
BRAF V600D	2	1.83, 1.85	NEK11	1	20
CRAF*1	4	5.0 ± 0.6	PKD2	1	57
			SIK	1	27
			SIK2	1	76

Mean ± standard deviation (SD) (individual values if n = 1 or 2); *1, Carboxyl terminal of constitutively activated CRAF; *2, Derived from yeast

Since dabrafenib was shown to inhibit ALK5 (the table above), the inhibitory effects of dabrafenib (free base) on phosphorylation of Smad2/3, an intracellular signaling molecule located in the downstream of ALK5, was determined by Western blotting. The IC_{50} value of dabrafenib against Smad2/3 was 3900 nmol/L.

The inhibitory effects of dabrafenib (free base) and vemurafenib (Vem), a compound with BRAF-inhibiting activity, on phosphorylation of 14 different human kinases were determined based on fluorescence polarization of fluorescence-labeled kinases. The IC_{50} values of dabrafenib and Vem against CRAF were both <100 nmol/L. The IC_{50} values of dabrafenib against LIMK1, NEK11, PERK, SIK, and TIE (R849W) were ≤84 nmol/L, and the IC_{50} values of Vem against those, ≥391 nmol/L. The IC_{50} values of dabrafenib against C-KIT, ACK1, BRK, and LCK were ≥336 nmol/L, and Vem against those, ≤90 nmol/L.

The inhibitory effects of dabrafenib (free base) on phosphorylation of wild-type BRAF (recombinant protein) of rats, dogs, and monkeys were determined based on ATPase activity of MEK. The IC_{50} value of dabrafenib was 4.3, 4.0, and 4.1 nmol/L, respectively.

3.(i).A.(1).2) Effects on RAF (Report UH2008/00147/01)

The inhibitory effect of dabrafenib (free base) on the binding activity of BRAF was determined based on fluorescence polarization of the fluorescence-labeled ligand after dabrafenib was added to BRAF that had been reacted with a fluorescence-labeled ligand that binds to the ATP-binding site of BRAF. Results showed that dabrafenib inhibited BRAF by competing with ATP at the ATP-binding site.

The inhibitory effect of dabrafenib (free base) on the binding activity of CRAF was determined based on MEK1 phosphorylation with ^{33}P-labeled ATP. Results showed that dabrafenib inhibited CRAF by competing with ATP at the ATP-binding site.

3.(i).A.(1).3) Inhibitory effects on phosphorylation of MEK and ERK (Reports UH2008/00132/02 and UH2008/00145/03)

The inhibitory effect of dabrafenib (free base) on ERK phosphorylation was determined by Western blotting in BRAF (BRAF V600E) mutant cell lines derived from human malignant tumors (e.g., malignant melanoma-derived A375P F11 and SK-MEL-28 cell lines, ovarian cancer-derived ES-2 cell line) and BRAF wild-type cell lines derived from human malignant tumors (e.g., malignant melanoma-derived SK-MEL-2 cell line, colon cancer-derived HCT116 cell line, hepatoma-derived HepG2 cell line). The inhibitory effect of dabrafenib was observed in all BRAF V600E mutant cell lines derived from human malignant tumors assessed. On the other hand, dabrafenib had no inhibitory effects on any BRAF wild-type cell lines derived from human malignant tumors assessed.

The inhibitory effects of dabrafenib (free base) on phosphorylation of MEK and ERK were determined by Western blotting in the ES-2 cell line, and the results showed that dabrafenib inhibited phosphorylation of MEK and ERK.

A single oral dose of dabrafenib (free base) 0.3-300 mg/kg was administered to athymic mice (nude mice) subcutaneously transplanted with A375P F11 cell line, to evaluate the inhibitory effect of dabrafenib on phosphorylation of ERK within the tumor by enzyme-linked immunosorbent assay (ELISA). Results showed the inhibitory effect of dabrafenib.

The persistence and reversibility of the inhibitory effect of dabrafenib (free base) on ERK phosphorylation were investigated in SK-MEL-28 cell line. Thus, after the cells were treated with dabrafenib 300 nmol/L, the amount of ERK phosphorylation was determined by Western blotting at 0, 0.5, 2, 4, 6, and 24 hours after the removal of dabrafenib. The inhibitory effect of dabrafenib vanished at 6 hours after the removal of dabrafenib, thus showing that the inhibitory effect of dabrafenib on ERK phosphorylation was reversible.

3.(i).A.(1).4) Cell cycle arrest and apoptosis induction (Report UH2008/0132/02)

The effects of dabrafenib (free base) on cell cycle were analyzed by flow cytometry in BRAF V600E mutant cell lines, A375P F11 and SK-MEL-28, and BRAF wild-type human normal foreskin fibroblast-derived HFF cell line Dabrafenib arrested the cell cycle of A375P F11 and SK-MEL-28 cell lines at G0/G1 phase. However, dabrafenib had no effect on the cell cycle of HFF cell line.

The apoptosis inducing effects of dabrafenib (free base) were determined based on caspase 3 and 7 activation, in A375P F11 cell line, SK-MEL-28 cell line, and human colon cancer-derived cell line Colo205, all expressing BRAF V600E mutation, and HFF cell line and human head and neck squamous cell carcinoma-derived cell line HN5, both expressing wild-type BRAF. Apoptosis-inducing effects of dabrafenib have been demonstrated in A375P F11, SK-MEL-28, and Colo205 cell lines, but not in HFF or HN5 cell lines.

3.(i).A.(1).5) Growth-inhibitory effects on human malignant tumor cell lines (Reports UH2008/00132/02, 2011N116394_00, 2011N116395_00, UH2008/00145/03, and 20011N120928_00)

i) *In vitro*

(a) Human malignant melanoma-derived cell lines

The growth-inhibitory effects of dabrafenib (free base) were determined under high- and low-density cell culture conditions, in 11 BRAF V600 mutant human malignant melanoma cell lines by measuring the intracellular ATP levels. The IC_{50} values of dabrafenib were as shown in the following table.

Growth-inhibitory effects of dabrafenib on BRAF V600 mutant cell lines derived from human malignant melanoma

Malignant melanoma-derived cell line	BRAF mutation	IC_{50} (nmol/L)	
		High cell density	Low cell density
MALME-3M	V600E	1	1
UACC-62		1	1
C32TG		1	2
SK-MEL-1		-	2
M14		2	3
SK-MEL-28		2	3
A375		3	6
SK-MEL-3		3	11
UACC-257		5	6
SH-4		6	10
WM-115	V600D	3	7

n = 1; -, Not tested

The growth-inhibitory effects of dabrafenib (free base) were determined in 17 BRAF V600 mutant cell lines derived from human malignant melanoma based on intracellular ATP levels. The IC_{50} values of dabrafenib were as shown in the following table.

Growth-inhibitory effects of dabrafenib on BRAF V600 mutant cell lines derived from human malignant melanoma

Malignant melanoma-derived cell line	BRAF mutation	n	IC_{50} (nmol/L)
UACC-257	V600E	12	10 ± 2
SK-MEL-1		7	17 ± 5
COLO-829		14	23 ± 12
A101D		10	42 ± 23
SK-MEL-24		4	151 ± 111
SK-MEL-5		8	171 ± 119
SK-MEL-3		7	>10,000
A2058		14	>10,000
SK-MEL-28		4	10 ± 3
UACC-62		11	12 ± 6
A375P F11		13	43 ± 23
WW165	V600K	6	5 ± 1
IGR-1		6	>10,000
YUMAC		8	7 ± 2
YULAC		4	18 ± 11
YUSIT1		4	14 ± 3
WM-115	V600D	≥2	65*

Mean ± SD; *, Mean

(b) Cell lines derived from human malignant tumors other than malignant melanoma

The growth-inhibitory effects of dabrafenib (free base) were determined in BRAF V600 mutant cell lines derived from human malignant tumors other than malignant melanoma based on intracellular ATP levels. The IC_{50} values of dabrafenib were as shown in the following table.

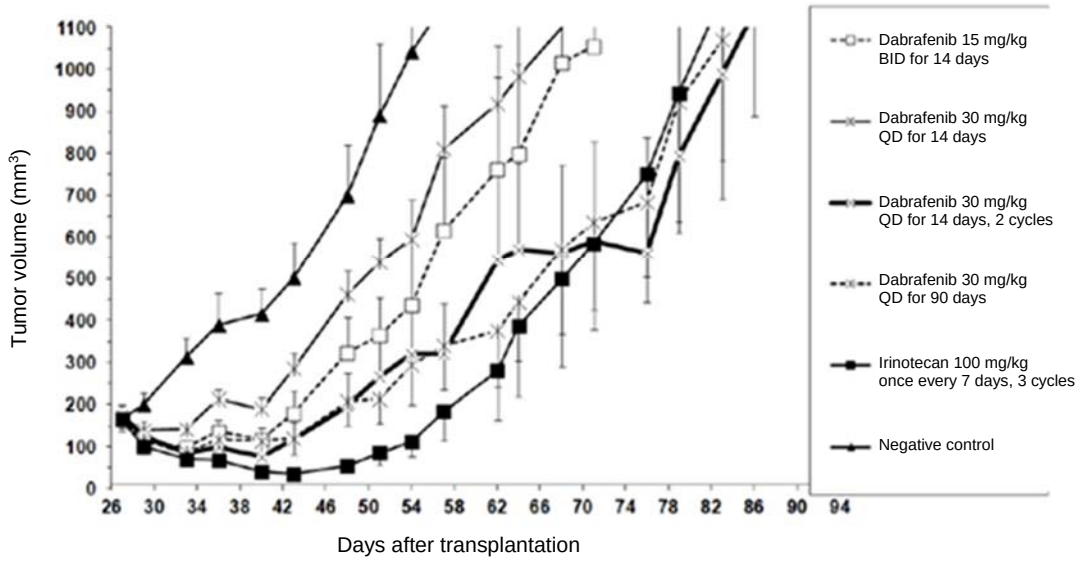
Growth-inhibitory effects of dabrafenib on BRAF V600 mutant cell lines derived from human malignant tumors other than malignant melanoma

Cell line	Cancer type	BRAF mutation	IC_{50} (nmol/L)	
			High cell density	Low cell density
Colo205	Colorectal cancer	V600E	4	9
SW 1417			158	-
RKO			2142	2901
DU-4475	Breast cancer		6	4
ES-2	Ovarian cancer		31	91
SW 872	Liposarcoma		-	439
A673	Ewing's sarcoma		>10,000	>10,000
HT-29	Colorectal cancer	T119S, V600E	1956	66
NCI-H292	Lung cancer	T119S, V600E	>10,000	>10,000

n = 1; -, Not tested

ii) *In vivo*

The inhibitory effects of dabrafenib (free base) was investigated in nude mice subcutaneously transplanted with A375P F11 cell line. Starting from approximately 4 weeks post-transplantation when the tumor volume reached approximately 150 to 200 mm^3, animals were subjected to one of the following treatments: (a) 14-day repeated oral administration of dabrafenib 15 mg/kg twice daily (BID), (b) 14-day repeated oral administration of dabrafenib 30 mg/kg once daily (QD), (c) 90-day repeated oral administration of dabrafenib30 mg/kg QD, and (d) 14-day repeated oral administration of dabrafenib 30 mg/kg QD. The treatment was then terminated and, when the tumor volume reached approximately 500 mm^3, dabrafenib 30 mg/kg QD was administered for an additional 14 days, and the tumor volume was measured after this additional treatment was completed. Animals in the negative control group received 0.5% hydroxypropylmethylcellulose (HPMC) and 0.2% polyoxyethylene (20) sorbitan monooleate (Tween 80), and animals in the comparator group received irinotecan hydrochloride hydrate 100 mg/kg, both intraperitoneally once weekly, 3 times in total. All dabrafenib groups showed a tumor growth-inhibitory effect compared with the negative control group.



Tumor growth-inhibitory effects of dabrafenib on A375P F11 cell line
Mean ± standard error; n = 7 to 8

3.(i).A.(1).6) Pharmacological effects of dabrafenib metabolites (Reports UH2010/00045/02, 2011N111729_00, 2012N139510_00, 2013N178509_00, 2012N147468_00, and UH2009/00016/01)

Pharmacological effects of M4 (carboxy-dabrafenib), M7 (hydroxy-dabrafenib), and M8 (desmethyl-dabrafenib), the major metabolites of dabrafenib (free base) in human plasma [see "4.(ii).A.(1) Japanese clinical studies" and "4.(ii).A.(2) Foreign clinical studies"], were evaluated. The following results were obtained.

- The inhibitory effects of dabrafenib metabolites (M4, M7, and M8) on phosphorylation of wild-type human BRAF, BRAF mutations (V600E, V600K, and V600D), and carboxyl terminal of constitutively activated CRAF (recombinant protein) were determined based on ATPase activity of MEK. The IC_{50} values of each metabolite were as shown in the following table.

Inhibitory effects of dabrafenib metabolites on RAF phosphorylation

Kinase	IC_{50} (nmol/L)			
	Dabrafenib (free base)	M4	M7	M8
Wild type BRAF	2.8, 1.7	77.8, 136.1	12.7, 12.2	3.5, 2.9
BRAF V600E mutation	0.70, 0.60	15.1, 18.0	1.8, 2.0	1.3, 1.0
BRAF V600K mutation	0.51, 0.50	6.0, 6.6	1.3, 1.3	0.55, 0.58
BRAF V600D mutation	1.83, 1.85	51.3, 48.8	6.44, 6.32	2.9, 2.7
CRAF*	2.9, 2.2	37.3, 72.1	15.0, 14.6	3.8, 2.5

n = 2, individual values; *, Carboxyl terminal of constitutively activated CRAF

- The inhibitory effects of dabrafenib metabolites (M4, M7, and M8) on ERK phosphorylation were determined in SK-MEL-28 cell line by Western blotting. The IC_{50} values of dabrafenib (free base), M7, M8, and M4 were 9, 7, 8, and 156 nmol/L, respectively.

- The growth-inhibitory effects of dabrafenib metabolites (M4, M7, and M8) were evaluated based on intracellular ATP levels in 11 BRAF V600 mutation-positive cell lines derived from human malignant melanoma. Dabrafenib (free base) inhibited the growth in 8 strains (YUMAC, UACC-257, COLO-829, WM-115, A101D, SK-MEL-5, A375P F11, and SK-MEL-24) with IC_{50} of 5 to 166 nmol/L. Against these 8 strains, the IC_{50} values of M7 and M8 were 10 to 308 nmol/L, whereas the IC_{50} value of M4 was >1000 nmol/L.

3.(i).A.(2) Secondary pharmacodynamics (Reports UH2009/00010/00 and UH2008/00132/02)

The effects of dabrafenib (free base) on the activation etc., of 30 different types of receptors, ion channels, transporters, kinases, and enzymes were evaluated based on intracellular calcium ion concentration etc. Dabrafenib exhibited an agonistic effect on α2C adrenergic receptor with a 50% effective concentration (EC_{50}) of 300 nmol/L. The IC_{50} values of dabrafenib against LCK, GSK3β, and Aurora B were 600, 800, and 3200 nmol/L, respectively.

The growth-inhibitory effects of dabrafenib (free base) were evaluated based on ATP levels in human umbilical vein endothelial cells (HUVEC) in the presence and absence of vascular endothelial growth factor (VEGF). Dabrafenib had no effect (IC_{50} >20,000 nmol/L) on HUVEC growth in the absence of VEGF, but showed a weak growth-inhibitory effect (IC_{50} 276 nmol/L) in the presence of VEGF.

Human myeloma cells were cultured in the presence of recombinant human GM-CSF, and the effect of dabrafenib (free base) on colony formation was measured by the CFU-GM colony formation method. The IC_{50} value of dabrafenib against CFU-GM colony formation was 3600 nmol/L.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effects on central nervous system (Report VD2008/00869/00)

A single oral dose of dabrafenib (free base) 5, 20, or 200 mg/kg was administered to rats (n = 8/group), and the effects of dabrafenib on body temperature and neurobehavior were studied. Dabrafenib had no effects on the central nervous system.

3.(i).A.(3).2) Effects on cardiovascular and respiratory systems

i) Effect on human *ether-a-go-go*-related gene potassium current (Reports FD2008/00376/00 and UH2010/00045/02[non- GLP])

The effect of dabrafenib (free base; 1.5-30 μmol/L) on human *ether-a-go-go*-related gene (hERG) potassium current was studied in human embryonic kidney-derived cell line HEK293 transfected with hERG. Dabrafenib at ≥5 μmol/L (2.6 μg/mL) inhibited hERG potassium current with IC_{50} of >30 μmol/L. The IC_{50} values of the metabolites of dabrafenib (M4, M7, and M8) were all >30 μmol/L.

ii) Effects on cardiovascular system of rats and dogs (Reports CD2008/01717/00 [non-GLP] and CD2008/001280/00)

A single oral dose of dabrafenib (free base) 5, 20, or 200 mg/kg was administered to rats (n = 4/group) according to a Latin square design, and the effects of dabrafenib on arterial blood pressure, heart rate, and body temperature were evaluated. A mild to moderate increase (maximum 18%) in heart rate was noted in a dose-dependent manner. A single oral dose of dabrafenib (free base) 1, 5, or 50 mg/kg was administered to dogs (n = 4/group) according to a Latin square design, and the effects of dabrafenib on blood pressure, heart rate, electrocardiogram, and body temperature were studied. A mild increase in heart rate and a decrease in PR interval were noted after administration of dabrafenib 50 mg/kg.

iii) Effects on left ventricular coronary perfusion preparation of rabbits (Report UD2009/00043/00 [non-GLP])

QT interval, QRS interval, transmural dispersion of repolarization (or Tp-e interval), and torsades de pointes (TdP) score were studied in left ventricular coronary perfusion samples of rabbits (n = 4). A concentration-dependent decrease in QT interval was noted over the dabrafenib (free base) concentrations of 1 to 30 μmol/L, but effects on QRS interval were not noted. Dabrafenib 30 μmol/L decreased Tp-e interval by approximately 47%, but the TdP score was negative (-1.3 to 2 points). Dabrafenib 30 μmol/L also decreased myocardial contractility by up to 64%.

The risk of dabrafenib-induced cardiac disorders and QT/QTc interval prolongation will be described in "4.(iii).B.(3).3) Cardiac disorders" and "4.(iii).B.(3).9).(d) QT/QTc interval prolongation", taking account of the clinical study results also.

3.(i).A.(3).3) Effects on respiratory system (Report CD2008/01279/00)

A single oral dose of dabrafenib (free base) 5, 20, or 200 mg/kg was administered to rats (n = 4/group) according to a Latin square design, and the effects on respiratory rate, tidal volume, minute ventilation,

airway resistance, and body temperature were evaluated. Dabrafenib had no effects on the respiratory system.

3.(i).A.(3).4) Others (Reports 2013N159876_00, 2013N160976_00, and 2012N153974_00)

Pyrexia was observed in clinical studies of dabrafenib [see "4.(iii).B.(3).5) Pyrexia"]. Therefore, the effects of dabrafenib (free base) on prostanoid receptor and on cytokine release were studied. The following results were obtained.

- The effects of dabrafenib on human prostanoid receptors (EP1, EP2, EP3, and EP4) were tested by calcium influx assay. Dabrafenib showed neither agonistic nor antagonistic effects on these receptors.

- The effects of dabrafenib (free base) on the release of 9 types of cytokines (IFN-α, IFN-γ, IP-10, IL-1β, IL-6, IL-8, IL-10, IL-12p70, and TNF-α) were determined in human peripheral blood mononuclear cells (PBMC) by electrochemiluminescence immunoassay. Dabrafenib had no effects on the release of these cytokines.

3.(i).A.(4) Pharmacodynamic drug interactions

3.(i).A.(4).1) Growth-inhibitory effects on BRAF V600 mutant cell lines derived from human malignant melanoma (Reports 2011N116395_00, 2011N116394_00, 2012N132871_01, 2012N139280_00, and 2012N152372_01)

i) *In vitro*

The growth-inhibitory effects of dabrafenib monotherapy, TRA monotherapy, and their combination (dabrafenib/TRA) were evaluated based on intracellular ATP levels in 17 different types of BRAF V600 mutant cell lines derived from human malignant melanoma. The IC_{50} values and the combination index (CI) of dabrafenib/TRA were as shown in the following table. The applicant explained that the results demonstrated the enhancement of growth inhibition (CI <1.1) by dabrafenib/TRA in 13 of 17 cell lines.

Growth-inhibitory effects on BRAF V600 mutant cell lines derived from human malignant melanoma

Malignant melanoma-derived cell line	BRAF mutation	n	IC_{50} (nmol/L)			CI
			Dabrafenib	TRA	Dabrafenib/TRA[*1]	
UACC-257	V600E	6	11 ± 1	4.1 ± 6.5	5 ± 2	0.75 ± 0.13
SK-MEL-1		6	18 ± 7	2.3 ± 0.6	5 ± 2	0.53 ± 0.06
COLO-829		8	26 ± 11	4.3 ± 1.4	9 ± 2	0.66 ± 0.16
A101D		6	33 ± 7	5.3 ± 1.2	10 ± 2	0.56 ± 0.09
SK-MEL-24		4	78 ± 72	5.8 ± 2.8	10 ± 3	0.40 ± 0.20
SK-MEL-5		6	188 ± 174	3.5 ± 1.6	11 ± 4	0.57 ± 0.37
SK-MEL-3		5	>10,000	>1000	>10,000	-
A2058		7	>10,000	>1000	>10,000	-
SK-MEL-28		2	10[*2]	1.4[*2]	4[*2]	0.76[*2]
UACC-62		6	11 ± 2	2.6 ± 2.6	5 ± 2	0.87 ± 0.06
A375P F11		≥2	49[*2]	6.3[*2]	16[*2]	0.65[*2]
WW165	V600K	2	5[*2]	0.3[*2]	2[*2]	1.18[*2]
IGR-1		2	>10,000	45.4[*2]	96[*2]	-
YUMAC		2	7[*2]	0.5[*2]	2[*2]	0.91[*2]
YULAC		2	17[*2]	0.8[*2]	4[*2]	0.90[*2]
YUSIT1		2	13[*2]	0.7[*2]	3[*2]	0.83[*2]
WM-115	V600D	4	41 ± 6	6.4 ± 4.1	14 ± 4	0.64 ± 0.03

Mean ± SD; -, Not calculated; *1, IC_{50} of dabrafenib when dabrafenib and TRA were coadministered in a molar ratio of 10:1; *2, Mean

The apoptosis-inducing effects of dabrafenib/TRA (molar ratio 10:1) were studied in A101D, A2058, A375P F11, SK-MEL-1, SK-MEL-3, UACC-62, UACC-257, and YUMAC cell lines. No enhanced apoptosis induction was found in dabrafenib/TRA combination treatment compared with either dabrafenib or TRA treatment alone.

ii) *In vivo*

Nude mice subcutaneously transplanted with A375P F11 cell line orally received dabrafenib alone (30, 100 mg/kg QD), TRA alone (0.3, 1 mg/kg QD), or dabrafenib/TRA (100 mg/kg + 0.3 mg/kg or 30 mg/kg + 1 mg/kg QD) for 60 days starting from 21 days post-transplantation when the tumor volume reached 108 to 221 mm^3. A statistically significant increase ($P < 0.001$, Log-rank test) in survival rate was observed in the dabrafenib/TRA group compared with the vehicle (0.5% HPMC, 0.2% Tween 80) group.

Nude mice subcutaneously transplanted with A375P F11 cell line orally received dabrafenib alone 30, 300 mg/kg QD, TRA alone 0.3 mg QD, or dabrafenib/TRA30 mg/kg + 0.3 mg/kg QD, for 90 days starting from approximately 4 weeks post-transplantation when the tumor volume reached 100 to 300 mm^3, and the tumor volume was measured after the treatment was completed. The tumor growth-inhibitory effects was enhanced in the dabrafenib/TRA group compared with the dabrafenib or TRA alone groups, albeit not evaluated statistically.

3.(i).A.(4).2) Safety pharmacology (Reports 2013N160976_00 and 2012N153974_00)

Peripheral blood mononuclear cells (PBMC) collected from healthy adult subjects (n = 3) were treated with dabrafenib, TRA, or any dabrafenib metabolites (hydroxylated form, carboxylated form, and demethylated form [3 dabrafenib metabolites]), and the concentrations of 9 cytokines (IFN-α, IFN-γ, IP-10, IL-1β, IL-6, IL-8, IL-10, IL-12p70, and TNF-α) were determined in the culture supernatant by electrochemiluminescence immunoassay. Treatment with dabrafenib, any 3 dabrafenib metabolites, or TRA did not increase cytokine concentrations.

3.(i).B Outline of the review by PMDA

On the basis of the submitted data and on the results of the following reviews, PMDA has concluded that the efficacy of dabrafenib against BRAF V600 mutation-positive malignant melanoma can be expected.

Mechanism of action and efficacy of dabrafenib

The applicant's explanation for the mechanism of action of dabrafenib against BRAF V600 mutation-positive malignant melanoma:

With the BRAF mutations, serine/threonine kinase is constitutively activated, resulting in the activation of MEK and ERK in the downstream of the signal transduction pathway (*Cell.* 2004;116:855-867), leading to enhanced tumor growth, inhibition of tumor apoptosis, etc.

The applicant considered that dabrafenib inhibits kinase activity of BRAF V600 mutations, thereby inhibiting the phosphorylation of MEK and ERK in the downstream, leading to cell growth inhibition of BRAF V600 mutation-positive tumors [see "3.(i).A.(1).3) Inhibitory effects on phosphorylation of MEK and ERK" and "3.(i).A.(1).5) Growth-inhibitory effects on human malignant tumor cell lines"]. Since *V600E* and *V600K* gene mutations account for approximately 80% to 90% and 10% to 20%, respectively, of *BRAF* mutations in malignant melanoma (*J Translational Med.* 2010;8:67), the efficacy of dabrafenib against BRAF V600 mutation-positive malignant melanoma can be expected.

PMDA accepted the applicant's explanation.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

Pharmacokinetics (PK) of dabrafenib in animals was investigated in mice, rats, dogs, and monkeys. The plasma protein binding, drug metabolizing enzymes, and transporters of dabrafenib were studied in biomaterials of human or animal origin. Pulverized dabrafenib or dabrafenib (free base) was used in *in vitro* studies unless otherwise specified.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose administration

Male mice, rats, dogs, and monkeys received a single oral dose of dabrafenib (free base) 10, 4, 0.7, or 1 mg/kg, respectively, under fasted conditions, or a single intravenous dose of dabrafenib (free base) 2.5, 2, 0.6, or 0.5 mg/kg, respectively, and concentration of unchanged dabrafenib in blood was determined (the table below). Bioavailability (BA) following oral administration of dabrafenib (free base) to mice, rats, dogs, and monkeys was 70%, 77%, 82%, and 46%, respectively. Blood clearance of dabrafenib in these respective animals was 48%, 32%, 12%, and 52% of hepatic blood flow rate (90.0, 55.2, 30.9, and 43.6 mL/min/kg, respectively [*Pharm Res*. 1993;10:1093-1095]). The applicant explained that blood clearance observed was the lowest in dogs possibly because dabrafenib is less prone to be metabolized in dogs than in other animals, on the following grounds: (a) Of unchanged dabrafenib and dabrafenib metabolites (dabrafenib-related substances) observed in dog plasma, unchanged dabrafenib was the

major compound detected [see "3.(ii).A.(3).2) *In vivo* metabolism"], (b) Species difference in hepatic drug-metabolizing enzymes has been reported (e.g., *Expert Opin Drug Metab Toxicol.* 2006;2:875-894), and (c) No clear species difference was found in the urinary excretion rate of dabrafenib [see "3.(ii).A.(4) Excretion"]

PK parameters of unchanged dabrafenib in each animal species

Animal species	Dose (route of administration)	C_{max} (μg/mL)	t_{max} *1 (h)	AUC_{inf} (μg·h/mL)	AUC_t (μg·h/mL)	$t_{1/2}$ (h)	CLb (mL/min/kg)	Vd_{ss} (L/kg)
Mice	2.5 mg/kg (intravenously)	3.11 ± 0.33	-	1.23 ± 0.20	1.21 ± 0.19	0.3 ± 0.1	43.5 ± 6.8	1.0 ± 0.1
	10 mg/kg*2 (orally)	3.91 ± 0.82	0.3 (0.3, 0.5)	-	2.51*3	-	-	-
Rats	2 mg/kg (intravenously)	1.42 ± 0.29	-	2.13 ± 0.46	2.10 ± 0.47	0.7 ± 0.1	17.6 ± 4.3	1.0 ± 0.1
	4 mg/kg (orally)	1.21 ± 0.09	0.7 (0.3, 1.0)	3.18 ± 0.29	3.13 ± 0.28	0.8 ± 0.2	-	-
Dogs	0.6 mg/kg (intravenously)	1.20 ± 0.15	-	2.71 ± 0.20	2.70 ± 0.20	2.8 ± 0.7	3.6 ± 0.3	0.4 ± 0.1
	0.7 mg/kg (orally)	0.90 ± 0.13	1.0 (0.7, 1.0)	2.74 ± 0.20	2.72 ± 0.20	3.0 ± 0.5	-	-
Monkeys	0.5 mg/kg (intravenously)	0.37 ± 0.05	-	0.42 ± 0.05	0.41 ± 0.05	0.3 ± 0.1	22.5 ± 1.8	0.5 ± 0.1
	1 mg/kg (orally)	0.22 ± 0.04	0.7 (0.7, 1.0)	0.33 ± 0.01	0.32 ± 0.13	1.0 ± 0.2	-	-

n = 3; Mean ± SD; -, Not calculated; *1, Median (range); *2, n = 21; *3, Mean; CLb, Blood clearance

Male and female rats received a single oral dose of non-pulverized dabrafenib 20-600 mg/kg under fed conditions, and plasma concentration of unchanged dabrafenib was determined (the table below). No clear sex difference was observed in the exposure to unchanged dabrafenib.

PK parameters of unchanged dabrafenib (male and female rats, single oral administration)

Dose (mg/kg)	C_{max} (μg/mL)		t_{max} (h)*		AUC_t (μg·h/mL)	
	Male	Female	Male	Female	Male	Female
20	1.73 ± 0.40	1.70 ± 0.38	2.0 (1.0, 2.0)	1.0 (1.0, 1.0)	8.70 ± 2.51	6.61 ± 2.22
200	2.67 ± 0.59	2.39 ± 0.43	2.0 (2.0, 4.0)	2.0 (2.0, 2.0)	29.4 ± 15.0	28.8 ± 14.6
400	4.20 ± 0.89	3.58 ± 0.25	2.0 (2.0, 4.0)	2.0 (2.0, 24.0)	48.0 ± 26.9	42.3 ± 21.0
600	9.69 ± 1.47	16.9 ± 4.8	1.0 (0.5, 1.0)	1.0 (1.0, 1.0)	49.3 ± 2.2	81.6 ± 15.7

n = 3; Mean± SD; *, Median (range)

Male dogs received a single oral dose of dabrafenib (free base) 10 mg/kg or dabrafenib 10 mg/kg under fed conditions, and plasma concentration of unchanged dabrafenib was determined. C_{max} after administration of dabrafenib (free base) and dabrafenib was 2.87 ± 1.16 and 6.65 ± 3.39 μg/mL, respectively, and AUC_t was 17.5 ± 8.3 and 26.8 ± 13.5 μg·h/mL, respectively.

3.(ii).A.(1).2) Repeat-dose administration

Male and female rats orally received dabrafenib (free base) 20, 200, or 400 mg/kg QD under fed conditions for 13 weeks, and plasma concentration of unchanged dabrafenib was measured (the table below). No clear sex difference was observed in the exposure to unchanged dabrafenib. The exposure to unchanged dabrafenib decreased on Day 28 compared to Day 1 in all doses tested. The exposure on Day 91 was roughly similar to that on Day 1. Because the exposure to unchanged dabrafenib on Day 91 increased compared to Day 28, the applicant explained that the reason is unknown for the decrease in the exposure from Day 1 to Day 28, although the possibility of induced drug-metabolizing enzymes or saturated absorption was considered.

PK parameters of unchanged dabrafenib (male and female rats, 13-week repeated oral administration)

Dose (mg/kg/day)	Time points (Day)	C_{max} (μg/mL)		t_{max} (h)*		AUC_t (μg·h/mL)	
		Male	Female	Male	Female	Male	Female
20	1	1.42 ± 0.06	1.78 ± 0.35	4.0 (1.0, 4.0)	1.0 (1.0, 4.0)	11.7 ± 3.1	11.2 ± 4.9
	28	0.84 ± 0.17	1.48 ± 0.22	2.0 (1.0, 4.0)	1.0 (0.5, 1.0)	4.54 ± 1.66	6.32 ± 2.05
	91	1.16 ± 0.32	1.93 ± 0.42	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	6.32 ± 3.11	10.1 ± 1.9
200	1	1.46 ± 0.19	1.95 ± 0.53	4.0 (4.0, 8.0)	4.0 (1.0, 8.0)	14.5 ± 0.6	17.3 ± 2.1
	28	0.92 ± 0.17	1.36 ± 0.22	2.0 (0.5, 1.0)	1.0 (1.0, 1.0)	6.41 ± 1.06	7.39 ± 3.13
	91	1.94 ± 0.25	5.83 ± 2.61	1.0 (1.0, 2.0)	0.5 (0.5, 1.0)	18.4 ± 4.0	21.2 ± 9.9
400	1	1.76 ± 0.62	1.76 ± 0.60	4.0 (2.0, 8.0)	2.0 (1.0, 4.0)	31.5 ± 11.2	24.6 ± 16.3
	28	0.82 ± 0.24	1.75 ± 0.52	4.0 (4.0, 8.0)	1.0 (1.0, 1.0)	8.64 ± 2.03	12.6 ± 7.4
	91	1.69 ± 0.06	3.19 ± 0.47	1.0 (1.0, 2.0)	0.5 (0.5, 1.0)	16.8 ± 1.6	26.8 ± 8.4

n = 3; Mean± SD; *, Median (range)

Male and female dogs orally received dabrafenib (free base) 1, 5, or 50 mg/kg QD under fed conditions for 4 weeks, and plasma concentration of unchanged dabrafenib was determined (the table below). No clear sex difference was observed in the exposure to unchanged dabrafenib.

PK parameters of dabrafenib (free base) (male and female dogs, 4-week repeated oral administration)

Dose (mg/kg/day)	n	Time points (Day)	C_{max} (μg/mL)		t_{max} (h)*		AUC_t (μg·h/mL)	
			Male	Female	Male	Female	Male	Female
1	3	1	1.13 ± 0.40	1.21 ± 0.78	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	4.47 ± 0.76	5.83 ± 4.90
		28	0.89 ± 0.26	0.84 ± 0.10	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	4.10 ± 0.69	4.48 ± 2.57
5	3	1	3.69 ± 1.68	3.23 ± 2.06	2.0 (1.0, 2.0)	1.0 (1.0, 1.0)	19.2 ± 4.2	17.3 ± 12.6
		28	2.73 ± 1.19	2.62 ± 0.96	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	10.5 ± 3.4	14.0 ± 7.0
50	5	1	8.87 ± 4.81	6.58 ± 1.74	1.0 (0.5, 4.0)	1.0 (1.0, 2.0)	48.9 ± 22.9	35.7 ± 13.3
		28	8.41 ± 2.66	6.85 ± 1.87	1.0 (1.0, 4.0)	1.0 (1.0, 1.0)	40.2 ± 8.2	45.2 ± 25.3

Mean ± SD; *, Median (range)

In rats and dogs, the exposure to unchanged dabrafenib increased less than dose-proportionally. The applicant explained that these results were caused by the decrease in the solubility of dabrafenib with the increase in dose, resulting in the decreased absorption of dabrafenib from the intestinal tract.

3.(ii).A.(1).3) *In vitro* membrane permeability

The digestive tract permeability of dabrafenib and its metabolites M4 (carboxy-dabrafenib), M7 (hydroxy-dabrafenib), and M8 (desmethyl-dabrafenib) was investigated in dog kidney-derived MDCKII cell line engineered to express human P-glycoprotein (P-gp) (P-gp-expressing MDCKII cell line). In the presence of the P-gp inhibitor GF120918 (2 μmol/L), the apparent permeability coefficient of dabrafenib, M4, M7, and M8 (5 μmol/L each) from the apical surface to the basal surface ($P_{app\ A\rightarrow B}$) was 14.8 $\times 10^{-6}$, 0.2×10^{-6}, 7.7×10^{-6}, and 37.4×10^{-6} cm/sec, respectively. The applicant explained that dabrafenib, M7, and M8 have a high membrane permeability and M4 has a low membrane permeability, given that $P_{app\ A\rightarrow B}$ of amprenavir (5 μmol/L), a compound with a high permeability, was 11.0×10^{-6} cm/sec in the presence of GF120918 (2 μmol/L).

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Tissue distribution

Pigmented male and female rats received a single oral dose of ^{14}C-labeled dabrafenib (free base) 10 mg/kg, and tissue distribution of radioactivity was determined by quantitative whole-body autoradiography.

In males, radioactivity was distributed in a wide range of tissues after oral administration, and tissue radioactivity concentration reached the maximum level at 4 hours after administration in most tissues including blood. The maximum tissue radioactivity concentrations in the liver (12.87 μg Eq./g), kidneys (1.26 μg Eq./g), brown fat (0.89 μg Eq./g), intestinal mucosa (cecum [173.56 μg Eq./g], large intestine [79.19 μg Eq./g], small intestine [11.93 μg Eq./g], and stomach [2.27 μg Eq./g]) were higher than that in blood (0.86 μg Eq./g). No radioactivity was detected in the brain. Tissue radioactivity concentrations decreased below the lower limit of quantitation (0.040 μg Eq./g) in most tissues including melanin-containing tissues (uvea, meninges, and pigmented skin) within 24 hours after administration. Tissue distribution of radioactivity in females was similar to that observed in males.

3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells

Plasma samples of mice, rats, dogs, monkeys, and humans were incubated with dabrafenib or a dabrafenib metabolite (M4, M7, or M8 [only M7 was incubated with monkey plasma]), 2 μg/mL each for 4 hours at 37°C, and plasma protein binding of dabrafenib and its metabolites was investigated by equilibrium dialysis. The mean plasma protein binding rate of dabrafenib, in mice, rats, dogs, monkeys, and humans, was 99.5%, 99.7%, 99.0%, 98.4%, and 98.6%, respectively. The plasma protein binding rate of metabolites in mice, rats, dogs, monkeys, and humans was 93.3%, 99.3%, 95.1%, unknown, and 99.2%, respectively, for M4; 97.2%, 98.1%, 94.9%, 95.7%, and 96.3%, respectively, for M7; and 99.2%, 99.7%, 99.2%, unknown, and 99.9%, respectively, for M8.

Human plasma samples were incubated with dabrafenib (0.1-5 μg/mL) or its metabolites (M4 [0.25-20 μg/mL], M7 [0.1-5 μg/mL], or M8 [4-10 μg/mL]) for 10 hours at 37°C, and plasma protein binding of dabrafenib and its metabolites was investigated by equilibrium dialysis. The plasma protein binding rate of dabrafenib, M4, M7, and M8 was 99.6% to 99.7%, 99.5%, 96.3%, and 99.9%, respectively, roughly constant over the concentration range tested.

Blood samples of mice, rats, dogs, monkeys, and humans were incubated with dabrafenib or its metabolites (M4, M7, M8 [only M7 was incubated with monkey blood]), 2 μg/mL each for 30 minutes at 37°C, to investigate the distribution of dabrafenib or its metabolites in blood cells. The mean blood/plasma ratio of radioactivity of dabrafenib in mice, rats, dogs, monkeys, and humans was 0.63, 0.58, 0.49, 0.53, and 0.54, respectively. The blood/plasma ratio of radioactivity of metabolites was 0.57, 0.52, 0.52, unknown, and 0.51, respectively, for M4; 0.61, 0.66, 0.50, 0.64, and 0.55, respectively, for M7; and 0.53, 0.45, 0.71, unknown, and 0.56, respectively, for M8. The applicant explained that the distribution of dabrafenib and its metabolites in blood cells was considered low in all species tested.

3.(ii).A.(2).3) Placental and fetal transfer

The applicant's explanation:
Although placental transfer of dabrafenib was not investigated, such a possibility cannot be excluded since dabrafenib is a lipophilic low molecular weight compound with a high membrane permeability.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) *In vitro* metabolism

Hepatocytes of mice, rats, dogs, monkeys, rabbits, and humans were incubated with ^{14}C-labeled dabrafenib (20 μmol/L) for 24 hours (6 or 24 hours in monkeys) at 37°C, and dabrafenib metabolites were evaluated. M7 and M4 were detected in hepatocytes of all species tested, M6 (di-oxidation of *t*-butyl group) was detected only in animals, M3 (oxidation and glucuronide conjugate) in animals other than mice, M8 in animals other than dogs, and M5 (*N*-glucuronidation) in animals other than mice and monkeys. In human hepatocytes, M14 (hexose conjugation), M10 and M13 (hexose conjugate of oxidized dabrafenib), and M11 (*N*-glucuronidation) were detected in 1 of 3 samples. These metabolites were not detected in other species.

The applicant explained that CYP2C8 and CYP3A4 are likely to be mainly involved in the metabolism of dabrafenib in humans on the basis of the following results of the studies of cytochrome P450 (CYP) isoforms involved in the metabolism of dabrafenib.

- Dabrafenib (0.5 μmol/L) was incubated with human liver microsomes or with membrane vesicles of insect ovary-derived Sf9 cell line expressing CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4) for 30 minutes. Dabrafenib was metabolized by CYP2C8, CYP3A4, and CYP2C9-expression systems, and their contribution to dabrafenib metabolism, calculated from intrinsic clearance, was 56%, 23%, and 10%, respectively.

- ^{14}C-labeled dabrafenib (5 μmol/L) was incubated with human liver microsomes in the presence of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A inhibitors for 8 minutes. CYP2C8 inhibitor (montelukast sodium) and CYP3A inhibitor (azamulin), as compared with their absence, inhibited the metabolism of dabrafenib to M7 by 35% and 20%, respectively. Inhibitors of the other CYP isoforms did not inhibit the metabolism of dabrafenib markedly.

The following were investigated on the metabolism of dabrafenib metabolites (M4, M7, and M8).

- M4, M7, or M8 (0.5 μmol/L each) was incubated with human liver microsomes or with membrane vesicles of insect ovary-derived Sf9 cell line expressing human CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4) for 30 minutes. M7 and M8 were metabolized by the CYP3A4 expression system, and M8 was metabolized by CYP2C9 and CYP 2C19 expression systems as well. M4 was not metabolized by any of the CYP isoform expression systems tested.

- The contribution of alcohol dehydrogenase and aldehyde dehydrogenase to the metabolism of M7 was evaluated by incubating M7 (10 or 20 μmol/L) with human liver cytosol for 180 minutes. M7 was not metabolized in human liver cytosol.

3.(ii).A.(3).2) *In vivo* metabolism

A single oral dose of ^{14}C-labeled dabrafenib (free base) 30, 10, 10, and 10 mg/kg was administered to female mice, male and female rats, male and female dogs, and biliary-cannulated male rats, respectively, and metabolites in plasma, urine, feces, and bile were investigated as described below. The applicant explained that the major dabrafenib-related substance detected in the plasma of mice, rats, and dogs was M4, M7, and unchanged dabrafenib, respectively.

- In female mice, the percentage of unchanged dabrafenib, M4, M8, and M7 to the total amount of dabrafenib-related substances in plasma at 0.5 hours after treatment was 26.8%, 41.6%, 11.7%, and 11.3%, respectively, and decreased below the lower limit of quantitation at 24 hours after treatment.

- In male and female rats, unchanged dabrafenib and M7 were the major dabrafenib-related substance detected in plasma at 2 hours after treatment (23.3% and 51.7%, respectively, in male; 26.2% and 62.5%, respectively, in female). M4 and M8 were also detected. M7 and M4 were the major dabrafenib-related substance detected in plasma at 24 hours after treatment (51.0% and 11.7%, respectively, in male; 69.0% and 8.9%, respectively, in female). The fecal excretion rate of unchanged dabrafenib, M4, M7, and M8 (percentage of administered dose of dabrafenib excreted) up to 48 hours after treatment (up to 72 hours in 1 of 3 females) was 59%, 2.0%, 12%, and 13%, respectively, in males and 58%, 1.5%, 12%, and 8.0%, respectively, in females. In females, M4, M7, M6, and M26 were detected in the urine collected up to 24 hours after treatment (percentage of administered dose of dabrafenib excreted was <3% for all metabolites), while unchanged dabrafenib was not detected.

- In male and female dogs, unchanged dabrafenib was the major dabrafenib-related substance detected in plasma. The percentage of unchanged dabrafenib at 2 and 24 hours after treatment was 72.0% and 63.9%, respectively, in males and 80.4% and 39.9%, respectively, in females. In both males and females, the major metabolite in plasma was M7, and M4 and M26 were detected as well. Unchanged dabrafenib was the major dabrafenib-related substance detected in feces up to 48 hours after treatment (up to 24 hours in 1 each of 3 males and 3 females), and the fecal excretion rate of unchanged dabrafenib (percentage of administered dose of dabrafenib excreted) in males and females was 92% and 95%, respectively,. In both males and females, M4, M7, and M8 were detected in feces up to 48 hours after treatment.

- In biliary-cannulated male rats, M4, M8, M1 (oxidation, defluorination, glutathione conjugation), M3, M5, and M6 were detected up to 24 hours after treatment (up to 48 hours in 1 of 3 rats), and biliary excretion rate (percentage of administered dose of dabrafenib excreted) was 8.3%, 2.0%, 1.3%, 5.7%, 1.7%, and 3.6%, respectively. Unchanged dabrafenib was not detected in bile.

3.(ii).A.(4) Excretion

3.(ii).A.(4).1) Urinary, fecal, and biliary excretion

Male and female mice, male and female rats, male and female dogs, and biliary cannulated male mice and rats received a single oral dose of ^{14}C-labeled dabrafenib (free base in rats and dogs, dabrafenib mesilate in mice) 100, 10, 10, 100, and 10 mg/kg, respectively, (dabrafenib free base to rats and dogs, dabrafenib mesilate to mice) and the urinary and fecal excretion rates (percentage of administered

radioactivity excreted) were evaluated. On the basis of the results, the applicant explained that dabrafenib is mainly excreted in feces via bile.

- In mice, urinary and fecal excretion rates up to 96 hours after treatment were 3.4% and 95.2%, respectively, in males and 3.3% and 90.7%, respectively, in females, showing no clear sex difference.

- In rats, urinary and fecal excretion rates up to 168 hours after treatment were 0.8% and 92.9%, respectively, in males and 3.1% and 90.2%, respectively, in females, showing no clear sex difference.

- In dogs, urinary and fecal excretion rates up to 168 hours after treatment were 0.6% and 101%, respectively, in males and 0.5% and 103%, respectively, in females, showing no clear sex difference.

- In biliary cannulated male mice, urinary, fecal, and biliary excretion rates up to 96 hours after treatment were 1.9%, 18.3%, and 79.0%, respectively.

- In biliary cannulated male rats, urinary, fecal, and biliary excretion rates up to 96 hours after treatment were 3.4%, 64.4%, and 32.2%, respectively.

3.(ii).A.(4).2) Excretion in milk

The applicant's explanation:
Although excretion of dabrafenib in milk was not investigated, such a possibility cannot be excluded since dabrafenib is a lipophilic low molecular weight compound with a high membrane permeability.

3.(ii).A.(5) Pharmacokinetic interaction

3.(ii).A.(5).1) Enzyme inhibition

Substrates of CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A)[*3] were incubated with human liver microsomes in the presence of dabrafenib[*1] (0.1-100 μmol/L), dabrafenib (free base; 0.05-25 or 0.1-100 μmol/L[*2]), M4 (0.1-100 μmol/L), M7 (0.1-100 μmol/L), or M8 (0.1-100 μmol/L), and the effects of dabrafenib or its metabolites on the metabolism of each CYP isoform substrate were examined as follows.

*1: Effects of dabrafenib on the metabolism of the substrates of CYP1A2, CYP2C9, CYP2C19, and CYP2D6 were examined.
*2: Substrates of CYP1A2, CYP2C9, CYP2C19, and CYP3A were investigated over the concentration range of 0.05 to 25 μmol/L, and substrates of CYP2A6, CYP2B6, CYP2C8, and CYP 3A over the concentration range of 0.1 to 100 μmol/L.
*3: The substrates of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A used were phenacetin, coumarin, bupropion, rosiglitazone, diclofenac, S-mephenytoin, bufuralol, and testosterone, midazolam, atorvastatin and nifedipine, respectively.

- Dabrafenib inhibited CYP1A2, CYP2C9, and CYP2C19 (IC_{50}; 87, 7.2, and 22.4 μmol/L, respectively) and did not show, at the maximum concentration tested, any clear inhibitory effects on the metabolism of the substrate of CYP2D6.

- Dabrafenib (free base) inhibited CYP2C8, CYP2C9, CYP2C19, and CYP3A (IC_{50}; 8.2, 10.9, 11, and 15.6-32 μmol/L, respectively) and did not show, at the maximum concentration tested, any clear inhibitory effects on CYP1A2, CYP2A6, CYP2B6, or CYP2D6.

- M4 did not show, at the maximum concentration tested, any clear inhibitory effects on the metabolism of the substrate of any CYP isoform.

- M7 inhibited CYP1A2, CYP2C9, and CYP3A (IC_{50}; 83, 29, and 44 μmol/L, respectively) and did not show, at the maximum concentration tested, any clear inhibitory effects on the metabolism of the substrates of CYP2A6, CYP2B6, CYP2C8, CYP2C19, and CYP2D6.

- M8 inhibited CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A (IC_{50}; 78, 47, 6.3, 36, and 17-28 μmol/L, respectively) and did not show, at the maximum concentration tested, any clear inhibitory effects on the metabolism of the substrates of CYP1A2, CYP2A6, and CYP2D6.

The applicant's explanation on the possibility that dabrafenib and its metabolites induce pharmacokinetic interactions mediated by the inhibition of CYP isoforms:
In multiple oral administration of dabrafenib 150 mg BID in Japanese patients with solid tumors, C_{max} of dabrafenib, M4, M7, and M8 was 4.0, 16.9, 2.2, and 1.1 μmol/L, respectively [see "4.(ii).A.(1) Japanese clinical studies"]. Therefore, dabrafenib and its metabolites are unlikely to induce pharmacokinetic interactions mediated by the inhibition of CYP1A2, CYP2A6, CYP2B6, or CYP2D6 in clinical use. Although dabrafenib inhibited CYP2C9 and CYP3A, the results of pharmacokinetic interaction studies between dabrafenib and the substrates of CYP2C9 and CYP3A showed that exposure to the substrates of CYP2C9 and CYP3A was decreased by concomitant use of dabrafenib with either substrate of CYP2C9 or CYP3A [see "4.(ii).A.(3) Drug-drug interactions"], which suggests that dabrafenib induces CYP2C9 and CYP3A in clinical use.

3.(ii).A.(5).2) Enzyme induction
Human hepatocytes were incubated for 48 hours in the presence of dabrafenib (0.1-100 μmol/L), and the effects of dabrafenib on the induction of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) was investigated. mRNA of CYP2B6 and CYP3A4 increased in a dabrafenib concentration-dependent manner; mRNA of CYP2B6 and CYP3A4 in the dabrafenib 30 μmol/L group increased 32 and 30 fold, respectively, compared with the dabrafenib-untreated group. At the maximum concentration of dabrafenib tested, no increase in mRNA of CYP1A2 was observed.

Consequently, the applicant explained that CYP2B6 and CYP3A4 may be induced in the clinical use of dabrafenib.

3.(ii).A.(5).3) Transporters
The applicant explained that the following study results demonstrated that: (a) dabrafenib is a substrate of P-gp and breast cancer resistance protein (BCRP) and not a substrate of organic cation transporter (OCT) OCT1 or organic anion transporter polypeptide (OATP) OATP1A2, OATP1B1, OATP1B3, or OATP2B1, (b) M4 is a substrate of organic anion transporter (OAT) OAT1 and OAT3, OATP1A2, OATP1B1 and OATP1B3, and not a substrate of P-gp, and (c) M7 and M8 are substrates of P-gp and not substrates of OATP1A2, OATP1B1, or OATP1B3.

- P-gp-mediated transport of dabrafenib, M4, M7, and M8 (5 μmol/L) was investigated in P-gp-expressing MDCKII cell line. The ratio of permeability coefficient of dabrafenib, M4, M7, and M8 in the direction of secretion to that in the direction of absorption (efflux ratio) was 1.0, 1.3, 1.0, and 0.9, respectively, in the presence of a P-gp inhibitor (GF120918, 2 μmol/L) and 36, 1.8, 121, and 21, respectively, in the absence of a P-gp inhibitor.
- BCRP-mediated transport of dabrafenib (3 μmol/L) was investigated in MDCKII cell line engineered to express human BCRP (BCRP-expressing MDCKII cell line). The efflux ratio of dabrafenib in the presence and absence of BCRP inhibitor (GF120918, 5μmol/L) was 3.1 and 22, respectively.
- OAT1- or OAT3- mediated transport of M4 (0.5-100 μmol/L) was investigated in mouse proximal renal tubule-derived S2 cell line expressing human OAT1 or OAT3. M4 uptake was observed at 10 and 100 μmol/L.
- OCT1-, OATP1B1-, OATP1B3-, or OATP2B1-mediated transport of dabrafenib (0.3, 1 μmol/L), M4 (1-100 μmol/L), M7 (0.1-30 μmol/L) and M8 (0.1-30 μmol/L) was investigated in human hepatocyte slices. Intracellular uptake of dabrafenib was not inhibited in the presence of 10 μmol/L each of the inhibitor of OCT1 (quinidine), OATP1B1 and OATP1B3 (rifamycin) or OATP2B1 (montelukast), whereas intracellular uptake of M4, M7, and M8 was inhibited.
- OATP1B1- or OATP1B3-mediated transport of M4 (1-100 μmol/L), M7 (1 μmol/L), or M8 (1 μmol/L) was investigated in human embryonic kidney-derived HEK293 cell line expressing human OATP1B1 or OATP1B3. Transport of M7 and M8 was not inhibited in the presence of the inhibitor of OATP1B1 and OATP1B3 (rifamycin, 10 μmol/L), whereas transport of M4 was inhibited.
- OATP1A2-mediated transport of dabrafenib (0.3 μmol/L), M4 (0.5-50 μmol/L), M7 (0.3, 3 μmol/L) and M8 (0.3 μmol/L) was investigated in HEK293 cell line expressing human OATP1A2. Transport of dabrafenib, M7, and M8 was not inhibited in the presence of OATP1A2 inhibitor (ketoconazole 10 μmol/L), whereas transport of M4 was inhibited.

The applicant's explanation:
In multiple oral administration of dabrafenib 150 mg BID to Japanese patients with solid tumors, C_{max} of dabrafenib, M4, M7, and M8 was 4.0, 16.9, 2.2, and 1.1 μmol/L, respectively, [see "4.(ii).A.(1) Japanese clinical studies"] and the plasma protein non-binding rate of them was <1%, <1%, 3.7%, and <1%, respectively [see "3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells"]. In light of these and the following study results, dabrafenib and its metabolites are unlikely to cause pharmacokinetic interactions mediated by P-gp, BCRP, OATP1B1 and OATP1B3, OAT1 and OAT3, or OCT2 in the clinical use of dabrafenib.

- The inhibitory effects of dabrafenib (0.3-30 μmol/L), M4 (0.08-80 μmol/L), M7 (0.1-100 μmol/L), and M8 (0.1-100 μmol/L) on P-gp-mediated transport of ^{3}H-labeled digoxin (30 nmol/L) were investigated in P-gp-expressing MDCKII cell line. Dabrafenib, M4, M7, and M8 did not show, at their maximum concentrations tested, a clear inhibitory effect on P-gp.
- The inhibitory effects of dabrafenib (0.3-30 μmol/L), M4 (0.6-200 μmol/L), M7 (0.6-200 μmol/L), and M8 (0.6-200 μmol/L) on BCRP-mediated transport of ^{14}C-labeled cimetidine (0.1 μmol/L) were investigated in BCRP-expressing MDCKII cell line. M7 and M8 inhibited the transport of the substrate of BCRP (IC_{50}; 82 and 5.4 μmol/L, respectively). Dabrafenib (10, 30 μmol/L) and M4 (200 μmol/L) also inhibited the transport of the substrate of BCRP although they did not have an inhibitory effect at low concentrations within the concentration range tested, precluding the calculation of IC_{50}.
- The inhibitory effects of dabrafenib (0.1-30 μmol/L) on OATP1B1- or OATP1B3-mediated transport of each transporter substrate* were investigated in Chinese hamster ovary-derived cell line (CHO cell line) expressing human OATP1B1 and HEK293 cell line expressing human OATP1B3. Also, the inhibitory effects of M4, M7, and M8 (0.01-100 μmol/L) on OATP-mediated transport of each transporter substrate* were investigated in HEK293 cell line expressing human OATP1B1 or OATP1B3. As a result, dabrafenib, M4, M7, and M8 inhibited the transport of the substrate of OATP1B1 (IC_{50}; 1.4, 18, 4.3, and 0.83 μmol/L, respectively). Dabrafenib, M4, M7, and M8 inhibited the transport of the substrate of OATP1B3 as well (IC_{50}; 4.7, 20, 23, and 4.3 μmol/L, respectively).
- The inhibitory effects of dabrafenib, M4, M7, and M8 (0.027-100 μmol/L each) on OAT1- or OAT3-mediated transfer of each transporter substrate* were investigated in HEK293 cell line expressing human OAT1 or OAT 3. Dabrafenib, M7, and M8 inhibited the transport of OAT1 substrate (IC_{50}; 6.9, 29, and 10 μmol/L, respectively). Dabrafenib, M4, M7, and M8 inhibited the transport of OAT3 substrate (IC_{50}; 3.4, 9.0, 7.3, and 3.4 μmol/L, respectively). M4 (100 μmol/L) also inhibited OAT1 although IC_{50} could not be calculated.
- The inhibitory effects of dabrafenib, M4, M7, and M8 (0.003-50 μmol/L each) on OCT2-mediated transport of ^{14}C-metformin (10 μmol/L) were investigated in HEK293 cell line expressing human OCT2. Dabrafenib and M8 inhibited OCT2-mediated transport (IC_{50}; 9.3 and 27.9 μmol/L, respectively). In contrast, M4 and M7 did not show clear inhibitory effects on OCT2 at the maximum concentration tested.

  *: ^{3}H-labeled estradiol-17β-glucuronide (0.02 μmol/L) was used as the substrate of OATP1B1 and OATP1B3, and 6-carboxyfluorescein (5 μmol/L) as the substrate of OAT1 and OAT3.

3.(ii).B Outline of the review by PMDA

On the basis of the submitted data and the results of the following review, PMDA concluded that the applicant's discussions on the absorption, distribution, metabolism, excretion, and pharmacokinetic interactions of dabrafenib are acceptable.

Pharmacokinetic interactions

Results of the *in vitro* studies suggested that (a) dabrafenib inhibits CYP2C8 and CYP2C19 [see "3.(ii).A.(5).1) Enzyme inhibition"], (b) dabrafenib induces CYP2B6 [see "3.(ii).A.(5).2) Enzyme induction"], and (c) dabrafenib is a substrate of P-gp and BCRP [see "3.(ii).A.(5).3) Transporters"]. The applicant's explanation on the pharmacokinetic interactions of dabrafenib with the substrates of CYP2C8, CYP2C19, and CYP2B6 and with inhibitors of P-gp and BCRP in clinical use:

- In clinical studies, no adverse events caused by interaction of dabrafenib in patients concomitantly treated with a substrate of CYP2C8 or CYP2C19 was reported, which suggests that dabrafenib is unlikely to cause pharmacokinetic interactions mediated by CYP2C8 or CYP2C19 inhibition in clinical use.

- Given that (a) efavirenz, a substrate of CYP2B6, is unlikely to be used concomitantly with dabrafenib in clinical settings, and that (b) the dose of methadone hydrochloride, a CYP2B6 substrate used concomitantly in clinical studies, is adjusted according to the patient's condition, pharmacokinetic interactions mediated by CYP2B6 induction are unlikely to cause problems in the clinical use of dabrafenib.
- In light of the observation that (a) dabrafenib has a high membrane permeability [see "3.(ii).A.(1).3) *In vitro* membrane permeability"] and the BA of dabrafenib in humans is 94.5% [see "4.(i).A.(3) Foreign phase I study"], and that (b) no adverse events caused by drug interaction in patients concomitantly treated with a P-gp inhibitor were reported in the clinical studies, dabrafenib is unlikely to cause pharmacokinetic interaction with P-gp inhibitors in clinical use.
- In clinical studies, no adverse events caused by drug-drug interaction in patients concomitantly treated with BCRP inhibitors were reported, which suggests that dabrafenib is unlikely to cause pharmacokinetic interactions with BCRP inhibitors in clinical settings.

The applicant's explanation:
Taking account that *in vitro* studies showed dabrafenib is mainly metabolized by CYP3A4 and CYP2C8 [see "3.(ii).A.(3).1) *In vitro* metabolism"], the applicant is now studying the effects of concomitant use with rifampicin (Study 200072), a CYP3A- and CYP2C8-inducing drug, on the PK of dabrafenib, and will obtain the results in the ■ quarter of 20■.

PMDA's view:
In clinical studies conducted so far, pharmacokinetic interactions of dabrafenib with substrates of CYP2B6, CYP2C8, and CYP2C19 and with P-gp and BCRP inhibitors have not caused any clinically significant concerns. However, since information on pharmacokinetic interactions of dabrafenib mediated by drug-metabolizing enzymes and transporters is important for the proper use of dabrafenib, such information should be collected continuously and results of Study 200072 and other useful information should be provided to healthcare professionals in clinical settings appropriately.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

In *in vivo* studies, the solution containing 0.5% HPMC and 0.1% Tween 80 was used as vehicle unless otherwise specified.

3.(iii).A.(1) Single-dose toxicity

3.(iii).A.(1).1) Single oral dose toxicity study in rats (Reference data)

Rats (SD, n = 3/sex/group) received a single oral dose of dabrafenib 0 [vehicle], 20, 200, 400, or 600 mg/kg.

No deaths occurred. Decreased body weight was observed on Day 2 in the ≥20 mg/kg groups.

Consequently, the approximate lethal dose in this study was considered to be >600 mg/kg.

3.(iii).A.(1).2) Maximum tolerated dose study in dogs (Reference data)

Dogs (beagle, n = 2/sex/group) received dabrafenib 2.5, 20, 40, or 80 mg/kg/day orally on Day 1, 8, 15, and 36, respectively, by stepwise dose escalation, followed by a single oral dose of 80 mg/kg on Day 43, and by a single dose of 20 mg/kg twice, approximately 8 hours apart, on Day 58.

No deaths occurred. Decreased food consumption and decreased body weight occurred in females after dosing at ≥2.5 mg/kg, and vomiting after dosing at 20 mg/kg (twice daily) and 80 mg/kg.

Consequently, the approximate lethal dose in this study was considered to be >80 mg/kg.

3.(iii).A.(2) Repeat-dose toxicity

3.(iii).A.(2).1) Twenty six-week repeated oral dose toxicity study in mice

Mice (ICR, n = 22/sex/group) received dabrafenib 0 (vehicle, 25 mmol/L citrate solution containing 0.5% HPMC), 15, 50, or 150 mg/kg/day in repeated oral doses. The treatment period was 13 weeks (n = 10/sex/group) or 26 weeks (n = 12/sex/group).

No dabrafenib-related death occurred.

Adverse events observed in animals treated for 13 weeks were as follows: eosinophil count increased, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increased, hypertrophy/discoloration/sclerosis and necrosis/inflammation in liver, splenic hypertrophy, increased extramedullary hematopoesis in spleen, eosinophilic corpuscles in the respiratory epithelium of the nasal cavity, and vascular/perivascular inflammation and vascular wall necrosis in various tissues in the ≥15 mg/kg/day groups; hepatocellular hypertrophy, Kupffer cell hypertrophy/hyperplasia and increased mitotic figure in liver, increased cell density in bone marrow, hyperplasia/hyperkeratosis of mucosal epithelia in tongue, esophagus, and anterior stomach, and retention of sperm cells in testis in the ≥50 mg/kg/day groups; and decreased body weight, increased white blood cell, neutrophil, lymphocyte, and basophil counts, decreased glucose and albumin, increased liver and spleen weight, decreased thymus weight, thickening of forestomach wall, inflammation of tongue, esophagus, and stomach, pericholangitis, gallbladder inflammation, inflammation and necrosis of mandibular and mesenteric lymph nodes, decreased thymic lymphocyte count, and eosinophilic corpuscles in airway epithelium in the 150 mg/kg/day group.

Adverse events observed in animals treated for 26 weeks were as follows: increased white blood cell, neutrophil, lymphocyte, eosinophil, and basophil counts, decreased glucose, increased cell density in bone marrow, increased extramedullary hematopoiesis in spleen, hyperplasia/hyperkeratosis of mucosal epithelia in tongue, esophagus, and anterior stomach, stomach inflammation, eosinophilic corpuscles in the respiratory epithelium of the nasal cavity, inflammation of mandibular lymph node, and retention of sperm cells and cellular debris in testis in the ≥15 mg/kg/day groups; thickening of forestomach wall, necrosis/inflammation and increased mitotic figure in liver, hepatocellular hypertrophy, inflammation of esophagus, vascular/perivascular inflammation and vascular wall necrosis in various tissue, and inflammation of mesenteric lymph nodes in the ≥50 mg/kg/day groups; and tendency of reduced body weight gain, increased ALT and AST, decreased albumin, increased liver and spleen weight, decreased thymus weight, hypertrophy of mandibular and mesenteric lymph nodes, hypertrophy of spleen, adhesion/hypertrophy/discoloration of liver, hypertrophy/hyperplasia of Kupffer cells in liver, pericholangitis, gallbladder inflammation, tongue inflammation, esophageal ulcer, ectasia of rete testis, eosinophilic corpuscles in airway epithelium, and hypertrophy of bronchiolar epithelium in the 150 mg/kg/day group.

Consequently, the no observed adverse effect level (NOAEL) in this study was considered to be <15 mg/kg/day. $AUC_{0\text{-}24h}$ in the 15 mg/kg/day group (5.44-9.6 μg·h/mL) was approximately 0.5 to 0.8 times the clinical exposure.*

*: In the Japanese phase I study (Study BRF116056) in which dabrafenib 150 mg BID was administered orally to Japanese patients with solid tumors, $AUC_{0\text{-}24h}$ calculated from $AUC_{0\text{-}12h}$ observed in multiple administration was 11.8 μg·h/mL.

3.(iii).A.(2).2) Four-week repeated oral dose toxicity study in rats

Rats (SD, n = 10-16/sex/group) received dabrafenib free base; 0 (vehicle), 5, 20, or 200 mg/kg/day orally for 4 weeks. Six rats/sex/group in the 0 and 200 mg/kg groups were evaluated for reversibility after a 2-week recovery period following 4-week administration.

One of 16 males in the 200 mg/kg/day group was sacrificed moribund because of deteriorated conditions. The animal showed swelling of the hind limb, facial crust, chronic inflammation around phalanx, and vesicles and bleeding in the epidermis, from which the cause of the deteriorated conditions was determined to be external injury caused by fighting. This animal also showed localized degeneration of hepatic artery and spermatic granuloma in the epididymis, but they were not considered to be dabrafenib-related findings because they were not observed in other animals in this study and these findings are within the range (10%-20%) of the historical data in rats of the same strain (*Toxicologic Pathol.* 1998;26:843).

Adverse events observed were as follows: decreased triglycerides, localized degeneration of keratinocytes of epithelium in the border between forestomach and glandular stomach, increased red blood cell count in mandibular and cervical lymph node, degeneration of elongated spermatids and

retention of sperm cells in testis, and cellular debris in epididymis in the ≥5 mg/kg/day groups; increased frequency of cardiomyopathy in males in the ≥20 mg/kg/day groups; and decreases in body weight and food consumption, increased spleen weight, localized reddening and surface irregularity in the border between forestomach and glandular stomach in the 200 mg/kg/day group. All these findings were considered to be of little toxicological significance, for the following reasons: (i) decreased body weight and food consumption were not accompanied by changes in clinical conditions suggestive of debility, (ii) gastric findings did not show any effects on the mucosal epithelium or submucosa, (iii) increased red blood cells in mandibular and cervical lymph node did not show a dose-response relationship, and (iv) decreased triglycerides and increased spleen weight were not accompanied by related histopathological findings.

Cardiomyopathy was observed at a higher frequency in males of the ≥20 mg/kg/day groups, but the applicant concluded that the finding is unlikely to be related to dabrafenib and has little toxicological significance, for the following reasons:

- Cardiomyopathy is reported as a spontaneous event observed at a high frequency in male rats, and that the frequency in the 20 and 200 mg/kg/day groups of this study (40% and 60%, respectively) was within the laboratory historical range (maximum, 50%) or the range of rats with similar age (maximum, 100%) (*Pathobiology of the Aging Rat*. Washington DC: ILSI Press 1992, *Toxicol Pathol*. 2013;41:1126-1136). Cardiomyopathy was observed in the vehicle control group and in the 5 mg/kg/day group as well (incidence of 20% in both groups).

- Cardiomyopathy observed in this study was not histopathologically different from spontaneous cardiomyopathy (accompanied by diffuse mononuclear cell infiltration and occasionally by degeneration/necrosis of cardiomyocytes) (*Toxicol Pathol*. 2013;41:1126-1136).

- Cardiomyopathy observed in this study was mild in all cases and did not become aggravated with the increase in the dose of dabrafenib.

- In the 13-week repeat-dose toxicity study in rats [see "3.(iii).A.(2).3) Thirteen-week repeated oral dose toxicity study in rats"], findings suggestive of spontaneous cardiomyopathy (mixed cell infiltration) were observed. However, neither the frequency nor severity of the findings increased in the dabrafenib group compared with the vehicle control group.

After the recovery period, decreased elongated spermatid count in testis and atrophy of seminiferous tubules were observed in addition to the findings in testis and epididymis observed after the treatment period in the 200 mg/kg/day group, but all findings, except those in testis and epididymis, were reversible.

Thus, considering the findings in testis in males of all treatment groups, the NOAEL was determined to be <5 mg/kg/day in males and 200 mg/kg/day in females.

3.(iii).A.(2).3) Thirteen-week repeated oral dose toxicity study in rats

Rats (SD, n = 12-18/sex/group) orally received dabrafenib free base 0 (vehicle), 20, 200, or 400 mg/kg/day for 13 weeks. Six rats/sex/group in the 0, 200, and 400 mg/kg groups were evaluated for reversibility after a 4-week recovery period following 13-week treatment.

Animals in the ≥20 mg/kg/day groups showed skin lesions (dryness, detachment, swelling, and redness) from Week 1 of the study until the end of the recovery period, and some of them received adjunct therapy for the skin lesions. Females in the 400 mg/kg/day group showed emaciation and dehydration but the symptoms mostly resolved after supplying supplementary food and installing drinking bottles for individual rats by Week 4.

Animals in the ≥20 mg/kg/day groups showed increased lymphocyte count, decreased phosphorus, decreased triglycerides and total protein, acanthosis/hyperkeratosis of the skin at the footpad and interdigital regions of the front and hind legs, protrusion/thickening of fore stomach, hyperplasia of mucosal epithelia of fore stomach, mixed inflammatory cell infiltration and growth of mucosal epithelia

beneath muscular layer of mucosa, hyperplasia of pancreatic lymph nodes, increased spleen weight, findings suggestive of spontaneous cardiomyopathy (mixed cell infiltration), degenerated/decreased spermatocytes, round spermatids, elongated spermatids, and spermatids in testis, retention of spermatids in testis, atrophy of seminiferous tubules, and decreased spermatid count/azoospermia in epididymis. Animals in the ≥200 mg/kg/day groups showed decreased albumin, decreased testis weight, and vacuolation of hepatocytes in intermediate zone of lobule. Animals in the 400 mg/kg/day group showed mixed cell infiltration/crust/thickening/ulcer/nodes in the skin at the footpad and interdigital regions of front and hind legs. Animals in the ≥20 mg/kg/day groups showed increased spleen weight, but since no related histopathological findings were found, the observed event was considered to be of little toxicological significance. Animals in the ≥20 mg/kg/day groups showed findings suggestive of spontaneous cardiomyopathy (mixed cell infiltration), but since neither frequency nor severity increased in the dabrafenib groups compared with the vehicle control group, the findings were considered to be of little toxicological significance.

After the recovery period, findings in testis and epididymis were noted in almost all animals in the ≥200 mg/kg/day groups, but the other findings were reversible or tended to be reversible.

Consequently, the NOAEL in this study was determined to be <20 mg/kg/day. $AUC_{0\text{-}t}$ in the 20 mg/kg/day group (6.32-10.1 μg·hr/mL) was approximately 0.5 to 0.9 times the exposure at the clinical dose.*

*: In the Japanese phase I study (Study BRF116056) in which dabrafenib 150 mg BID was administered orally to Japanese patients with solid tumors, $AUC_{0\text{-}24h}$ calculated from $AUC_{0\text{-}12h}$ observed in multiple administration was 11.8 μg·h/mL.

3.(iii).A.(2).4) Seven-day repeated oral dose toxicity study in dogs (Reference data)

Dogs (beagle, n = 1/sex/group) orally received dabrafenib 0 (vehicle), 10, 100, or 300 mg/kg/day for 7 days.

The female in the 300 mg/kg/day group was sacrificed moribund on Day 7 because of deteriorated conditions. Necropsy of the animal showed degeneration/necrosis of coronary arteries in the right atrium and papillary muscle, degeneration/necrosis of cardiac muscles, and decreased lymphocyte count in thymus.

Animals in the ≥10 mg/kg/day group showed decreased body weight, right atrial hemorrhage and inflammatory cell infiltration in cardiac muscles, and decreased lymphocyte count in thymus. Animals in the ≥100 mg/kg/day groups showed decreased reticulocyte count, vomiting, abnormal feces (yellow-brown colored feces, mucous feces, watery stool). Animals in the 300 mg/kg/day group showed degeneration of right atrium and myocarditis.

Consequently, the NOAEL in this study was considered to be <10 mg/kg/day.

3.(iii).A.(2).5) Four-week repeated oral dose toxicity study in dogs

Dogs (beagle, n = 3-5/sex/group) orally received dabrafenib free base 0 (empty gelatin capsule), 1, 5, or 50 mg/kg/day for 4 weeks. Two dogs/sex/group in the 0 and 50 mg/kg/day groups were evaluated for reversibility after a 2-week recovery period following 4-week treatment.

No deaths occurred.

Animals in the 50 mg/kg/day group showed bronzing/protrusion of skin at muzzle and jaw, pedunculated mass in the skin of jaw and ear, thickening/nodes of external ear, localized epithelial thickening at muzzle and external ear, hyperkeratosis of the skin of external ear, papilloma accompanied by skin ulcer, and thickening of tricuspid valve and localized hemorrhage in heart.

All findings were reversible at the end of the recovery period.

Consequently, the NOAEL in this study was considered to be 5 mg/kg/day. Skin lesions were subjected to electron microscopy and detection of viral DNA by real time PCR. Electron microscopy did not reveal

structures consistent with viral particles and PCR did not detect canine papilloma virus DNA. The applicant explained that the skin lesions were not caused by canine papilloma virus infection.

3.(iii).A.(2).6) Thirteen-week repeated oral dose toxicity study in dogs

Dogs (beagle, n = 4-7/sex/group) orally received dabrafenib 0 (empty gelatin capsule), 5, 20, 60 (male only), or 100 (female only) mg/kg/day (i.e., filled in capsules; 2.5, 10, 30, or 50 mg/kg, respectively, twice daily) for a maximum of 13 weeks. Three dogs/sex in the 0 mg/kg/day group, 3 males in the 60 mg/kg/day group, and 3 females in the 100 mg/kg/day group were evaluated for reversibility after a 4-week recovery period following 13-week treatment.

Males in the 60 mg/kg/day group and females in the 100 mg/kg/day group showed decreased body weight, anorexia, emaciation, dehydration, redness of gum, gingivitis, liquid stool, vomiting, etc. Administration was suspended from Day 14 or 15 and adjunct therapy was given. However, animals were necropsied on Day 22 or 23 (Day 46 or 47 in animals that had been scheduled to undergo the recovery period) because of aggravated conditions.

Animals in the ≥5 mg/kg/day groups showed skin papules, reddening, and crust, swelling of limbs, and otorrhea, and received adjunct therapy.

Animals in the ≥5 mg/kg/day groups showed vomiting, dehydration, increased frequency of redness of gum and abnormal feces (liquid stool, blackish feces), decreased thymus weight, thickening of epidermis, hyperkeratosis, mixed inflammatory cell infiltration, erosion and crust of skin, hypertrophy and increased plasma cells/red blood cells/erythrophagia in popliteal lymph nodes, degeneration/elimination of seminiferous epithelium in testis, and decreased spermatid count, azoospermia, and cellular debris in epididymis. Animals in the 20 mg/kg/day group showed labored respiration/shallow breathing, tremor, increased neutrophil and monocyte counts, increased alkaline phosphatase (ALP), decreased urea, creatinine, albumin, cholesterol, and potassium, decreased phosphorus (20 mg/kg/day group only), decreased thymus size, adhesion/discoloration/darkening/hardening of lung, pleural thickening, darkening of popliteal lymph nodes, decreased lymphocyte count in thymus, marrow hyperplasia, inflammation of bronchial tube/pulmonary alveoli, and fibrovascular growth of right atrial wall accompanied by right atrial hypertrophy. Males in the 60 mg/kg/day group and females in the 100 mg/kg/day group showed decreased reticulocyte and red blood cell counts, hemoglobin, and hematocrit, increased sodium, chlorine, and phosphorus, decreased total protein, decreased urine specific gravity and urine pH, hepatocyte vacuolation, and subacute inflammation of mouth. Animals with findings of right atrial wall did not show abnormality in electrocardiogram or echocardiogram.

Males in the 60 mg/kg/day group showed fibrovascular growth of right atrial wall and findings in testis and epididymis after the recovery period. The other findings observed after 13-week treatment were reversible.

Consequently, the NOAEL in this study was considered to be <5 mg/kg/day. $AUC_{0\text{-}t}$ in the 5 mg/kg/day group (13.4-28.7 μg·hr/mL) was approximately 1.1 to 2.4 times the exposure at the clinical dose.*

*: In the Japanese phase I study (Study BRF116056) in which dabrafenib 150 mg BID was administered orally to Japanese patients with solid tumors, $AUC_{0\text{-}24h}$ calculated from $AUC_{0\text{-}12h}$ observed in multiple administration was 11.8 μg·h/mL.

3.(iii).A.(3) Genotoxicity

Genotoxicity studies consisted of a bacterial reverse mutation assay using dabrafenib as the test substance, and a bacterial reverse mutation assay, a mouse lymphoma TK assay, and a rat micronucleus assay using dabrafenib free base as the test substance. No genotoxicity was observed in any of the assays. In the rat micronucleus assay, the exposure to unchanged dabrafenib in the maximum dose group (100 mg/kg/day group) was estimated to be 223 μg·hr/mL,[*1] which was approximately 18.9 times the exposure at the clinical dose.[*2]

*1: Estimated from AUC on Day 1 in males of the 1000 mg/kg/day group in the 10-day repeat-dose toxicity study in rats.

*2: In the Japanese phase I study (Study BRF116056) in which dabrafenib 150 mg BID was administered to Japanese patients with solid tumors, $AUC_{0\text{-}24h}$ calculated from $AUC_{0\text{-}12h}$ observed in multiple oral administration was 11.8 μg·h/mL.

On the basis of the above results and the observation that mesilate showed no genotoxicity in a mouse micronucleus assay (from data base of the U.S. Environmental Protection Agency, US EPA 2015),* the applicant explained that dabrafenib at the clinical dose (300 mg/day) has only an extremely low genotoxicity potential.

*: The maximum dose tested 500 mg/kg was 450 times the dose of mesilate 55.0 mg/day when dabrafenib 300 mg/day was administered to humans.

3.(iii).A.(4) Carcinogenicity

Since dabrafenib is intended to be used for treating malignant melanoma, no carcinogenicity study was conducted.

However, the applicant explained that since BRAF inhibitors are considered to promote cell growth by activating MAPK signal transduction pathway (*Nature.* 2010;464:431-435, *PLoS One.* 2013;8:e67583, *N Engl J Med.* 2012;366:207-215), dabrafenib may cause malignant tumor of skin or other tissues. Occurrences of secondary malignant tumor (e.g., squamous cell carcinoma of skin, squamous cell carcinoma) in clinical settings are described in "4.(iii).B.(3).2) Secondary malignant tumor."

3.(iii).A.(5) Reproductive and developmental toxicity

The applicant conducted a study of fertility and embryo-fetal development in female rats as a reproductive and developmental toxicity study.

3.(iii).A.(5).1) Evaluation of male fertility

Although no study was conducted on male fertility, the applicant explained possible adverse effects of dabrafenib on male fertility, on the basis of the following findings:

- In repeat-dose toxicity studies in mice, rats, and dogs [see "3.(iii).A.(2) Repeat-dose toxicity"], effects on testis were observed (e.g., degeneration/decrease of elongated spermatids, round spermatid, and spermatocyte, atrophy of seminiferous tubules, and decreased spermatid count and cellular debris in epididymis).
- BRAF protein is expressed in postmeiotic germ cells, suggesting an important role in cell differentiation during spermatogenesis (*J Biol Chem.* 1995;270:23381-23389).
- In mice, BRAF protein is expressed in round and elongated spermatids (*Exp Cell Res.* 2000;257:172-179), and degeneration of elongated spermatids observed in the repeat-dose toxicity studies of dabrafenib is likely to be associated with the pharmacological effects of dabrafenib.
- In the testis of mice with *hop* and hop^{hpy} gene mutations showing sperm tail dysplasia, BRAF kinase activity is decreased (*Mamm Genome.* 1998;9:905-906).

3.(iii).A.(5).2) Study of fertility and embryo-fetal development in female rats

Female rats (SD, n = 25/group) orally received dabrafenib free base; 0 (vehicle), 5, 20, 300 or mg/kg/day from 15 days before mating until Gestation Day 17.

One of 25 animals in the 300 mg/kg/day group showed decreased body weight, lethargy, dehydration, and contact hypersensitivity reaction, and the animal was sacrificed moribund on Day 6.

Findings observed in maternal animals were reduced body weight gain and decreased uterine weight on Gestation Day 0 to 18 in the ≥20 mg/kg/day groups, and decreased body weight, decreased number of corpora lutea and implantation, increased post-implantation mortality, and decreased number of live fetuses from Day 2 of start of treatment in the 300 mg/kg/day group. No effects on estrous cycle, copulation rate, or conception rate were observed in any of treatment groups.

Findings in embryos/fetuses were decreased fetal weight, thymus deformity, and incomplete ossification of thoracic vertebrae in the ≥20 mg/kg/day groups and detached thymus, unossified metacarpal bone/sternebrae, wavy/knobby ribs, and ventricular septal defect (membranous) in the 300 mg/kg/day group. The incidence of ventricular septal defect (2.42%) exceeded the laboratory historical range (0.54%-0.79%), suggesting the teratogenicity of dabrafenib.

Consequently, the NOAEL in this study was considered to be 5 mg/kg/day for maternal general toxicity and embryo-fetal development, and 20 mg/kg/day for female fertility.

$AUC_{0\text{-}t}$ (2.62 μg·h/mL) at the NOAEL (5 mg/kg/day) for maternal animals and embryo-fetal toxicity was approximately 0.2 times the exposure at the clinical dose.*

*: In the Japanese phase I study (Study BRF116056) in which dabrafenib 150 mg BID was administered orally to Japanese patients with solid tumors, $AUC_{0\text{-}24h}$ calculated from $AUC_{0\text{-}12h}$ observed in multiple administration was 11.8 μg·h/mL.

The applicant's explanation:
On the basis of the above results and on the following published reports, dabrafenib may have adverse effects on female fertility and embryo-fetal toxicity including teratogenicity in humans.

- Embryonic lethality was observed in BRAF-deficient mice, and effects on blood vessels, nerve degeneration, growth retardation, and apoptotic abnormality in liver, brain, and heart were reported in BRAF-deficient embryos (*Nat Genet.* 1997;16:293-297, *Proc Natl Acad Sci USA.* 2006;103:1325-1330).
- Placental abnormality is confirmed in BRAF-deficient mice, suggesting the importance of BRAF protein in normal placental formation and embryogenesis (*Proc Natl Acad Sci USA.* 2006;103:1325-1330).

3.(iii).A.(5).3) Study on juvenile animals
Results of studies in juvenile animals were not submitted in the present regulatory application.

PMDA asked the applicant to explain the results of studies in juvenile animals and the risk of dabrafenib treatment in pediatric patients.

The applicant's response:
There is a study report in which dabrafenib (free base) was administered to juvenile rats (7-35 days after birth) (*Birth Defect Research Part A.* 2015;103:390). This study showed the effects on growth (reduced body weight gain and short femur/neck bone), effects on testis (degeneration, atrophy, and dilation, etc., of seminiferous tubules), effects on kidney (basophilic renal tubules, deposits, interstitial fibrosis, and pyelectasis, etc.), early vaginal opening accompanied by hyperplasia and hyperkeratosis of vulvar skin and vaginal epithelium. Also, the report suggested that the early vaginal opening is not caused by the effect of dabrafenib on sexual maturation but associated with the effect of dabrafenib on the epithelium (hyperkeratosis). The NOAEL in this study was below the minimum dose tested and AUC at the minimum dose (2.03 μg·h/mL) was below the exposure at the clinical dose.*

*: In the Japanese phase I study (Study BRF116056) in which dabrafenib 150 mg BID was administered orally to Japanese patients with solid tumors, $AUC_{0\text{-}24h}$ calculated from $AUC_{0\text{-}12h}$ observed in multiple administration was 11.8 μg·h/mL.

These results suggest that dabrafenib, if administered to pediatric patients, may cause safety problems such as effects on growth as observed in juvenile rats. The applicant will inform that the efficacy and safety of dabrafenib in patients aged <18 years have not been established through the package insert, etc. Also, since it is unknown whether or not dabrafenib is excreted in human milk, the possibility that children are exposed to dabrafenib via milk cannot be excluded. The applicant considers that breast-feeding must be discontinued when dabrafenib is administered to nursing mothers. Information on the above results of studies in juvenile animals will be supplied to healthcare professionals in clinical settings through appropriate materials.

3.(iii).A.(6) Other toxicities
3.(iii).A.(6).1) Phototoxicity studies
Since dabrafenib absorbs light with a wavelength of 290 to 700 nm with the maximum absorption at 331 nm, phototoxicity of dabrafenib was evaluated.

i) Neutral red uptake test using Balb/c mouse-derived fibroblast cell line Balb/c 3T3
Dabrafenib 0.316-1000 μg/mL was added to mouse fibroblast-derived Balb/c 3T3 cell line, and phototoxicity was evaluated. Photo irritation factor (IC_{50} in UVA-non-irradiated group / IC_{50} in UVA-irradiated group), calculated from IC_{50} of the cytolethal effect of dabrafenib under UVA irradiation and

under non-irradiation (<0.316 μg/mL under UVA irradiation, 26.076 μg/mL under non-irradiation), was >83, exceeding 5, the positive reference criterion, suggesting that dabrafenib is phototoxic.

ii) Phototoxicity test in hairless mice

Male hairless mice (SKH1-*hr*, n = 10/group) received a single oral dose of dabrafenib 0 (vehicle: 25 mmol/L citrate solution containing 0.5% HPMC), 10, 30, 100, or 300 mg/kg, followed by a single dose of UVA/UVB irradiation, and then, phototoxicity was evaluated. One of 10 animals in the 100 mg/kg group showed glossy and wrinkled skin, and all animals in the 300 mg/kg group showed phototoxicity reactions such as edema, erythema, and exfoliation of skin, from which the NOAEL for phototoxicity was considered to be 30 mg/kg.

Occurrences of phototoxicity-induced adverse events in clinical use are described in "4.(iii).B.(3).7) Skin disorder."

3.(iii).A.(6).2) Four-week repeated oral dose toxicity study of concomitant use of dabrafenib and TRA in dogs

Dogs (beagle, n = 3/sex/group) orally received dabrafenib/TRA 0/0 (empty gelatin capsule/vehicle [1.5% HPMC containing 5% mannitol, 0.2% sodium lauryl sulfate]), 5/0.0075, or 20/0.0225 mg/kg/day BID/QD for 4 weeks. TRA was administered once daily, and Dabrafenib twice daily in a gelatin capsule.

One of 3 males in the 20/0.0225 mg/kg/day group was sacrificed moribund on Day 11 because of deterioration of clinical conditions (pyrexia, decreased food consumption and body weight, and dark reddish/blackish liquid stool). Histopathological findings included degeneration/necrosis of adventitia of right coronary artery accompanied by transmural/perivascular neutrophilic/histiocytic inflammation, neutrophilic inflammation of colonic and rectal mucosa, and decreased thymic lymphocyte count.

One of 3 females in the 5/0.0075 mg/kg/day group and all females in the 20/0.0225 mg/kg/day group showed decreased body weight, and therefore supplemental food was given from Day 12 or 15 onward. As a result, the body weight of females in these groups became comparable to that in the control group at the end of the treatment period.

Animals in the ≥5/0.0075 mg/kg/day groups showed decreased body weight, anorexia, abnormal feces (dark reddish or blackish loose stool and liquid stool), nausea, vomiting, decreased thymus weight, granulomatous inflammation in mucosal epithelium of gastric pylorus, histiocytosis and intrahistiocytic foreign matters in mesenteric lymph nodes, decreased lymphocyte count in thymus, and degeneration of epididymis. Animals in the 20/0.0225 mg/kg/day group showed reddening of muzzle skin, crust on auricle, increased white blood cell, neutrophil, and monocyte counts, increased ALP, decreased albumin, decreased sperm count in epididymis, and degenerated sperm cells in lumen.

Of the findings observed when either dabrafenib or TRA was administered alone, systemic toxicity and neutrophilic inflammation in colon and rectum were found enhanced by the concomitant treatment of dabrafenib/TRA. On the other hand, skin lesions, which occurred with a high incidence in repeat-dose toxicity studies of dabrafenib [see "3.(iii).A.(2) Repeat-dose toxicity"], were not observed.

Histiocytosis and intrahistiocytic foreign matters in mesenteric lymph nodes and granulomatous inflammation in mucosal epithelium of gastric pylorus occurred in animals treated with dabrafenib/TRA, but not in animals treated with either drug alone. The applicant explained these findings as follows.

- The mechanism of the occurrence of histiocytosis and accumulation of intrahistiocytic foreign matters in mesenteric lymph nodes is unknown. However, dabrafenib is unlikely to pose safety problems related to this finding in its clinical use, for the following reasons:
  - The finding is observed when reactions to foreign matters occur; it is normally observed in the mesenteric lymph nodes.
  - The finding observed in this study was mild.
- The mechanism of occurrence of granulomatous inflammation in stomach is also unknown because (a) histopathological change in gastrointestinal tract observed in repeat-dose toxicity studies of TRA is histologically different from granulomatous inflammation, and (b) the foreign matters observed

associated with the pathological change were not identified. Therefore, it is difficult to extrapolate the finding to humans. Nevertheless, dabrafenib is unlikely to cause safety problems related to the finding in routine clinical use, for the following reasons:

- The finding observed in this study was mild, suggesting that deterioration of clinical conditions is unlikely to occur.
- In the clinical study (Study MEK115306) [see "4.(iv).(9) Foreign phase III study (Study MEK115306)"], clear increase in the incidence of nausea or vomiting possibly related to gastritis was not observed in the treatment with dabrafenib/TRA compared with dabrafenib alone.

3.(iii).A.(6).3) Safety evaluation of impurities

The applicant explained the safety of Impurity A (an impurity contained in the drug substance in excess of the qualification threshold as stipulated in "Impurities in New Drug Substances" [PMSB/ELD Notification No. 1216001 dated December 16, 2002]) and of methanesulfonate alkyl ester (a potential genotoxic impurity possibly contained in the manufacturing process of dabrafenib), as follows:

- The estimated dose of Impurity A in administration of the maximum tolerated dabrafenib dose in repeat-dose toxicity studies of dabrafenib in mice, rats, and dogs[*1] [see "3.(iii).A.(2) Repeat-dose toxicity"] and in the negative dose in the micronucleus assay of dabrafenib exceeded the dose of Impurity A[*2] in the clinical use of dabrafenib, suggesting that the safety of Impurity A is established.
- Dabrafenib in clinical use is unlikely to cause genotoxicity induced by methanesulfonate alkyl ester for the following reasons: (a) Methanesulfonate alkyl ester can be removed in the manufacturing process, and (b) the level of methanesulfonate alkyl ester can be controlled to be <1.5 μg/day, the Threshold of Toxicological Concern (ICH M7 Harmonized Tripartite Guideline [ICH, 2014]), throughout the manufacturing process by setting the control level of the content of alcohol in acetone and content of methanesulfonate alkyl ester in methanesulfonate.

*1: Studies excluding the 13-week study in dogs [see "3.(iii).A.(2).6) Thirteen-week repeated oral dose toxicity study in dogs"]

*2: The maximum level of Impurity A that may be contained when dabrafenib 300 mg/day is administered to humans was calculated based on the acceptance criterion (the upper limit) of Impurity A.

3.(iii).B Outline of the review by PMDA

On the basis of the submitted data and the results of the following review, PMDA concluded that non-clinical toxicity data do not pose any concerns about clinical use of dabrafenib, except in pregnant women, etc.

3.(iii).B.(1) Effects on cardiovascular system

PMDA asked the applicant to explain the possible effects of dabrafenib on the cardiovascular system in clinical use in relation to the findings on the cardiovascular system in repeat-dose toxicity studies in mice, rats, dogs [see "3.(iii).A.(2) Repeat-dose toxicity"].

The applicant's response:

In the repeat-dose toxicity studies in dogs, heart-related findings were inflammatory cell infiltration in cardiac muscles and hemorrhage of right atrium, degeneration/necrosis of coronary arteries in the right atrium and papillary muscle, degeneration/necrosis of cardiac muscles, thickening of tricuspid valve and localized hemorrhage (characterized by increased myxomatous matrix and severe multifocal angiogenesis), and fibrovascular growth of right atrial wall. Reversibility of fibrovascular growth of right atrial wall was not confirmed. In the repeat-dose toxicity studies in rats, animals showed increased frequency of arterial degeneration accompanied by inflammatory cell infiltration in perivascular regions of liver and mesenteric perivasculitis. In the repeat-dose toxicity studies in mice, animals showed vasculitis/perivasculitis in various tissues and necrosis of vascular walls. Vascular lesions observed in mice and rats are considered to be of the same nature as those observed in dogs (degeneration/necrosis of right atrial coronary artery) since both are characterized by arterial degeneration/necrosis, inflammation, and hemorrhage, albeit observed in different tissues.

Although the mechanism of the above cardiovascular lesions observed in animals was not evaluated, the BRAF-inhibitory effects of dabrafenib may possibly be involved in the cardiovascular lesions, given that vascular dilation, hemorrhage, and apoptotic abnormality of vascular endothelium are reported in the BRAF deficient embryos (*Nat Genet*. 1997;16:293-297).

In addition, in light of the observation that the exposures at the NOAEL or corresponding to the dose that caused cardiovascular lesions are similar to the exposure at the clinical dose, similar cardiovascular lesions may occur in the clinical use of dabrafenib. Therefore, information regarding the observed cardiovascular lesions in toxicological studies of dabrafenib will be provided through the package insert, etc.

The incidence of cardiovascular adverse events in clinical studies of dabrafenib is described below. Their relationship to the cardiovascular lesions observed in toxicological studies is unknown.

- In the foreign phase III study (Study BRF113683), 3 of 187 patients (2%) met the criteria for abnormal ejection fraction requiring study interruption (Grade 2 decrease in LVEF in 2 patients, Grade 3 myocardial infarction in 1 patient) and 3 of 187 patients (2%) had 4 events of Grade 3 decrease in LVEF or cardiac valve abnormality that did not meet the criteria for study discontinuation.
- In Study MEK115306 and Study MEK116513, heart-related adverse events such as decreased ejection fraction were observed in 12 patients and 29 patients, respectively, after concomitant use of dabrafenib with TRA.

PMDA accepted the applicant's explanation.

3.(iii).B.(2) Inflammation of pulmonary alveoli

On the basis of the inflammation of pulmonary alveoli observed in the 13-week repeat-dose toxicity study in dogs [see "3.(iii).A.(2).6) Thirteen-week repeated oral dose toxicity study in dogs"], PMDA asked the applicant to explain the possibility of the occurrence of respiratory adverse events related to the observed finding in clinical use of dabrafenib.

The applicant's response:

In the 13-week repeat-dose toxicity study in dogs, inflammation of pulmonary alveoli, shallow breathing, and labored respiration were observed, but the mechanism of occurrence of these findings is unknown. In clinical studies of dabrafenib, respiratory adverse events considered to be related to inflammation of pulmonary alveoli were not observed.

PMDA's view:

Respiratory adverse events related to inflammation of pulmonary alveoli may occur in clinical use of dabrafenib. Information on inflammation of pulmonary alveoli observed in the repeat-dose toxicity study in dogs should be provided through the package insert, etc.

3.(iii).B.(3) Administration of dabrafenib in women known or suspected to be pregnant

PMDA asked the applicant to explain the reason why dabrafenib was not contraindicated in women known or suspected to be pregnant in the proposed package insert when the regulatory application was submitted.

The applicant's response:

Since animal studies showed reproductive and developmental toxicity and teratogenicity of dabrafenib [see "3.(iii).A.(5) Reproductive and developmental toxicity"], administration of dabrafenib to women known or suspected to be pregnant should be avoided. However, because the indicated disease, malignant melanoma, is known for its poor prognosis, dabrafenib treatment in pregnant women should be decided individually by evaluating the clinical benefits and risks for patients to be treated. Therefore, dabrafenib was not contraindicated without exception in women known or suspected to be pregnant. The package insert will describe the findings observed in animal experiments and include the following cautions: (i) Patients should be instructed to take appropriate contraceptive measures, and (ii) patients should be informed of the risk in fetus when they become pregnant.

PMDA's view:

Given that dabrafenib showed teratogenicity in the study of embryo-fetal development and that the exposure to dabrafenib in embryos and fetuses at the NOAEL was below the exposure at the clinical dose [see "3.(iii).A.(5).2) Study of fertility and embryo-fetal development in female rats"], dabrafenib at the clinical dose is considered to have a high risk for embryos and fetuses. Therefore, dabrafenib should be contraindicated in women known or suspected to be pregnant.

4. Clinical data

The dose of dabrafenib mesilate (hereinafter referred to as dabrafenib) is expressed as free-base equivalent.

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

Two oral formulations were developed for dabrafenib: gelatin capsules and hypromellose (HPMC) capsules. Pharmacokinetics (PK) was investigated in both the formulations (the table below). The difference between HPMC capsules 50 and 75 mg formulations corresponds to "Level A" according to the "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012), and bioequivalence between these formulations has been confirmed by a dissolution test. The to-be-marketed formulations are the same as those of HPMC capsules 50 and 75 mg used in clinical studies.

Formulation used in each clinical study

Formulation	Studies
Gelatin capsules (1, 5, 25, 50, 75, 100 mg)	Foreign phase I studies (Studies BRF112680 and BRF113468[*1]), foreign phase I/II study (Study BRF113220 [*2]), foreign phase II study (Study BRF113710)
HPMC capsules (50, 75 mg)	Japanese phase I study (Study BRF116056), Japanese phase I/II study (Study MEK116885), foreign phase I studies (Studies BRF113468,[*1] BRF113479, and BRF113771), foreign phase I/II study (Study BRF113220[*2]), foreign phase II study (Study BRF113929), foreign phase III studies (Studies BRF113683, MEK115306, and MEK116513)

*1: HPMC capsules were used in the study of the food effect on PK of dabrafenib.

*2: HPMC capsules were used in comparing the PK between multiple administration of dabrafenib alone and multiple administration of concomitant use of dabrafenib with trametinib dimethyl sulfoxide. In other investigations, gelatin capsules were used but, in some patients, capsules were changed to HPMC capsules 50 mg during the treatment period.

4.(i).A.(1) Analytical methods

The table below shows the method employed in each clinical study for testing BRAF mutations, i.e., mutation in codon 600 (for valine), in the protein encoded by v-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene. An application for "THxID BRAF Kit" of SYSMEX bioMérieux Co., Ltd. was submitted on March 19, 2015 as an *in vitro* diagnostic to support evaluating the indication of dabrafenib and trametinib dimethyl sulfoxide (TRA).

Testing method employed in each clinical study

Test	Studies
Direct sequencing of LSI Medience Corporation	Japanese phase I study (Study BRF116056), Japanese phase I/II study (Study MEK116885 [phase I part])
Allele-specific PCR of Response Genetics Inc.	Foreign phase II studies (Studies BRF113929 and BRF113710), foreign phase III study (Study BRF113683)
Real time PCR using THxID BRAF Kit of Sysmex bioMérieux Co., Ltd.	Japanese phase I/II study (Study MEK116885 [phase II part]), foreign phase III studies (Studies MEK115306 and MEK116513)
Testing method not specified	Foreign phase I studies (Studies BRF112680, BRF113468, BRF113479, and BRF113771), foreign phase I/II study (Study BRF113220)

PCR: Polymerase chain reaction

4.(i).A.(2) Assay

Dabrafenib and its major metabolites M4 (carboxy-dabrafenib), M7 (hydroxy-dabrafenib), and M8 (desmethyl-dabrafenib) in human plasma and urine were assayed by LC-MS/MS. The lower limit of quantitation of dabrafenib and its metabolites M4, M7, and M8 was 1, 5, 1, and 1 ng/mL, respectively, in both plasma and urine.

4.(i).A.(3) Foreign phase I study (5.3.1.1, Study BRF113479 [June to September 2011])

An open-label study was conducted in 4 patients with BRAF V600 mutation-positive solid tumors to investigate the absolute BA of dabrafenib. A single oral dose of dabrafenib 150 mg was administered, and 1.75 hours thereafter, a single dose of ^{14}C-labeled dabrafenib (0.05 mg) was administered intravenously.

The absolute BA [90% confidence interval (CI)], calculated from AUC_{inf} of dabrafenib, was 94.5% [81.3, 109.7]. Given the high absolute BA and the low blood clearance (CL) of dabrafenib after intravenous administration (approximately 24.0 L/h*) compared with the hepatic blood flow rate (approximately 81 L/h) (*Pharm Res.* 1993;10:1093-1095), the applicant explained that the contribution of the hepatic first-pass effect to dabrafenib metabolism is minor.

*: Calculated from plasma CL of dabrafenib (12.0 L/h) and blood/plasma ratio of dabrafenib in humans (approximately 0.5) [see "3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells"]

4.(i).A.(4) Foreign phase I study (5.3.1.1, Study BRF113468 [October 2010 to May 2011])

A two-treatment, two-period, crossover study was conducted in 14 patients with BRAF V600 mutation-positive solid tumors (14 patients included in PK analysis) to evaluate the effects of the particle size on the PK of dabrafenib. Under fasted conditions (administration after overnight fasting, and 4-hour fasting thereafter), a single oral dose of dabrafenib 150 mg was administered in gelatin capsules filled with micronized and non-micronized drug substance.

Gelatin capsules filled with non-micronized drug substance prolonged t_{max} of dabrafenib compared to those filled with micronized drug substance. The geometric mean ratios [90% CI] of C_{max}, AUC_t, and AUC_{inf} of dabrafenib when it was administered as gelatin capsules filled with non-micronized drug substance to the respective parameters when administered as gelatin capsules filled with micronized drug substance were 1.42 [1.06, 1.91], 1.23 [0.95, 1.61], and 1.44 [1.13, 1.83].

A two-treatment, two-period, crossover study was conducted in 14 patients with BRAF V600 mutation-positive solid tumors (14 patients included in PK analysis) to investigate the food effect. A single oral dose of dabrafenib (150 mg in HPMC capsule) was administered under fasted conditions (administration after overnight fasting, and 4-hour fasting thereafter) or at 30 minutes after intake of a high fat/high calorie diet (1020 kcal in total, of which fat accounts for 51% to 66%). The washout period between Period 1 and Period 2 was ≥7 days.

Median t_{max} of dabrafenib was prolonged when dabrafenib was administered after a high fat/high calorie diet compared to when dabrafenib was administered under fasted conditions, and the geometric mean ratios [90% CI] of C_{max}, AUC_t, and AUC_{inf} of dabrafenib following administration after a high fat/high calorie diet to the respective parameters following administration under fasted conditions were 0.49 [0.35, 0.69], 0.70 [0.58, 0.85], and 0.69 [0.57, 0.85], respectively (the table below). According to the applicant, the above results were caused by the following mechanisms: (a) food intake decreased gastric emptying rate, thus dabrafenib reaching the absorption site delayed, which in turn decreased the dabrafenib absorption rate, therefore leading to a reduced rate of increase in plasma dabrafenib concentration, and (b) food intake caused an increase in pH in the stomach which decreased solubility of dabrafenib, thus resulting in decreased BA.

Results of the above study on administration under fasted conditions showed that the geometric mean ratios [90% CI] of C_{max}, AUC_t, and AUC_{inf} of dabrafenib when it was administered as HPMC capsules filled with micronized drug substance to the respective parameters when administered as gelatin capsules filled with micronized drug substance were 2.02 [1.42, 2.87], 1.81 [1.36, 2.41], and 1.80 [1.32, 2.46], respectively.

PK parameters of dabrafenib following administration under fasted or fed conditions

Condition of administration	C_{max} (μg/mL)	t_{max}*1 (h)	$t_{1/2}$ (h)	AUC_t (μg·h/mL)	AUC_{inf} (μg·h/mL)
Under fasted conditions	2.16 (56)	2.0 (1.0, 4.0)	8.4 (113)*2	11.8 (49)	12.1 (49)*2
After high fat/high calorie diet	1.07 (50)	6.0 (2.0, 10.0)	10.6 (104)*2	8.33 (41)	8.47 (43)

n = 14; Geometric mean (coefficient of variation [CV] %); *1, Median (range); *2, n = 13

4.(i).B Outline of the review by PMDA

4.(i).B.(1) Food effect

The applicant's explanation on the timing of dabrafenib treatment:

Results of Study BRF113468 suggested that exposure to dabrafenib is decreased by food intake [see "4.(i).A.(4) Foreign phase I study"]. Also, the efficacy and safety of dabrafenib were demonstrated in foreign phase III studies (Studies BRF113683 and MEK115306) and other studies in which protocols

required that dabrafenib be administered at "1 hour before meal or 2 hours after meal." Accordingly, a caution to the effect that dabrafenib should not be administered during the period from 1 hour before to 2 hours after meal will be provided to healthcare professionals in clinical settings through the package insert.

PMDA accepted the applicant's explanation.

4.(i).B.(2) Effects of gastric pH on PK of dabrafenib

PMDA asked the applicant to explain how an increase in gastric pH caused by the administration of proton pump inhibitors (PPIs) affects the PK of dabrafenib.

The applicant's response:

Since the solubility of dabrafenib depends on pH, the PK of dabrafenib may be affected by a low-gastric acid condition or by an increase in gastric pH caused by PPIs. Plasma dabrafenib concentration was lower when it is administered under fed conditions than under fasted conditions [see "4.(i).A.(4) Foreign phase I study"]. Increased gastric pH after food intake was assumed to be a factor contributing to the decreased solubility of dabrafenib. Cautions will be provided through the package insert, etc., for the concomitant use with drugs influencing gastric pH. A clinical study (Study 200072) to investigate the effects of concomitant use of a PPI (sodium rabeprazole) on the PK of dabrafenib is currently ongoing, and the results will be obtained in the [redacted] quarter of 20[redacted].

PMDA's view:

PMDA accepted the applicant's explanation. The results of Study 200072 should be provided to healthcare professionals in clinical settings in an appropriate manner as soon as they become available.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

The PK of dabrafenib in cancer patients was evaluated when it was administered alone and in combination with TRA, ketoconazole, or gemfibrozil. Also, the effects of dabrafenib on the PK of midazolam and warfarin sodium (warfarin) were investigated.

4.(ii).A.(1) Japanese clinical studies

4.(ii).A.(1).1) Japanese phase I study (5.3.5.2, Study BRF116056 [May 2012 – ongoing (data cut-off; August 1, 2014)])

An open-label, uncontrolled study was conducted in 12 patients with BRAF V600 mutation-positive solid tumors (12 patients included in PK analysis) to evaluate PK, etc., of dabrafenib. Dabrafenib 75, 100, 150 mg was administered in a single oral dose under fasted conditions and, after a 6-day washout period, dabrafenib 75, 100, 150 mg was administered in multiple oral doses twice daily (BID). Plasma concentrations of dabrafenib and its metabolites (M4, M7, and M8) were investigated (the table below).

CL/F (geometric mean) after a single-dose administration of dabrafenib 75, 100, 150 mg was 14.0, 8.1, and 14.5 L/h, respectively. In the single-dose administration, the exposure to dabrafenib increased less than dose-proportionally. The applicant explained that the above results were caused by inter-individual variability, taking account of the dose-proportional response observed in the foreign phase I study (Study BRF112680) [see "4.(ii).A.(2).3) Foreign phase I study"]. The applicant explained that $AUC_{0\text{-}12h}$ of dabrafenib in multiple administration was lower at all doses tested than in single-dose administration, due to the auto-induction of drug-metabolizing enzymes by dabrafenib, given that dabrafenib is metabolized mainly by cytochrome P450 (CYP) 3A4 [see "3.(ii).A.(3).1) *In vitro* metabolism] and that dabrafenib has an activity to induce CYP3A [see "4.(ii).A.(3).1) Study on interaction with midazolam"].

PK parameters of dabrafenib and its metabolites (M4, M7, and M8)

Time points	Dose (mg)	Analyte	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{inf} (ng·h/mL)	$AUC_{0\text{-}12h}$ (ng·h/mL)	$t_{1/2}$ (h)
After single-dose administration	75	Dabrafenib	1390 (29.9)	4.0 (3.0, 4.0)	5374 (35.1)	4628 (35.6)	15.2 (2140)
		M4	2785 (38.6)	8.0 (8.0, 9.9)	75,073 (34.9)	18,419 (49.9)	21.7 (10.2)
		M7	705 (28.7)	4.0 (4.0, 4.0)	4357 (15.5)	3715 (18.7)	7.5 (176)
		M8	55.7 (45.1)	24.1 (24.0, 47.8)	2383 (40.3)	133 (42.1)	29.2 (63.0)
	100	Dabrafenib	3806 (32.2)	1.0 (0.9, 2.0)	12,275 (43.6)	11,417 (42.9)	13.1 (55.4)
		M4	3937 (27.5)	10.0 (6.1, 11.7)	102,250 (40.9)	30,164 (18.6)	19.3 (31.0)
		M7	1542 (33.7)	2.9 (1.6, 4.0)	9458 (56.1)	7829 (49.1)	12.1 (51.6)
		M8	147 (42.9)	23.9 (23.9, 24.8)	6242 (26.2)	266 (48.9)	20.0 (55.0)
	150	Dabrafenib	2412 (40.1)	2.5 (1.0, 4.0)	10,369 (31.4)*2	9239 (29.3)	5.1 (47.0)*2
		M4	4064 (49.0)	8.0 (8.0, 10.0)	100,304 (54.5)	29,624 (57.6)	21.4 (43.7)
		M7	1255 (47.3)	4.0 (1.9, 6.0)	7749 (36.6)	6516 (39.9)	10.8 (213)
		M8	119 (52.1)	24.0 (10.0, 24.1)	5120 (41.1)	287 (113.1)	22.0 (42.3)
Day 21 of multiple administration	75	Dabrafenib	1429 (75.5)	3.0 (1.5, 4.0)	-	2852 (41.5)	-
		M4	7316 (21.1)	6.0 (4.0, 6.0)	-	65,215 (26.9)	-
		M7	944 (37.3)	3.0 (1.5, 4.0)	-	2549 (9.8)	-
		M8	356 (122)	2.0 (0, 10.0)	-	2472 (47.9)	-
	100	Dabrafenib	2899 (22.1)	1.0 (0.9, 2.0)	-	6017 (17.3)	-
		M4	9881 (41.8)	2.9 (2.8, 4.2)	-	85,211 (52.9)	-
		M7	1423 (41.3)	1.0 (0.9, 2.0)	-	4384 (32.1)	-
		M8	515 (31.2)	3.8 (2.8, 4.2)	-	3942 (34.2)	-
	150	Dabrafenib	2083 (37.0)	1.5 (1.0, 3.0)	-	5902 (33.3)	-
		M4	9309 (29.3)	4.0 (3.1, 6.0)	-	84,090 (29.5)	-
		M7	1184 (46.8)	3.0 (1.0, 4.0)	-	4462 (35.0)	-
		M8	556 (58.7)	4.0 (3.1, 12.1)	-	4410 (55.7)	-

Geometric mean (CV%); -, Not calculated; *1, Median (range); *2, n = 5

4.(ii).A.(1).2) Japanese phase I/II study (5.3.5.2, Study MEK116885 [August 2013 – ongoing (data cut-off; September 18, 2014)])

An open-label, uncontrolled study was conducted in 6 patients with BRAF V600 mutation-positive solid tumors (6 patients included in PK analysis) to evaluate the PK etc., of dabrafenib. Single oral doses of dabrafenib 150 mg and TRA 2 mg were administered on Day 1, followed by multiple oral administration of dabrafenib 150 mg BID and TRA 2 mg once daily (QD) on and after Day 2, and plasma concentrations of dabrafenib, its metabolites, and TRA were investigated (the table below).

The applicant explained that plasma trough concentrations (C_{min}, geometric mean) of dabrafenib and TRA were 78.1 to 121.85 ng/mL and 13.5 to 14.5 ng/mL, respectively, during Week 3 to Week 24, remained almost unchanged, and thus they were considered to have reached the steady state in Week 3.

PK parameters of dabrafenib and its metabolites (M4, M7, and M8)

Time points	Analyte	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{inf} (ng·h/mL)	$AUC_{0\text{-}12h}$ (ng·h/mL)	$t_{1/2}$ (h)
Day 1	Dabrafenib	2497 (69.7)	2.4 (1.4, 3.9)	13,486 (36.9)	11,415 (41.3)	4.9 (45.2)
	M4	3689 (75.5)	9.8 (7.9, 23.8)	125,749 (41.8)*2	18,964 (256)	15.7 (21.7)*2
	M7	1336 (70.1)	3.4 (2.9, 11.9)	13,904 (67.9)	7930 (64.3)	6.4 (145)
	M8	50.4 (150)	23.9 (11.7, 24.3)	4628*3	116 (270)	55.9*3
Day 21	Dabrafenib	3431 (12.0)	1.7 (1.0, 2.0)	-	10,138 (33.1)	-
	M4	12,303 (32.5)	5.0 (2.8, 6.0)	-	113,205 (36.8)	-
	M7	1996 (14.8)	2.0 (1.5, 2.9)	-	7273 (30.6)	-
	M8	324 (82.4)	4.5 (2.0, 9.9)	-	2755 (122)	-

n = 6; Geometric mean (CV%) (individual value for n = 1); -, Not calculated; *1, Median (range); *2, n = 5; *3, n = 1

PK parameters of TRA

Time points	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{inf} (ng·h/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	$t_{1/2}$ (h)
Day 1	7.82 (112)	1.0 (0.9, 23.8)	376 (23.1)*2	82.5 (23.1)*2	82.9 (46.8)*2
Day 21	32.5 (20.2)	1.2 (0.9, 5.9)	-	448 (25.5)	-

n = 6; Geometric mean (CV%); -, Not calculated; *1, Median (range); *2, n = 5

4.(ii).A.(2) Foreign clinical studies

4.(ii).A.(2).1) Foreign phase I study (5.3.3.2, Study BRF113463 [January to April 2011])

An open-label study was conducted in 4 patients with BRAF V600 mutation-positive solid tumors (4 patients included in PK analysis) to determine the mass balance of dabrafenib. A single oral dose of a suspension containing ^{14}C-labeled dabrafenib 95 mg was administered under fasted conditions, and radioactivity concentrations in blood, plasma, urine, and feces as well as plasma concentrations of dabrafenib and metabolites (M4, M7, and M8) were measured.

Radioactivity in plasma and blood and PK parameters of dabrafenib and its metabolites in plasma were as shown in the following table. Blood/plasma concentration ratio of radioactivity up to 216 hours after administration remained within the range from 0.48 to 0.69. AUC_{inf} of dabrafenib was approximately 11% of AUC_{inf} of plasma radioactivity. In plasma, M4 was the predominant metabolite of dabrafenib, accounting for approximately 54% of plasma radioactivity. Urinary and fecal excretion rates (percentage of administered radioactivity excreted) up to 10 days after administration were 22.7% and 71.1%, respectively.

PK parameters of dabrafenib, its metabolites, and radioactivity

Analyte	Sample	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
Radioactivity	Blood	1616 (27)*2	5.0 (2.0, 8.0)	37,028 (53)*3	20.8 (56)
	Plasma	2364 (18)*2	3.0 (2.0, 8.0)	59,447 (48)*3	26.4 (44)
Dabrafenib	Plasma	1662 (31)	1.0 (0.6, 2.0)	6535 (28)	5.3 (28)
M4	Plasma	1283 (23)	10.0 (6.1, 12.0)	33,948 (57)	17.5 (36)
M7	Plasma	666 (29)	3.0 (2.0, 4.0)	5022 (31)	5.7 (34)
M8	Plasma	36 (87)	30.0 (12.0, 36.0)	1674 (59)	20.4 (21)

n = 4; Geometric mean (CV%), *1, Median (range); *2, ng/g; *3, ng·h/g

4.(ii).A.(2).2) Foreign phase III study (5.3.5.1, Study BRF113683 [February 2011 – ongoing (data cut-off; December 19, 2011)])

An open-label, randomized, comparative study in 187 patients with unresectable malignant melanoma with BRAF V600 mutations (183 patients included in PK analysis) was conducted to investigate the PK etc., of dabrafenib. Multiple oral doses of dabrafenib 150 mg BID were administered, and plasma concentrations of dabrafenib and its metabolites (M4, M7, and M8) were investigated.

The following table shows PK parameters of dabrafenib and its metabolites at Week 6. The applicant explained that C_{min} of dabrafenib, M4, M7, and M8 from Week 3 to Week 24 of administration was nearly constant, at 30 to 49, 2856 to 3562, 48 to 67, and 282 to 316 ng/mL, respectively.

PK parameters of dabrafenib and its metabolites

Analyte	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{tau} (ng·h/mL)	C_{min} (ng/mL)
Dabrafenib	1478 (37)	1.9 (0.9, 6.0)	4341 (38)	26.1 (119)
M4	6153 (33)	5.9 (2.0, 8.0)	51,485 (39)	2805 (46)
M7	1009 (36)	2.0 (1.0, 6.0)	4067 (38)	46.3 (124)
M8	347 (40)	4.0 (0, 8.0)	3068 (35)	235 (45)

n = 17; Geometric mean (CV%); *1, Median (range)

4.(ii).A.(2).3) Foreign phase I study (5.3.5.2, Study BRF112680 [May 2009 to March 2012])

An open-label, uncontrolled study was conducted in 114 patients with solid tumors with BRAF mutations (114 patients included in PK analysis) to evaluate the PK of dabrafenib. Patients received multiple oral doses of dabrafenib 12 mg QD, 35 mg QD, 35 mg BID, 70 mg BID, 100 mg BID, 100 mg 3 times daily (TID), 150 mg BID, 200 mg BID, 300 mg BID, or 75/150 mg BID* during the dose escalation period, and dabrafenib 50 or 150 mg BID during the cohort expansion period. Plasma and urinary concentrations of dabrafenib and its metabolites were investigated in these patients.

PK parameters during the dose escalation period were as shown in the following table. No dabrafenib accumulation was observed at any doses tested. After the single-dose administration, C_{max} and AUC of dabrafenib increased generally dose-proportionally within the dose range tested, whereas during the multiple administration period, C_{max} and AUC of dabrafenib increased less than dose-proportionally.

The applicant explained that these results were caused by more potent CYP3A4 induction by high doses than at low doses, taking account of the observations that dabrafenib is metabolized mainly by CYP3A4 [see "3.(ii).A.(3).1) *In vitro* metabolism"] and that dabrafenib has CYP3A-inducing activity [see "4.(ii).A.(3).1) Study on interaction with midazolam"]. On Day 15 of dabrafenib (200 mg BID) administration, no unchanged dabrafenib was detected in urine, and M4 was the metabolite present at the highest concentration in urine.

*: Multiple BID administration of 75 mg up to Day 15, and the dose was allowed to be increased to 150 mg BID thereafter.

PK parameters of dabrafenib

Dosage regimen	Time points	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC*2 (ng·h/mL)	$t_{1/2}$ (h)
12 mg QD	Day 1	1	37.5	4.0	-	-
	Day 8	1	34.7	4.0	429	-
35 mg QD	Day 1	3*3	349 (7.1)	2.0 (1.0, 3.0)	1658, 1704*10	6.2, 6.9*10
	Day 8	3	339 (54.5)	3.0 (1.0, 3.0)	1515 (18.3)	-
35 mg BID	Day 1	4*4	254 (51.8)	2.0 (1.0, 3.0)	1247 (27.7)	5.2 (30.2)
	Day 8	7	280 (55.4)	2.0 (1.0, 6.0)	1038 (45.7)*11	-
	Day 15	1	182	2.1	492	-
70 mg BID	Day 1	4*5	611 (28.9)	1.0 (1.0, 3.0)	2736 (23.2)	6.2 (32.7)
	Day 8	12	528 (53.7)	1.8 (0, 3.0)	2045 (31.7)*12	-
	Day 15	1	404	3.0	1669	-
75 mg BID	Day 1	6	665 (56.7)	2.5 (1.0, 4.0)	3821 (55.2)*13	6.8 (31.8)*13
	Day 15	6	583 (39.9)	2.0 (1.0, 3.0)	2062 (29.7)	-
100 mg BID	Day 1	6*6	484 (106)	1.6 (0.5, 8.0)	4668 (43.5)*14	4.0 (23.1)*14
	Day 8	10	763 (44.8)	2.0 (0.5, 4.0)	2646 (37.8)	-
100 mg TID	Day 1	6*7	900 (38.2)	2.0 (1.9, 6.0)	4462 (39.2)	6.1 (26.3)
	Day 8	12	854 (58.9)	2.0 (0.5, 2.1)	2568 (45.9)	-
	Day 15	2	406, 421	2.0, 2.0	1224, 2630	-
150 mg BID	Day 1	11*8	986 (73.2)	2.0 (1.0, 10.0)	4943 (36.7)*15	5.0 (28.1)*15
	Day 8	11	1353 (57.1)	2.0 (1.0, 2.2)	4189 (47.2)	-
	Day 15	7	806 (95.1)	1.8 (1.0, 3.0)	2619 (76.7)	-
200 mg BID	Day 1	7*9	1508 (71.6)	2.0 (1.0, 2.1)	8164 (51.7)*13	6.5 (33.2)*13
	Day 8	2	1824, 2439	2.0, 2.9	5369, 6134	-
	Day 15	15	850 (54.2)	2.0 (0.9, 4.0)	2994 (51.1)	-
300 mg BID	Day 1	8	1456 (121)	2.0 (1.0, 8.0)	9980 (47.0)*13	5.1 (33.1)*13
	Day 15	6	1126 (81.1)	1.5 (1.0, 3.0)	3744 (56.9)	-

Geometric mean (CV%) (individual value(s) if n = 1 or 2); -, Not calculated.
*1, Median (range)
*2, AUC_{inf} on Day 1, AUCτ on Day 8 or 15
*3, 1 patient was excluded from parameter calculation.
*4, 5 patients were excluded from parameter calculation.
*5, 10 patients were excluded from parameter calculation.
*6, 4 patients were excluded from parameter calculation.
*7, 14 patients were excluded from parameter calculation.
*8, 9 patients were excluded from parameter calculation.
*9, 13 patients were excluded from parameter calculation.
*10, n=2; *11, n=6; *12, n=11; *13, n=5; *14, n=3; *15, n=7

4.(ii).A.(2).4) Foreign phase I/II study (5.3.5.1, Study BRF113220, phase I part [March 2010 – ongoing (data cut-off; September 25, 2012)])

An open-label, uncontrolled study was conducted in 8 patients with BRAF V600 mutation-positive solid tumors (8 patients included in PK analysis) to evaluate the PK of dabrafenib, its metabolites and TRA. The patients received multiple oral doses of TRA 2 mg QD from Day 2 to Day 15 and a single oral dose of dabrafenib 75 mg on Day 1 and Day 15.

The geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of dabrafenib when administered in combination with TRA (dabrafenib/TRA) to the respective parameters when administered alone were 1.03 [0.79, 1.34] and 0.94 [0.82, 1.08], showing that TRA did not affect the PK of dabrafenib.

In a separate study, 110 patients with BRAF V600 mutation-positive solid tumors (67 patients included in PK analysis) orally received (a) dabrafenib 75 mg BID alone, (b) dabrafenib 75 mg BID and TRA 2 mg QD in combination, (c) dabrafenib 150 mg BID alone, or (d) dabrafenib 150 mg BID and TRA 2 mg QD in combination. The PK of dabrafenib, its metabolites, and TRA were evaluated in these patients

(the table below).

The geometric mean ratios [90% CI] of C_{max} and AUC_{tau} of dabrafenib on Day 21 when dabrafenib 150 mg BID and TRA 2 mg QD were coadministered to the respective parameters when dabrafenib 150 mg BID alone was administered were 1.16 [0.80, 1.68] and 1.23 [0.89, 1.69], showing that TRA did not have any clear impact on PK of dabrafenib. The applicant explained that the difference in the dose of dabrafenib (75 or 150 mg) did not have any clear impact on the PK of TRA.

PK parameters of dabrafenib and its metabolites

Dosage regimen (dabrafenib/TRA)	Time points	Analyte	n	C_{max} (ng/mL)	t_{max} *1 (h)	$AUC_{0\text{-}12h}$ (ng·h/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
75 mg BID/-	Day 1	Dabrafenib	15	1117 (37.5)	2.0 (1.0, 3.0)	3593 (33.0)	3982 (32.0)*2	3.8 (23.3)*2
		M4	15	1475 (30.7)	10.0 (6.0, 10.1)	10,396 (38.5)*2	-	-
		M7	15	525 (37.8)	3.0 (1.5, 4.0)	3134 (39.9)	3963 (41.6)*2	4.3 (12.7)*2
		M8	13	50 (105)	24.0 (8.0, 24.1)	132 (95.0)*3	-	-
	Day 21	Dabrafenib	14	1050 (47.0)	1.5 (1.0, 2.0)	3020 (42.2)	-	-
		M4	14	3637 (27.1)	5.0 (3.0, 8.0)	34,283 (28.4)	-	-
		M7	14	596 (30.8)	2.0 (1.5, 3.0)	2568 (36.1)	-	-
		M8	14	210 (57.4)	0.8 (0, 10.0)	1775 (71.3)	-	-
75 mg BID/ 2 mg QD	Day 1	Dabrafenib	15	1277 (63.7)	2.0 (1.0, 3.0)	4618 (51.8)	5321 (41.1)*3	3.9 (21.0)*3
		M4	15	1478 (39.4)	10.0 (6.0, 24.0)	9575 (56.8)	-	-
		M7	15	597 (43.6)	3.0 (2.0, 6.0)	3694 (45.6)	5026 (44.4)*2	4.7 (19.8)*2
		M8	15	61 (81.7)	24.0 (23.5, 25.0)	89 (97.4)	-	-
	Day 21	Dabrafenib	14	1217 (57.2)	1.8 (1.0, 3.0)	3434 (45.1)	-	-
		M4	14	4158 (52.0)	6.0 (2.0, 10.0)	39,672 (54.9)	-	-
		M7	14	696 (42.4)	2.0 (1.5, 4.0)	2919 (41.3)*3	-	-
		M8	14	289 (69.9)	2.0 (1.0, 10.0)	2508 (60.1)*3	-	-
150 mg BID/-	Day 1	Dabrafenib	14	1669 (92.7)	2.0 (1.0, 6.0)	6507 (78.1)*3	7291 (76.9)*3	4.1 (19.9)*3
		M4	14	2268 (67.0)	8.9 (4.0, 24.0)	15,952 (82.3)	-	-
		M7	14	1055 (79.3)	3.5 (2.0, 6.2)	5950 (71.0)*3	7415 (73.2)*3	4.3 (16.3)*3
		M8	13	69 (141)	24.0 (6.0, 24.6)	190 (129)*4	-	-
	Day 21	Dabrafenib	11	1746 (40.5)	1.6 (1.0, 3.0)	4663 (44.2)	-	-
		M4	11	6743 (42.4)	4.0 (3.0, 6.0)	59,340 (44.5)	-	-
		M7	11	1203 (44.2)	2.0 (1.4, 3.0)	4262 (55.6)	-	-
		M8	11	355 (43.7)	2.0 (0.5, 10.0)	2707 (38.8)	-	-
150 mg BID/ 2 mg QD	Day 1	Dabrafenib	15	2289 (68.8)	1.5 (1.0, 10.0)	7331 (61.6)	8152 (62.2)*2	3.6 (36.4)*2
		M4	15	2551 (75.9)	8.0 (4.1, 24.0)	20,935 (105)*3	-	-
		M7	15	1363 (87.0)	2.1 (1.5, 10.0)	6524 (74.3)	7907 (72.5)*2	4.0 (17.7)*2
		M8	15	86 (143)	24.0 (10.0, 24.3)	354 (78.2)*4	-	-
	Day 21	Dabrafenib	12	2052 (56.0)	1.5 (1.0, 3.0)	5886 (40.0)	-	-
		M4	12	6319 (48.3)	4.0 (3.0, 6.1)	52,712 (45.2)	-	-
		M7	12	1120 (77.3)	2.0 (1.0, 4.0)	4216 (58.5)	-	-
		M8	12	440 (63.9)	1.8 (0, 9.9)	3632 (61.9)	-	-

Geometric mean (CV%); -, Not applicable; *1, Median (range); *2, n = 14; *3, n = 13; *4, n = 12

PK parameters of TRA

Dosage regimen (dabrafenib/TRA)	Time points	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_{tau} (ng·h/mL)
75 mg BID/2 mg QD	Day 1	15	6.8 (74.9)	2.0 (1.0, 3.0)	53.4 (57.8)
	Day 21	14	24.1 (30.2)	2.0 (1.0, 4.0)	366 (32.3)
150 mg BID/2 mg QD	Day 1	14	6.6 (85.7)	1.5 (1.0, 8.0)	50.7 (46.8)
	Day 21	13	22.6 (24.8)	2.0 (1.5, 4.0)	356 (19.3)

Geometric mean (CV%); *, Median (range)

4.(ii).A.(3) Drug-drug interactions

4.(ii).A.(3).1) Study on interaction with midazolam (5.3.5.2, Study BRF112680 [May 2009 to March 2012])

An open-label study was conducted in 12 patients with solid tumors with BRAF mutations (12 patients included in PK analysis) to evaluate the effects of dabrafenib on the PK of midazolam, a substrate of CYP3A. The patients orally received dabrafenib 150 mg BID on Day 2 to Day 16 and a single dose of midazolam 3 mg on Day 1 and Day 16, and the PK of midazolam was evaluated.

The geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of midazolam when dabrafenib and midazolam were coadministered (Day 16) to the respective parameters when midazolam alone was administered (Day 1) were 0.39 [0.24, 0.63] and 0.26 [0.21, 0.32].

These results suggested that dabrafenib induces CYP3A in clinical use, therefore the applicant explained that concomitant use of drugs that are metabolized by CYP3A should be alerted.

4.(ii).A.(3).2) Study on interaction with warfarin (5.3.3.4, Study BRF113771 [July 2011 to November 2012])

An open-label study was conducted in 14 patients with solid tumors with BRAF mutations (14 patients included in PK analysis) to evaluate the effects of dabrafenib on the PK of warfarin (*S* form is a substrate of CYP2C9 and *R* form is a substrate of CYP3A and CYP1A2). The patients received dabrafenib 150 mg BID orally from Day 8 to Day 29 and a single oral dose of warfarin 15 mg on Day 1 and Day 22, and the PK of warfarin was investigated.

The geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of *S*-warfarin when dabrafenib and warfarin were coadministered (Day 22) to the respective parameters when warfarin alone was administered (Day 1) were 1.18 [1.02, 1.37] and 0.63 [0.59, 0.68], and the corresponding geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of *R*-warfarin were 1.19 [1.08, 1.31] and 0.67 [0.62, 0.71], respectively.

These results suggested that dabrafenib induces CYP2C9 in clinical use, whereas results of *in vitro* studies showed that dabrafenib does not induce CYP1A2 [see "3.(ii).A.(5).2) Enzyme induction"]. Consequently, the applicant explained that concomitant use of drugs that are metabolized by CYP2C9 should be alerted.

4.(ii).A.(3).3) Study on interaction with ketoconazole (5.3.3.4, Study BRF113771 [July 2011 to November 2012])

An open-label study was conducted in 16 patients with solid tumors with BRAF mutations (16 patients included in PK analysis) to evaluate the effects of ketoconazole, a CYP3A inhibitor, on the PK of dabrafenib. The patients orally received dabrafenib 75 mg BID from Day 1 to Day 22 and ketoconazole 400 mg QD from Day 19 to Day 22, and the PK of dabrafenib was investigated.

The geometric mean ratios [90% CI] of C_{max} and AUC_{tau} of dabrafenib when ketoconazole was coadministered (Day 22) to the respective parameters when dabrafenib alone was administered (Day 18) were 1.33 [1.14, 1.55] and 1.71 [1.55, 1.90], respectively.

These results showed that concomitant use with a CYP3A inhibitor increased the exposure to dabrafenib, and therefore the applicant explained that concomitant use of dabrafenib with CYP3A inhibitors should be alerted.

4.(ii).A.(3).4) Study on interaction with gemfibrozil (5.3.3.4, Study BRF113771 [July 2011 to November 2012])

An open-label study was conducted in 17 patients with solid tumors with BRAF mutations (17 patients included in PK analysis) to evaluate the effects of gemfibrozil, a CYP2C8 inhibitor, on the PK of dabrafenib (the table below).

The patients orally received dabrafenib 75 mg BID from Day 1 to Day 22 and gemfibrozil 600 mg BID from Day 19 to 22, and the PK of dabrafenib was evaluated.

The geometric mean ratios [90% CI] of C_{max} and AUC_{tau} of dabrafenib when administered in combination with gemfibrozil (Day 22) to the respective parameters when administered alone (Day 18) were 0.98 [0.75, 1.29] and 1.47 [1.20, 1.80].

These results showed that concomitant use with a CYP2C8 inhibitor increased the exposure to dabrafenib, and thus the applicant explained that concomitant use of dabrafenib with CYP2C8 inhibitors should be alerted.

4.(ii).A.(4) Study on the relationship between exposure and change in QT/QTc interval

The applicant's explanation:

Neither dabrafenib nor its metabolites are likely to induce QT interval prolongation, taking account of the following study results. The risk of dabrafenib-induced prolongation of QT/QTc interval will be

described in "4.(iii).B.(3).9).(d) QT/QTc interval prolongation," after confirming the incidence of QT/QTc interval prolongation in clinical studies other than the foreign phase I study (Study BRF112680) and the Japanese phase I/II study (Study BRF116056).

- In the foreign phase I study (Study BRF112680), no clear relationship was observed between the exposure to dabrafenib and interval of QTcP, i.e., QT adjusted by the estimate of population-specific exponent (0.399). Estimated changes in QTcP (median [90% CI]) at C_{max} of dabrafenib, M4, M7, and M8 when dabrafenib 150 mg BID was administered were 0.2 [-1.7, 1.9], 5.0 [2.8, 7.8], 3.0 [1.4, 5.1] and 5.5 [3.7, 7.5] msec, respectively, with the upper limit of 90% CI <10 msec in all of them.
- In the Japanese phase I/II study (Study BRF116056), no clear relationship was observed between the exposure to dabrafenib or M7 and QT interval corrected by Bazett's equation (QTcB). QTcB tended to increase with increasing exposure to M4 or M8, but the estimated changes in QTcB at C_{max} of dabrafenib, M4, M7, and M8 during administration of dabrafenib 150 mg BID was -8.4, 8.3, -6.0, and 9.1 msec, respectively, with the upper limit of 90% CI <10 msec in all of them.

4.(ii).A.(5) Population pharmacokinetic (PPK) analysis

A non-linear mixed effect model (software NONMEM version 7.2.0) -based PPK analysis (PPK analysis in dabrafenib monotherapy) was performed on the PK data of dabrafenib (3787 time points in 595 patients) obtained from foreign clinical studies (Studies BRF112680, BRF113710, BRF113929, and BRF113683), where the PK of dabrafenib was described by a 2-compartment model with first order absorption process and delayed absorption process.

In this analysis, effects of covariates listed in the following table were investigated on CL/F, apparent distribution volume of the central compartment (Vc/F), apparent distribution volume of peripheral compartment (Vp/F), apparent inter-compartment clearance (Q/F), relative BA (F), and absorption rate constant (Ka).

Covariates investigated

PK parameters	Covariates
CL/F	Body weight, sex, age, hepatic impairment,*1 renal impairment,*2 concomitant use with CYP3A inhibitor, concomitant use with CYP3A-inducer, capsule type
Vc/F	Body weight, sex
Vp/F, Q/F	Body weight
F, Ka	Capsule type

*1, Classified according to National Cancer Institute Organ Dysfunction Working Group classification
*2, Classified according to The Modification of Diet in Renal Disease values

Consequently, body weight and sex were identified as significant covariates for CL/F. Body weight was identified as a significant covariate of Vc/F and Q/F as well, and capsule type was selected as a significant covariate of BA. On the basis of these results, the applicant explained the effects of body weight, sex, and capsule type on the PK of dabrafenib, as follows:

- In male patients weighing 50, 80, 110, and 140 kg, C_{max} under a steady state were estimated to be 1576, 1324, 1175, and 1072 ng/mL, respectively, and $AUC_{0\text{-}12h}$ under a steady state were 5115, 4378, 3940, and 3638 ng·h/mL, respectively. This shows that the differences in C_{max} and $AUC_{0\text{-}12h}$ among patients with different body weight were within the inter-individual variability of CL/F (coefficient of variation [CV], 59%), thus suggesting that body weight has only a minor impact on the PK of dabrafenib.
- CL/F in female patients treated with dabrafenib was estimated to be 9% lower than CL/F in male counterparts. However, since the inter-individual variability (CV%) of CL/F was 59% in the final model, sex is considered to have only a minor impact on the PK of dabrafenib.
- F of dabrafenib when administered in gelatin capsule was estimated to be 55.5% of that when administered in HPMC capsule. This was roughly consistent with the geometric mean ratios of C_{max} and AUC_{inf} of dabrafenib (2.02 and 1.80, respectively) when administered in HPMC capsule to the respective parameters when administered in gelatin capsule in the foreign phase I study (Study BRF113468) [see "4.(i).A.(4) Foreign phase I study"]. Thus, capsule type is considered to affect the PK of dabrafenib.

Also, a non-linear mixed effect model (software NONMEM version VII) -based PPK analysis (PPK analysis in dabrafenib /TAB combination therapy) was performed on the PK data of dabrafenib and its metabolites (1128 time points in 380 patients) obtained from foreign clinical studies (Studies BRF112680, BRF113710, BRF113929, and BRF113683).

In this analysis, effects of body weight, sex, renal impairment, hepatic impairment, concomitant use with CYP3A inhibitor, CYP3A inducer, and capsule type on the pre-dosing concentrations* of dabrafenib, M4, M7, and M8 were investigated.

*: Concentrations at 6 to 18 hours after dosing were considered as pre-dosing concentrations.

Consequently, these parameters were identified as significant covariates of pre-dosing concentrations as follows: (a) Body weight for M7 and M8, (b) age for M4 and M8, (c) capsule type for M4 and M8, (d) concomitant use with CYP3A inducer for M4, and (e) concomitant use with CYP3A inhibitor for dabrafenib and M7.

The applicant's explanation on these results:

- Body weight was positively correlated with the pre-dosing concentration of M7 and negatively with that of M8. These results suggested body weight exerts an effect on CL/F of dabrafenib, in the same manner as with PPK analysis in dabrafenib monotherapy.
- Pre-dosing M7 and M8 concentrations were estimated to be 41% and 42% higher, respectively, in patients aged >75 years, than in patients aged ≤75 years. This difference may be caused by the age-related decrease in the liver volume and hepatic blood flow (*Current Drug Metabolism.* 2011;12:601-610).
- Pre-dosing concentrations of M4 and M8 when dabrafenib in gelatin capsule was administered were estimated to be 12% and 19% lower, respectively, than those when dabrafenib in HPMC capsule was administered, suggesting that capsule type affects the PK of the metabolites of dabrafenib.
- Pre-dosing M4 concentration was estimated to be 14% lower when dabrafenib was administered in combination with a CYP3A inducer than that when administered alone, and pre-dosing concentrations of dabrafenib and M7 were estimated to be 23% and 31% higher, respectively, when dabrafenib was administered in combination with a CYP3A inhibitor than those when administered alone. These effects are considered to be caused by the involvement of CYP3A4 in the metabolism of dabrafenib and M7 [see "3.(ii).A.(3).1) *In vitro* metabolism"].

A non-linear mixed effect model (software NONMEM version 7.2.0) -based PPK analysis (PPK analysis in dabrafenib/TRA treatment) was performed on the PK data of dabrafenib (2405 time points in 349 patients) and TRA (1513 time points in 295 patients) obtained from the foreign clinical study (Study BRF113220) pooled with the PK data used in PPK analysis of dabrafenib or TRA monotherapy. In this analysis, the model developed for PPK analysis of dabrafenib or TRA monotherapy (see "Review Report (1) Mekinist Tablets 0.5 mg, 2 mg dated November 13, 2015") was used.

In this analysis, the effects of the following factors on the PK of dabrafenib and TRA were investigated: body weight, sex, renal impairment, hepatic impairment, concomitant use of CYP3A inhibitor and inducer, and capsule type used.

Body weight was identified as a significant covariate for CL/F, Vc/F, and Q/F, and sex as a significant variable for CL/F. These variables were identical to those identified in the PPK analysis of dabrafenib monotherapy mentioned above, and thus the applicant explained that the covariates identified were considered to have only a minimum impact on the PK of dabrafenib and TRA.

4.(ii).A.(6) Effects of renal impairment on PK of dabrafenib

The applicant explained that renal impairment is unlikely to affect the PK of dabrafenib, taking account of the following. An investigator-initiated foreign clinical study (Study BRF115947) to investigate the effects of renal impairment on the PK of dabrafenib is currently ongoing, and the results will become available in the [redacted] quarter of 20[redacted].

- Results of Study BRF113463 showed that the urinary excretion rate (percentage of administered radioactivity excreted) of dabrafenib and its metabolites combined was 22.7% [see "4.(ii).A.(2).1)

Foreign phase I study"], suggesting that the contribution of renal excretion in the elimination of dabrafenib is minimal.

- The absolute BA of dabrafenib was 94.5% [see "4.(i).A.(3) Foreign phase I study"].
- PPK analysis of dabrafenib included 233 patients with mild renal impairment and 30 patients with moderate renal impairment (39.2% and 5.0%, respectively, of the entire PPK population), but renal impairment was not selected as a significant covariate in the PK of dabrafenib [see "4.(ii).A.(5) Population pharmacokinetic (PPK) analysis].

4.(ii).A.(7) Relationship between exposure and efficacy or safety in dabrafenib monotherapy

On the basis of the data obtained from the foreign phase I study (Study BRF112680), the foreign phase II studies (Studies BRF113710 and BRF113629), and the foreign phase III study (Study BRF113683), the relationship between average plasma concentration (C_{avg}) of dabrafenib under a steady state or C_{min} of the metabolites of dabrafenib (M4, M7, and M8) and efficacy or safety was investigated. The individual C_{avg} values used in this analysis were calculated by dividing the AUC_{tau} by dosing interval, where the AUC_{tau} was estimated from the PPK analysis in dabrafenib monotherapy [see "4.(ii).A.(5) Population pharmacokinetic (PPK) analysis].

4.(ii).A.(7).1) Relationship between exposure and efficacy

The relationship between C_{avg} of dabrafenib or C_{min} of dabrafenib metabolites and progression-free survival (PFS) in the foreign phase II study (Study BRF113710) and the foreign phase III study (Study BRF113683) was investigated using Cox proportional hazards regression analysis. As a result, no clear relationship was observed between the exposure to dabrafenib or its metabolites and PFS.

The relationship between C_{avg} of dabrafenib and the response rate (initial assessment and final assessment) in the foreign phase I study (Study BRF112680), the foreign phase II study (Study BRF113710), and the foreign phase III study (Study BRF113683) was determined by a logistic regression model. Results suggested that the response rate increased with increasing exposure to dabrafenib. In an E_{max} model, C_{avg} achieving 50% of E_{max} at the initial assessment and at the final assessment was 68.9 and 77.4 ng/mL, respectively.

4.(ii).A.(7).2) Relationship between exposure and safety

The relationship between C_{avg} of dabrafenib or C_{min} of dabrafenib metabolites in the foreign phase I study (Study BRF112680), the foreign phase II studies (Studies BRF113710 and BRF113629), and the foreign phase III study (Study BRF113683), and the incidence of adverse events frequently observed in these clinical studies, i.e., hyperkeratosis, pyrexia, arthralgia, squamous cell carcinoma, and palmar-plantar erythrodysaesthesia syndrome (PPES), was investigated. Results suggested that the incidences of pyrexia and PPES increased with increasing exposure to dabrafenib and M7. No clear relationship was found between the incidences of other adverse events and C_{avg} of dabrafenib or C_{min} of dabrafenib metabolites.

4.(ii).A.(8) Relationship between exposure and efficacy or safety in dabrafenib/TRA treatment

On the basis of the data obtained from the foreign phase III study (Study MEK115306), the relationships were evaluated between the C_{avg} of dabrafenib, C_{min} of dabrafenib metabolites (M4, M7, and M8), or C_{min} of TRA and the efficacy or safety during concomitant treatment of dabrafenib and TRA. Individual C_{avg} and C_{min} used in this evaluation were estimated by PPK analysis in the above dabrafenib/TRA combination therapy [see "4.(ii).A.(5) Population pharmacokinetic (PPK) analysis"].

4.(ii).A.(8).1) Relationship between exposure and efficacy

Patients were classified into 4 groups by quartiles of C_{avg} of dabrafenib and C_{min} of TRA, and the relationship between exposure and PFS was investigated. As a result, no clear relationship was observed between exposure to TRA and PFS, whereas PFS tended to be lower in the group with the highest exposure to dabrafenib than in the other groups. The applicant explained that the reason for this result is unknown.

4.(ii).A.(8).2) Relationship between exposure and safety

Patients were classified into 4 groups by quartiles of C_{avg} of dabrafenib, C_{min} of dabrafenib metabolites (M4, M7, and M8), and C_{min} of TRA and the relationship between exposure and the incidence of pyrexia was investigated. Results suggested that the incidence of pyrexia increased with increasing exposure to dabrafenib, M7, and TRA.

4.(ii).A.(9) Difference in PK between Japanese and non-Japanese patients

The applicant explained that no clear difference was noted between Japanese and non-Japanese patients in the PK of dabrafenib when administered alone or in dabrafenib/TRA combination, given the following findings:

- Among the foreign phase I study (Study BRF113220), the foreign phase I study (Study BRF113468), and the Japanese phase I study (Study BRF116056), no clear difference was observed in the PK parameters of dabrafenib or its metabolites (M4, M7, and M8) after a single oral administration of dabrafenib under fasted conditions [see "4.(i).A.(4) Foreign phase I study," "4.(ii).A.(1).1) Japanese phase I study," and "4.(ii).A.(2).4) Foreign phase I/II study"].
- Between the foreign phase I study (Study BRF113220) and the Japanese phase I study (Study BRF116056), no clear difference was noted in the PK parameters of dabrafenib or its metabolites (M4, M7, and M8) following multiple oral administration of dabrafenib 75 or 150 mg BID [see "4.(ii).A.(1).1) Japanese phase I study" and "4.(ii).A.(2).4) Foreign phase I/II study"].
- Results of the foreign phase I study (Study BRF113220) and the Japanese phase I/II study (Study MEK116885) showed no clear difference in the PK of dabrafenib, its metabolites (M4, M7, and M8), or TRA following concomitant administration of dabrafenib 150 mg and TRA 2 mg between the studies [see "4.(ii).A.(1).2) Japanese phase I/II study" and "4.(ii).A.(2).4) Foreign phase I/II study"].

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Administration of dabrafenib in patients with hepatic impairment

No clinical study data are available regarding the PK of dabrafenib in patients with hepatic impairment.
The applicant's explanation on the administration of dabrafenib in patients with hepatic impairment:
In light of the following findings, mild hepatic impairment is unlikely to affect the PK of dabrafenib.

- PPK analysis of dabrafenib included 65 patients with mild hepatic impairment and 3 patients with moderate hepatic impairment (10.9% and 0.5% of the entire PPK population, respectively), but hepatic impairment was not selected as a significant covariate in PK of dabrafenib [see "4.(ii).A.(5) Population pharmacokinetic (PPK) analysis"].
- Results of clinical studies did not show any clear difference in the incidence of adverse events between patients with mild hepatic impairment and normal hepatic function.

However, hepatic impairment may possibly affect the PK of dabrafenib and its metabolites because (i) CYP3A4 and CYP 2C8 are shown to be involved in the metabolism of dabrafenib [see "3.(ii).A.(3).1) *In vitro* metabolism"] and (ii) dabrafenib is excreted mainly in feces [see "4.(ii).A.(2).1) Foreign phase I study"]. Also, taking account of the limited treatment experience with dabrafenib in patients with moderate or severe hepatic impairment, administering dabrafenib to patients with hepatic impairment needs careful attention. An investigator-initiated foreign clinical study (Study BRF115947) to investigate the effects of hepatic impairment on the PK of dabrafenib is currently ongoing, and the results will be obtained in the [redacted] quarter of 20[redacted].

PMDA's view:
PMDA accepted the applicant's explanation. Results of ongoing Study BRF115947 should be provided to healthcare professionals in clinical settings appropriately as soon as they become available.

4.(ii).B.(2) Pharmacokinetic interaction between dabrafenib and TRA

The applicant's explanation that a pharmacokinetic interaction between dabrafenib and TRA is unlikely to occur:

- In the foreign phase I/II study (Study BRF113220), dabrafenib/TRA treatment did not affect the PK of dabrafenib [see "4.(ii).A.(2).4) Foreign phase I/II study"].

- No clear difference in PK parameters of TRA was found between the dabrafenib 150 mg BID/TRA 2 mg QD group in the foreign phase I/II study (Study BRF113220) or the Japanese phase I/II study (Study MEK116885) and the TRA 2 mg QD group in the foreign phase I study (Study MEK111054) or the Japanese phase I study (Study MEK114784) [see "4.(ii).A.(1).2) Japanese phase I/II study" and "4.(ii).A.(2).4) Foreign phase I/II study"].

PMDA accepted the applicant's explanation.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A. Summary of the submitted data

The applicant submitted efficacy and safety evaluation data from a total of 10 studies: 1 Japanese phase I study; 1 Japanese phase I/II study; 4 foreign phase I studies; 1 foreign phase I/II study; and 3 foreign phase III studies. The applicant also submitted the results from 4 foreign clinical studies (1 phase I study, 1 phase I/II study, 2 phase II studies) as reference data.

List of clinical studies on efficacy and safety

Data category	Region	Study	Phase	Study population	No. of enrollment	Dosage regimen	Main endpoints
Evaluation	Japan	BRF116056	I	Patients with BRAF V600 mutation-positive solid tumors	12	Oral dose of dabrafenib 75, 100, or 150 mg BID	Safety Efficacy PK
	Japan	MEK116885	I/II	Patients with BRAF V600 mutation-positive solid tumors or with unresectable malignant melanoma with BRAF V600 mutations	12 6 in phase I 6 in phase II	Oral dose of dabrafenib 150 mg BID and TRA 2 mg QD	Efficacy Safety PK
	Foreign	BRF113479	I	Patients with BRAF V600 mutation-positive solid tumors	4	Single oral dose of dabrafenib 150 mg and single intravenous dose of ^{14}C-labeled dabrafenib 0.05 mg	PK Safety
	Foreign	BRF113468	I	Patients with BRAF V600 mutation-positive solid tumors	28	Single oral dose of dabrafenib (150 mg in gelatin or HPMC capsule) under fasted conditions or after high fat/high calorie meal intake	PK Safety
	Foreign	BRF113463	I	Patients with BRAF V600 mutation-positive solid tumors	4	Single oral dose of suspension containing ^{14}C-labeled dabrafenib 95 mg	PK Safety
	Foreign	BRF113771	I	Patients with BRAF V600 mutation-positive solid tumors	60 (a) 14 (b) 16 (c) 17 (d) 13	(a) Oral dose of dabrafenib 150 mg BID for 22 days from Day 8 and single oral dose of warfarin 15 mg on Day 1 and Day 22 (b) Single oral dose of dabrafenib 75 mg on Day 1, oral dose of dabrafenib 75 mg BID for 21 days from Day 2, and oral dose of ketoconazole 400 mg QD for 4 days from Day 19 (c) Single oral dose of dabrafenib 75 mg on Day 1, oral dose of dabrafenib 75 mg BID for 21 days from Day 2, and oral dose of gemfibrozil 600 mg BID for 4 days from Day 19 (d) Single oral dose of dabrafenib 150 mg on Day 1 and oral dose of dabrafenib 150 mg BID for 17 days from Day 2	PK Safety
	Foreign	BRF113220 (phase II part)	I/II	Patients with unresectable malignant melanoma with BRAF V600 mutations	162	Oral dose of dabrafenib 150 mg BID with TRA 1 or 2 mg QD, or dabrafenib 150 mg BID alone	Efficacy Safety PK
	Foreign	BRF113683 (BREAK-3)	III	Patients with unresectable malignant melanoma with BRAF V600 mutations	250 (a) 187 (b) 63	(a) Oral dose of dabrafenib 150 mg BID (b) Intravenous dose of dacarbazine 1000 mg/m^2 at 3-week intervals	Efficacy Safety

Data category	Region	Study	Phase	Study population	No. of enrollment	Dosage regimen	Main endpoints
	Foreign	MEK115306 (COMBI-D)	III	Patients with unresectable malignant melanoma with BRAF V600 mutations	423 (a) 211 (b) 212	Oral dose of dabrafenib 150 mg BID with (a) TRA 2 mg or (b) placebo QD	Efficacy Safety
	Foreign	MEK116513 (COMBI-V)	III	Patients with unresectable malignant melanoma with BRAF V600 mutations	704 (a) 352 (b) 352	(a) Oral dose of dabrafenib 150 mg BID with TRA 2 mg QD (b) Oral dose of vemurafenib 960 mg BID	Efficacy Safety
Reference	Foreign	BRF112680	I	Patients with solid tumors	184 (a) 114 (b) 70 (c) 12	(a) Oral dose of dabrafenib 12–300 mg QD, BID or TID (b) Oral dose of dabrafenib 50 or 150 mg BID (c) Oral dose of dabrafenib 150 mg BID for 15 days from Day 2 and single oral dose of midazolam 3 mg on Day 1 and Day 16	Safety PK
	Foreign	BRF113220 (phase I part)	I/II	(a) (b) Patients with BRAF V600 mutation-positive solid tumors (c) Patients with malignant melanoma with BRAF V600 mutations	253 (a) 8 (b) 135 (c) 110	(a) Oral dose of dabrafenib (75 mg in gelatin capsule) on Day 1 and Day 15 and oral dose of TRA 2 mg QD for 14 days from Day 2 (b) Oral dose of dabrafenib (75 or 150 mg in gelatin capsule) BID and TRA 1, 1.5, or 2 mg QD (c) Oral dose of dabrafenib (75 or 150 mg in HPMC capsule) BID and TRA 2 mg QD	Efficacy Safety PK
	Foreign	BRF113929	II	Patients with brain-metastatic malignant melanoma with BRAF V600 mutations	172	Oral dose of dabrafenib 150 mg BID	Efficacy Safety
	Foreign	BRF113710	II	Patients with unresectable malignant melanoma with BRAF V600 mutations	92	Oral dose of dabrafenib 150 mg BID	Efficacy Safety

Dabrafenib formulations used were the to-be-marketed formulation, unless otherwise specified.

The outline of each clinical study was described below.

Major adverse events other than death reported in each clinical study are described in "4.(iv) Adverse events etc., observed in clinical studies," and PK-related study results in "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and in "4.(ii) Summary of clinical pharmacology studies."

Evaluation data

(1) Clinical pharmacology

The applicant submitted the following 4 clinical pharmacology studies in patients with BRAF V600 mutation-positive solid tumors [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies." No deaths occurred except those due to disease progression, occurred.

1) Foreign phase I study (5.3.1.1, Study BRF113479 [June to September 2011])
2) Foreign phase I study (5.3.1.1, Study BRF113468 [October 2010 to May 2011])
3) Foreign phase I study (5.3.3.2, Study BRF113463 [January to April 2011])
4) Foreign phase I study (5.3.3.4, Study BRF113771 [July 2011 to November 2012])

(2) Japanese clinical studies

1) Japanese phase I study (5.3.5.2, Study BRF116056 [May 2012 – ongoing (data cut-off; August 1, 2014)])

An open-label, uncontrolled study in patients with BRAF V600 mutation-positive solid tumors* (maximum target sample size, 18 patients) was conducted to investigate the safety and PK of dabrafenib at 2 medical institutions in Japan.

*: Determined by direct sequencing method.

A single oral dose of dabrafenib 75, 100, or 150 mg was administered, and after a 6-day off period, dabrafenib 75, 100, or 150 mg BID, respectively, was administered orally until disease progression, death, or an unacceptable adverse event.

All 12 patients enrolled in the study (3 in the dabrafenib 75 mg group, 3 in the 100 mg group, 6 in the 150 mg group) received the study drug and were included in the efficacy analysis population and safety analysis population.

No dose-limiting toxicity (DLT) was observed, nor the maximum tolerated dose (MTD) was reached, up to the maximum dose tested, dabrafenib 150 mg.

As for efficacy, the response rate assessed by the investigator based on RECIST ver.1.1 criteria in patients with malignant melanoma was 54.5% (6 of 11 patients).

As for safety, death during the treatment period or within 14 days after the last dose occurred in 8.3% (1 of 12) of patients. The cause of death was disease progression, and a causal relationship to the study drug was ruled out.

2) Japanese phase I/II study (5.3.5.2, Study MEK116885 [August 2013 – ongoing (data cut-off; September 18, 2014)])

An open-label, uncontrolled study in (a) patients with BRAF V600 mutation-positive solid tumors[*1] (phase I part; target sample size, 6 patients) and (b) patients with unresectable malignant melanoma with BRAF V600 mutations[*1] (phase II part; target sample size, 6 patients) was conducted to investigate the efficacy, safety, and PK in dabrafenib/TRA[*2] treatment at 2 medical institutions in Japan.

*1: Determined by direct sequencing method in phase I part and by THxID BRAF Kit (Sysmex bioMérieux Co., Ltd.) in phase II part.
*2: Not approved in Japan at the start of the study

A single oral dose of dabrafenib 150 mg and TRA 2 mg were administered on Day 1 and, from Day 2, dabrafenib 150 mg BID and TRA 2 mg QD were administered orally and until disease progression, death, or an unacceptable adverse event.

All 12 patients enrolled in the study (6 in the phase I part, 6 in the phase II part) received the study drug and were included in the efficacy analysis population and safety analysis population.

In the phase I part, DLT was not noted in any of the 5 patients[*1] selected for DLT evaluation. Efficacy in the phase II part is determined based on the response rate[*2] assessed by the investigator based on RECIST ver.1.1, the primary endpoint, shown in the following table.

*1: One of 6 patients enrolled in the phase I part was excluded from DLT evaluation because of the aggravation of systemic symptoms associated with the progression of the primary disease.
*2: The threshold response rate was set at 10% by referring to the results of the clinical study on dacarbazine (DTIC) in patients with unresectable malignant melanoma with BRAF V600 mutations (*N Engl J Med.* 2011;364:2507-2516, *Lancet Oncol.* 2012;380:358-365).

Best overall response and response rate
(assessed by investigator, patients with malignant melanoma, data cut-off September 18, 2014)

Best overall response	Number of patients (%) N = 6
Complete response (CR)	2 (33.3)
Partial response (PR)	3 (50.0)
Stable disease (SD)	1 (16.7)
Progressive disease (PD)	0
Unknown	0
Response (CR + PR)	5
(response rate [95% CI] %)	(83.3 [35.9, 99.6])
P value (one-sided)*	<0.0001

*: Binomial test, significance level (one-sided) 0.05

No adverse events leading to death occurred during the treatment period or within 30 days after the last dose. Two of 12 patients (16.7%) died of disease progression.

(3) Foreign clinical studies

1) Foreign phase I/II study (5.3.5.1, Study BRF113220, phase II part [[redacted] 20[redacted] - ongoing (data cut-off; [redacted], 20[redacted])])

An open-label, randomized, comparative study was conducted at 16 medical institutions overseas in patients with unresectable malignant melanoma with BRAF V600 mutations* (target sample size, 150patients) to compare the safety, efficacy, and PK between the dabrafenib/TRA group and the dabrafenib group.

*: Neither testing laboratory nor testing method was specified. Pyrosequencing, Roche cobas 4800 BRAF V600 Mutation Test, etc., were used.

Dabrafenib 150 mg BID and TRA 1, or 2 mg QD in combination, or dabrafenib 150 mg BID alone, was administered orally until the disease progressed or patients met any of the other discontinuation criteria (e.g., occurrence of an adverse event, consent withdrawal).

All 162 patients enrolled and randomized in the study (54/group) were included in the intent-to-treat (ITT) population, in the efficacy analysis population, and also in the safety analysis population.*.

*: One patient assigned to the dabrafenib group received TRA 2 mg concomitantly by mistake and was therefore included in the dabrafenib/TRA 2 mg group.

Adverse events leading to death occurred during the treatment period or within 14 days after the last dose[*1] in 1.9% (1 of 54) of patients in the dabrafenib/TRA 1 mg group; 7.3% (4 of 55) of patients in the dabrafenib/TRA 2 mg group; and 9.4% (5 of 53) of patients in the dabrafenib group. The deaths were caused by sepsis in 1 patient in the dabrafenib/TRA 1 mg group; and by brain stem haemorrhage/cerebral haemorrhage,[*2] cerebrovascular accident,[*3] haemorrhage intracranial,[*4] and pulmonary embolism[*5] in 1 patient each in the dabrafenib/TRA 2 mg group. A causal relationship to the study drug was ruled out for all of them. Death due to disease progression occurred in 28 patients in the dabrafenib/TRA 1 mg group; 28 patients in the dabrafenib/TRA 2 mg group; and 5 patients in the dabrafenib group.

*1: Include events reported ≥15 days after the last dose at the discretion of the investigator.

*2: A woman aged 55 years with a history of hypertension etc. She was hospitalized for chest pain and respiratory failure on Day 261 of dabrafenib treatment (the last day). Head CT did not detect brain metastasis but revealed brain stem haemorrhage and cerebral haemorrhage. She was treated with blood transfusion and other treatments, but died of brain stem haemorrhage/cerebral haemorrhage on Day 262.

*3: A man aged 57 years with a history of hypertension. He was hospitalized for cerebrovascular accident on Day 955 of dabrafenib treatment (treatment ended on Day 944) and died of cerebrovascular accident on Day 961.

*4: A man aged 74 years. He experienced pulmonary embolism (Grade 3) on Day 335 of dabrafenib treatment, received heparin and other drugs, and recovered on Day 340. On Day 375 (treatment ended on Day 372), he was hospitalized for change in visual acuity and mental status. Head CT did not detect brain metastasis but showed intracranial haemorrhage rupturing into the cerebral ventricle. Osmotic diuretics and blood transfusion were given, but he died of intracranial haemorrhage on Day 376.

*5: A man aged 67 years with a history of pulmonary embolism, deep venous thrombosis, etc. On Day 124 of dabrafenib treatment (treatment ended on Day 107), he was hospitalized for acute renal failure, hypoxemia, and tachycardia. Detailed examination diagnosed pulmonary embolism. He was treated with physiological saline, antibiotics, diuretics, etc., but died of pulmonary embolism on Day 127.

2) Foreign phase III study (5.3.5.1, Study BRF113683 (BREAK-3) [February 2011 – ongoing (data cut-off; December 19, 2011)])

An open-label, randomized, comparative study was conducted in patients with unresectable malignant melanoma with BRAF V600 mutations* (target sample size, 200 patients) to compare the efficacy and safety between the dabrafenib group and the DTIC group at 70 medical institutions overseas.

*: Determined by PCR

Dabrafenib 150 mg BID was administered orally to the dabrafenib group, and DTIC 1000 mg/m^2 was administered intravenously once every 3 weeks to the DTIC group until disease progression, death, or study termination.

All 250 patients enrolled and randomized in the study (187 in the dabrafenib group, 63 in the DTIC group) were included in the ITT population and in the efficacy analysis population. Of those in the ITT

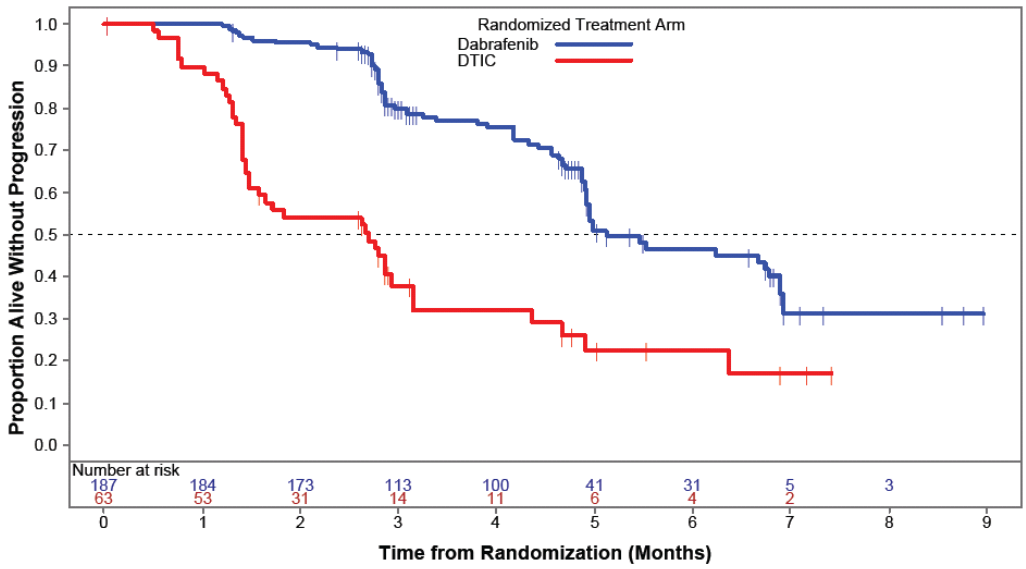
population, 246 patients (187 in the dabrafenib group, 59 in the DTIC group) who received 1 dose or more of the study drug were included in the safety analysis population.

The investigator-assessed PFS based on RECIST ver.1.1 criteria, the primary endpoint, was as shown in the following table, and Kaplan-Meier curves were as shown in the following figure.

Analysis of PFS (ITT population; assessed by investigator; data cut-off, December 19, 2011)

	Dabrafenib	DTIC
Number of patients	187	63
Number of death or aggravation (%)	77 (41.2)	41 (65.1)
Median [95% CI] (months)	5.1 [4.9, 6.9]	2.7 [1.5, 3.2]
Hazard ratio [95% CI]*1	0.30 [0.18, 0.51]	
P value (two-sided)*2	<0.0001	

*1, Pike's estimate; *2, Stratified log-rank test (stratified by disease stage); Significance level (two-sided) 0.05



Kaplan-Meier curves of PFS (ITT population; assessed by investigator; data cut-off, December 19, 2011)

Adverse event leading to death occurred during the treatment period or within 30 days after the last dose in 1 of 187 patients (0.5%) in the dabrafenib group. The cause of death was euthanasia in 1 patient, and its causal relationship to the study drug was ruled out. Death due to disease progression occurred in 20 patients in the dabrafenib group and in 9 patients in the DTIC group.

3) Foreign phase III study (5.3.5.1, Study MEK116513 (COMBI-V) [June 2012 – ongoing (data cut-off; April 17, 2014)])

An open-label, randomized, comparative study was conducted in patients with unresectable malignant melanoma with BRAF V600 mutations* (target sample size, 694 patients) to compare the efficacy and safety between the dabrafenib/TRA group and the vemurafenib (Vem) group at 163 medical institutions overseas.

*: Determined by THxID BRAF kit

Dabrafenib 150 mg BID and TRA 2 mg QD were administered orally in the dabrafenib/TRA group, and Vem 960 mg BID were administered orally in the Vem group, until disease progression, death, an unacceptable adverse event, or consent withdrawal.

A total of 704 patients enrolled and randomized in the study (352 in the dabrafenib/TRA group, 352 in the Vem group) were included in the ITT population and in efficacy analysis population. Of those, 699 patients who received ≥1 dose of the study drug (350 in the dabrafenib/TRA group, 349 in the Vem group) were included in the safety analysis.

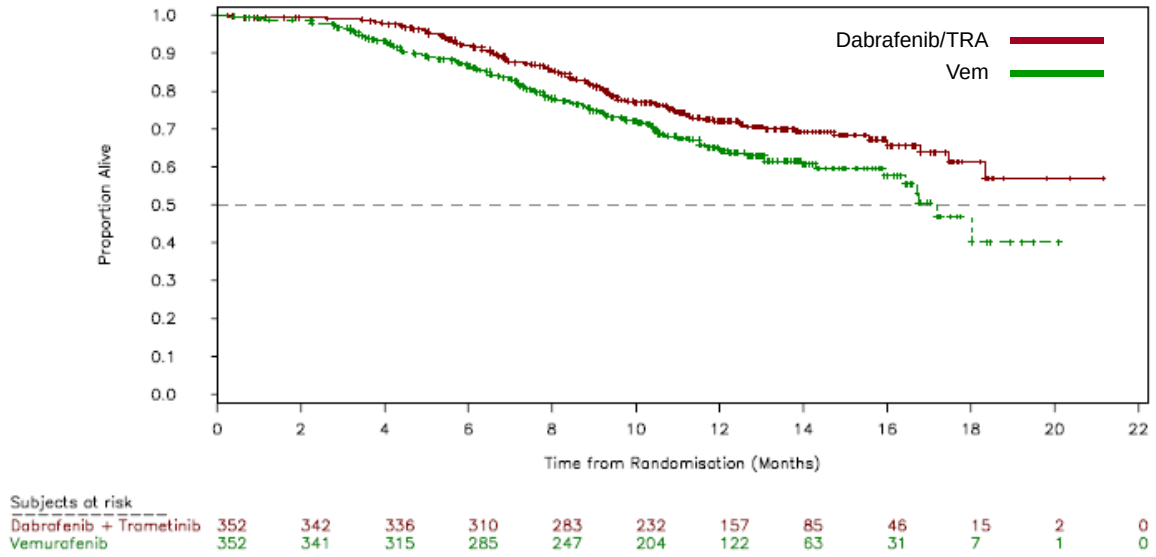
The primary endpoint of the study was overall survival (OS). An interim analysis for efficacy and futility was conducted at the time point when OS events summed up to 202 (70% of the target number of events). Type 1 error probability associated with the interim analysis of OS was adjusted for by O'Brien-Fleming type α-spending function based on the Lan-DeMets method.

Results of the interim analysis of OS and Kaplan-Meier curves were as shown in the following table and figure, respectively. Early termination of the study was recommended by the independent data monitoring committee (IDMC) meeting held on July 9, 2014.

Results of interim analysis of OS (ITT population; data cut-off, April 17, 2014)

	Dabrafenib/TRA	Vem
Number of patients	352	352
Number of deaths (%)	100 (28.4)	122 (34.7)
Median [95% CI] (months)	NE [18.3, NE]	17. 2 [16.4, NE]
Adjusted hazard ratio [95% CI][*1]	0.69 [0.53, 0.89]	
P value (two-sided)[*2]	0.005	

NE, Not estimable; *1, Pike's estimate; *2, Stratified log-rank test (stratified by lactic dehydrogenase (LDH) level and by *BRAF* mutation type), significance level (two-sided) 0.0214



Kaplan-Meier curves of OS by interim analysis (ITT population; data cut-off, April 17, 2014)

Adverse events leading to death occurred during the treatment period or within 30 days after the last dose in 0.9% (3 of 350) of patients in the dabrafenib/TRA group and in 0.9% (3 of 349) of patients in the Vem group. The causes of death were cerebral haemorrhage[*1, 2] in 2 patients and brain stem haemorrhage[*3] in 1 patient in the dabrafenib/TRA group, and acute coronary syndrome, cerebral ischaemia, and pleural infection in 1 patient each in the Vem group. A causal relationship to the study drug was ruled out for all of them. Death due to disease progression occurred in 96 patients in the dabrafenib/TRA group and in 115 patients in the Vem group.

*1: A man aged 42 years with a history of hypertension. On Day 148 of dabrafenib treatment (the last day of dabrafenib treatment), he was hospitalized because of light-headedness and hemiplegia. Head CT showed haemorrhage from a new brain metastatic lesions, and corticosteroid, antibiotics, etc., were administered. On Day 156, the brain metastatic lesions was surgically removed, but he died of cerebral haemorrhage on Day 166.

*2: A man aged 66 years. The patient was hospitalized because of increased white blood cell count and pulmonary embolism (Grade 3) on Day 320 of dabrafenib treatment. Acute myeloid leukaemia was diagnosed and chemotherapy was started. On Day 334 (the last day of dabrafenib treatment was Day 321), he fell over from light-headedness. Head CT did not detect brain metastasis but showed cerebral haemorrhage, and he died on the same day of cerebral haemorrhage. The cause of cerebral haemorrhage was unknown.

*3: A woman aged 71 years. She was hospitalized because of paralysis on her right side, vomiting, etc., on Day 236 of dabrafenib treatment (the last day of dabrafenib treatment was Day 235). Electrocardiography showed atrial fibrillation, coagulation test showed prolonged activated partial thromboplastin time, and head CT showed brain stem haemorrhage. Protamine sulfate etc., were administered, but she died of brain stem haemorrhage on the same day. Autopsy did not show findings such as brain metastatic lesions or cerebrovascular abnormality, and the cause of the brain stem haemorrhage was unknown.

4) Foreign phase III study (5.3.5.1, Study MEK115306 (COMBI-D) [May 2012 – ongoing (data cut-off; January 12, 2015)])

A double-blind, randomized, comparative study was conducted at 103 medical institutions overseas in patients with unresectable malignant melanoma with BRAF V600 mutations* (target sample size, 340 patients) to compare the efficacy and safety between the dabrafenib/TRA group and the dabrafenib/placebo (concomitant use of dabrafenib with placebo) group. Dabrafenib (150 mg BID) was concomitantly administered orally with TRA (2 mg QD) or placebo until disease progression, death, an unacceptable adverse event, or consent withdrawal.

*: Determined by THxID BRAF kit.

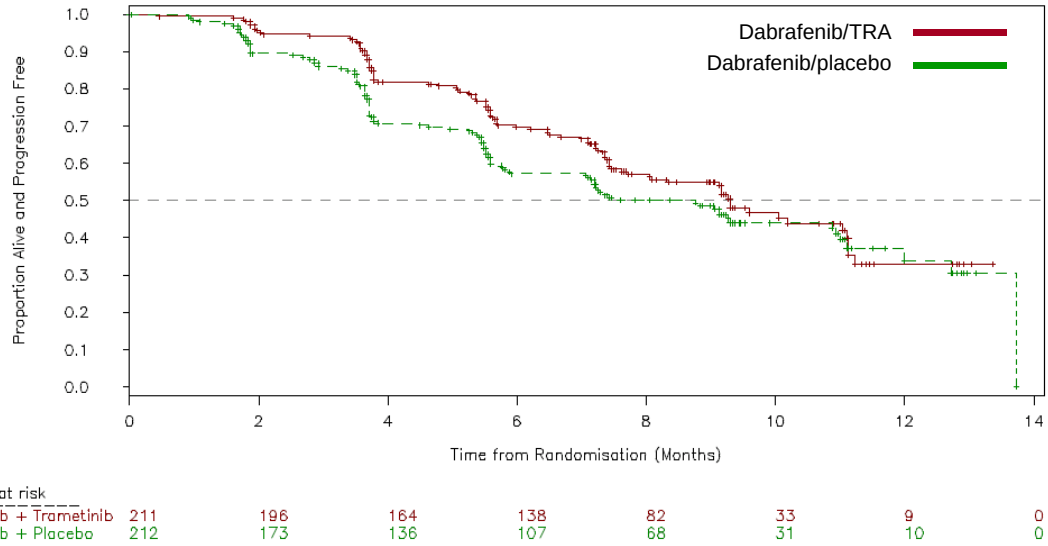
All 423 patients enrolled and randomized in the study (211 in the dabrafenib/TRA group, 212 in the dabrafenib/placebo group) were included in the ITT population and subjected to efficacy analysis. Of those, 420 patients (209 in the dabrafenib/TRA group, 211 in the dabrafenib/placebo group) receiving ≥1 dose of the study drug were included in safety analysis.

The investigator-assessed PFS based on RECIST ver.1.1 criteria, the primary endpoint, was as shown in the following table, and Kaplan-Meier curves were as shown in the following figure.

Analysis of PFS (ITT population; assessed by investigator; data cut-off, August 26, 2013)

	Dabrafenib/TRA	Dabrafenib/placebo
Number of patients	211	212
Number of deaths or aggravations (%)	102 (48.3)	109 (51.4)
Median [95% CI] (months)	9.3 [7.7, 11.1]	8.8 [5.9, 10.9]
Adjusted hazard ratio [95% CI]*1	0.75 [0.57, 0.99]	
P value (two-sided)*2	0.035	

*1, Pike's estimate; *2, Stratified log-rank test (stratified by LDH level and by *BRAF* mutation type), significance level (two-sided) 0.05



Kaplan-Meier curves of PFS (ITT population, assessed by investigator, data cut-off August 26, 2013)

Adverse events leading to death occurred during the treatment period or within 30 days after the last dose*1 in 2.4% (5 of 209) of patients in the dabrafenib/TRA group and in 0.5% (1 of 211) of patients in the dabrafenib/placebo group. The causes of death were cerebral haemorrhage*2*3 in 2 patients, cerebrovascular accident,*4 pneumonia and myocardial ischaemia*5 in 1 patient each in the dabrafenib/TRA group and bile duct adenocarcinoma*6 in 1 patient in the dabrafenib/placebo group. A causal relationship to the study drug could not be ruled out for bile duct adenocarcinoma in the dabrafenib/placebo group. Death due to disease progression occurred in 90 patients in the dabrafenib/TRA group and in 119 patients in the dabrafenib/placebo group.

*1: Include events reported ≥31 days after the last dose at the discretion of the investigator.

*2: A woman aged 67 years with a history of hypertension. On Day 124 of dabrafenib treatment (the last day was Day 121), she was hospitalized for vomiting. Detailed examination detected cerebral haemorrhage but not brain metastasis, and she died of cerebral haemorrhage on Day 126.
*3: A man aged 75 years with a history of hypertension. Hyperglycaemia was noted on Day 85 of dabrafenib treatment, and an oral hypoglycemic drug was administration from Day 92 onward. On Day 144 (dabrafenib therapy ended on Day 145), he was hospitalized for cerebral haemorrhage. Head CT did not detect brain metastasis but showed widely spread cerebral haemorrhage, and he died of cerebral haemorrhage on Day 154.
*4: A woman aged 61 years with a history of dyslipidaemia and aortic valve replacement for aortic stenosis who has been treated with anticoagulants etc. On Day 126 of dabrafenib treatment (the last day was Day 127), she was hospitalized with suspected cerebrovascular accident. Prolonged activated partial thromboplastin time and increased prothrombin time was noted, and blood pressure was 190/90 mmHg. Head CT showed cerebral haemorrhage and she died of cerebrovascular accident on Day 146.
*5: A man aged 55 years with a history of coronary stenting for angina pectoris, dyslipidaemia, etc. On Day 758 of dabrafenib treatment, decreased ejection fraction was noted, whereupon dabrafenib was discontinued on Day 759. On Day 761, he was found dead away from home.
*6: Death was confirmed after the data cut-off date.

Reference data

(1) Foreign clinical studies

1) Foreign phase I study (5.3.5.2, Study BRF112680 [May 2009 to March 2012])

An open-label, uncontrolled study was conducted in patients with solid tumors (target sample size, approximately 70 patients) to investigate the safety and PK of dabrafenib at 4 medical institutions overseas.

All 184 patients enrolled in the study and given with ≥1 dose of the study drug were included in the safety analysis.

No adverse events leading to death occurred during the treatment period or within 14 days after the last dose. Death due to disease progression occurred in 33 patients.

2) Foreign phase I/II study (5.3.5.2, Study BRF113220, phase I part [March 2010 – ongoing (data cut-off; September 25, 2012)])

An open-label, uncontrolled study was conducted at 16 medical institutions overseas in patients with unresectable malignant melanoma or colorectal cancer with BRAF V600 mutations (target sample size, 146 patients) to investigate the safety of dabrafenib, TRA, and dabrafenib/TRA.

All 253 patients who were enrolled in the study and given ≥1 dose of the study drug were included in the safety analysis.

Adverse events leading to death occurred during the period or within 14 days after the last dose in 2.0% (5 of 253) of patients. The causes of death were convulsion[*1] ventricular arrhythmia,[*2] hyponatraemia, completed suicide, and pulmonary embolism[*3] in 1 patient each. Among them, a causal relationship to the study drug could not be ruled out for ventricular arrhythmia. Death due to disease progression occurred in 72 patients.

*1: A man aged 77 years with a history of old myocardial infarction and left ventricular thrombosis treated with anticoagulants. On Day 259 of dabrafenib therapy, rectal haemorrhage was noted, whereupon dabrafenib was discontinued on Day 260. On Day 262, a pacemaker was implanted for atrioventricular block. During the implantation procedure, Grade 2 convulsions occurred, followed by consciousness distributed. Head CT on Day 264 revealed cerebral haemorrhage. On Day 270, convulsions occurred again and he died of convulsions on Day 272.
*2: A man aged 69 years with a history of hypothyroidism, deep vein thrombosis, and hypertension. Because he was aware of decreased appetite, fatigue, dizziness, and chill, he was advised by the attending physician on Day 327 to temporarily withdraw from the study, but continued to receive the study drug on his own will. Corticosteroid was prescribed at a local clinic, which resulted in the improvement of symptoms, but on Day 328 (the last day of dabrafenib therapy), he had cardiac arrest while driving a car. Ventricular fibrillation was diagnosed by the emergency medical assistance and he received defibrillation, epinephrine, and amiodarone. Cardiac catheter test did not detect coronary lesions but decreased cardiac output was noted. He did not respond to treatments given in the intensive-care unit and died of ventricular arrhythmia on Day 345. No abnormality was observed on electrocardiography or cardiac ultrasonography before the start of treatment.
*3: A woman aged 90 years with a history of coronary artery disease and gastrointestinal haemorrhage. She was hospitalized for acute pancreatitis on Day 310 of dabrafenib therapy (the last day of treatment was Day 291). Immediately after she got up to go to the bathroom on Day 315, she became unconscious and apneic. Pulmonary embolism was suspected from electrocardiography. In spite of intensive care, she did not recover and died of pulmonary embolism on the same day.

3) Foreign phase II study (5.3.5.2, Study BRF113929 [February 2011 to April 2013])

An open-label, uncontrolled study was conducted at 24 medical institutions overseas in patients with brain metastatic malignant melanoma with BRAF V600 mutations (target sample size, 120 patients) to investigate the efficacy and safety of dabrafenib.

All 172 patients who were enrolled in the study and given ≥1 dose of the study drug were included in the safety analysis.

Adverse events leading to death occurred during the treatment period or within 30 days after the last dose in 2.9% (5 of 172) of patients. The causes of death were cerebral haemorrhage[*1][*2] in 2 patients, cardiac arrest/pulmonary embolism/renal failure acute/urinary tract infection in 1 patient, metastases to meninges in 1 patient, and haemorrhage intracranial[*3] in 1 patient. A causal relationship to the study drug was ruled out for all of them. Death due to disease progression occurred in 128 patients.

*1: A woman aged 32 years. She was hospitalized because of headache, nausea, etc., on Day 47 of dabrafenib treatment. On Day 48 (the last day of dabrafenib therapy), consciousness distributed was noted. Detailed examination showed cerebral haemorrhage, and she died of cerebral haemorrhage on Day 49.

*2: A woman aged 65 years. On Day 66 and 67, she underwent radiation therapy for brain metastasis. On Day 97 (the last day of dabrafenib therapy), she was hospitalized for consciousness disturbed. Detailed examination showed haemorrhage caused by brain metastasis, and she died of cerebral haemorrhage and aggravation of the primary disease on Day 103.

*3: A woman aged 56 years with a history of pulmonary embolism. One day before the start of dabrafenib treatment, enoxaparin sodium treatment was started for pulmonary embolism. On Day 4 of dabrafenib treatment, she noticed headache and gradually increasing fatigue, and was hospitalized on Day 5 because of nausea and vomiting. Detailed examination showed intracranial haemorrhage and, on Day 10, she died of intracranial haemorrhage and aggravation of the primary disease.

4) Foreign phase II study (5.3.5.2, Study BRF113710 [August 2010 – ongoing (data cut-off; July 7, 2011)])

An open-label, uncontrolled study was conducted in patients with unresectable malignant melanoma with BRAF V600 mutations (target sample size, 100 patients) to investigate the efficacy and safety of dabrafenib at 21 medical institutions overseas.

All 92 patients who were enrolled in the study and received ≥1 dose of the study drug were included in the safety analysis.

No adverse events leading to death occurred during the period of study drug administration or within 30 days after the last dose. Death due to disease progression occurred in 28 patients.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Data for review

PMDA concluded that, among the evaluation data submitted, the most important studies for evaluating the efficacy and safety of dabrafenib were 2 foreign phase III studies (Study BRF113683 [BREAK-3 study] and Study MEK116513 [COMBI-V study]) in patients with unresectable malignant melanoma with BRAF V600 mutations, and decided to evaluate the submitted data focusing on these studies.

The efficacy and safety in Japanese patients were evaluated mainly on the basis of data from the Japanese phase I study (Study BRF116056) and the Japanese phase I/II study (Study MEK116885) in patients with unresectable malignant melanoma with BRAF V600 mutations.

4.(iii).B.(2) Efficacy

On the basis of the following review, PMDA has concluded that the effectiveness of dabrafenib is demonstrated in patients with unresectable malignant melanoma with BRAF V600 mutations.

4.(iii).B.(2).1) Selecting the control group

The applicant's explanation of the rationale for selecting the control group in the BREAK-3 and COMBI-V studies:

At the time when the BREAK-3 study was started (February 2011), DTIC was the standard therapy for patients with unresectable malignant melanoma with BRAF V600 mutations (National Comprehensive

Cancer Network Clinical Practice Guidelines in Oncology Melanoma [NCCN Guideline] [v.2.2009]; European Society for Medical Oncology clinical recommendations for diagnosis, treatment, and follow up, 2009). Therefore, the DTIC group was selected as the control group in the BREAK-3 study.

At the time when the COMBI-V study started (June 2012), Vem was the standard therapy for patients with unresectable malignant melanoma with BRAF V600 mutations (NCCN Guideline [v.3.2012]). Accordingly, the Vem group was selected as the control group in the COMBI-V study.

PMDA accepted the applicant's explanation.

4.(iii).B.(2).2) Efficacy endpoints

The applicant's explanation on the appropriateness of selecting the investigator-assessed PFS based on RECIST ver.1.1 criteria as the primary endpoint of the BREAK-3 study:

In patients with unresectable malignant melanoma with BRAF V600 mutations, the target patient population in the BREAK-3 study, prolonged PFS meant an increase in time to tumor aggravation, resulting in an improvement in QOL of patients and was of clinical significance. It is thus appropriate to have selected PFS as the primary endpoint in the BREAK-3 study.

PMDA's view:

Since the objective of treating patients with unresectable malignant melanoma with BRAF V600 mutations is life prolongation, OS should have been selected as the primary endpoint in the BREAK-3 study to evaluate the efficacy of dabrafenib in these patients. On the other hand, PFS may have a certain clinical significance depending on the intensity of its effect. In the BREAK-3 study, efficacy should be evaluated in a comprehensive manner based on the results of not only PFS (the primary endpoint) but also OS (the secondary endpoint). In the COMBI-V study, it was appropriate to select OS as the primary endpoint.

4.(iii).B.(2).3) Results of efficacy evaluation

(a) BREAK-3 study

The superiority of dabrafenib over DTIC has been demonstrated in investigator-assessed PFS, the primary endpoint, [see "4.(iii).A. *Evaluation data* (3).2) Foreign phase III study"].

Also, the following table shows the results of the independent PFS assessment performed as a sensitivity analysis.

Results of PFS analysis (ITT population; independent assessment; data cut-off, December 19, 2011)

	Dabrafenib		DTIC
Number of patients	187		63
Number of PD or deaths (%)	68 (36.4)		32 (50.7)
Median [95% CI] (months)	6.7 [5.0, 6.9]		2.9 [1.7, 4.9]
Hazard ratio [95% CI]*1		0.35 [0.20, 0.61]	
P value (two-sided)*2		<0.0001	

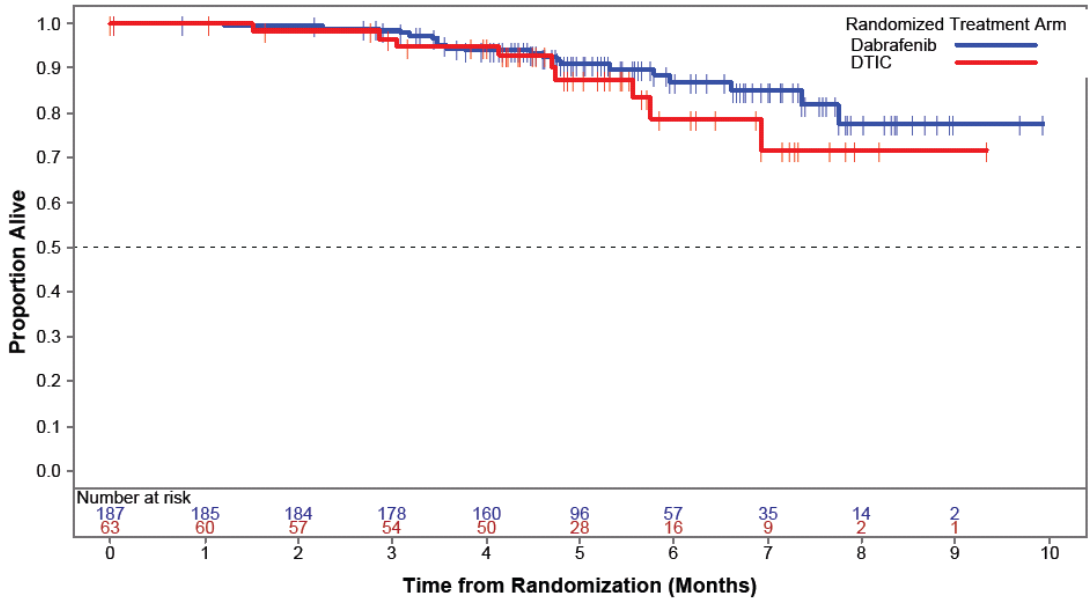
*1, Pike's estimate; *2, Stratified log-rank test (stratified by disease stage)

The results of OS, a secondary endpoint, and Kaplan-Meier curves were as shown in the following table and figure, respectively. At the time of OS analysis, dabrafenib was being administered to 44.4% (28 of 63) of patients in the DTIC group in a crossover manner.

Results of OS analysis (ITT population; data cut off, December 19, 2011)

	Dabrafenib		DTIC
Number of patients	187		63
Number of deaths (%)	21 (11.2)		9 (14.3)
Median [95% CI] (months)	NE		NE
Hazard ratio [95% CI]*1		0.61 [0.25, 1.48]	
P value (two-sided)*2		0.2147	

NE, Not estimable; *1, Pike's estimate; *2, Stratified log-rank test (stratified by disease stage)



Kaplan-Meier curves of OS (ITT population; data cut-off, December 19, 2011)

(b) COMBI-V study

The superiority of the dabrafenib/TRA group to the Vem group has been demonstrated in the primary endpoint [see "4.(iii).A. *Evaluation data* (3).3) Foreign phase III study"].

Since TRA, concomitantly administered with dabrafenib in the COMBI-V study, was not approved in Japan, and its effectiveness in the treatment of malignant melanoma was not demonstrated, PMDA asked the applicant to explain the efficacy of TRA in patients with malignant melanoma.

The applicant's response:

The efficacy of TRA in patients with unresectable malignant melanoma with BRAF V600 mutations can be considered demonstrated by the following clinical study results:

- Foreign phase III study (Study MEK114267 [METRIC study]) compared the efficacy and safety between TRA monotherapy and investigator-selected treatment of either DTIC or paclitaxel (chemotherapy) in patients with unresectable malignant melanoma with BRAF V600 mutations. The superiority of the TRA group over the chemotherapy group in investigator-assessed PFS, the primary endpoint, has been demonstrated (*N Engl J Med.* 2012;367:107-114).

PMDA's view:

PMDA has concluded that the efficacy of dabrafenib monotherapy has been demonstrated in patients with unresectable malignant melanoma with BRAF V600 mutations in the BREAK-3 study for the following reasons: (a) dabrafenib was superior to DTIC in the primary endpoint, i.e., the investigator-assessed PFS based on RECIST ver.1.1 criteria, and the PFS-prolonging effect achieved was clinically significant; and (b) OS in the dabrafenib group did not tend to decrease compared with OS in the DTIC group. On the basis of these and other findings, PMDA has concluded that the efficacy of dabrafenib monotherapy in patients with unresectable malignant melanoma with BRAF V600 mutations is established.

PMDA has concluded that the efficacy of dabrafenib/TRA has been demonstrated in patients with unresectable malignant melanoma with BRAF V600 mutations, taking account that METRIC and BREAK-3 studies also demonstrated the effectiveness of dabrafenib monotherapy and TRA monotherapy, respectively, in addition to the above COMBI-V study.

4.(iii).B.(2).4) Efficacy in Japanese patients

In the Japanese phase I study (Study BRF116056) in patients with BRAF V600 mutation-positive solid tumors, dabrafenib monotherapy was effective in 54.5% (6 of 11) of patients with unresectable malignant melanoma with BRAF V600 mutations ["4.(iii).A *Evaluation data* (2).1) Japanese phase I study"].

In the phase II part of the Japanese I/II study (Study MEK116885), the investigator-assessed response rate [95% CI], the primary endpoint, was 83.3% [35.9%, 99.6%], with the lower limit of 95% CI exceeding the pre-set threshold (10%) ["4.(iii).A *Evaluation data* (2).2) Japanese phase I/II study"].

PMDA's view:
On the basis of the above results, PMDA concluded that efficacy in both dabrafenib monotherapy and dabrafenib/TRA can be expected in these patients, although the efficacy in Japanese patients can only be evaluated to a limited extent since the numbers of Japanese patients in Studies BRF116056 and MEK116885 were very small.

4.(iii).B.(3) Safety [for adverse events, see "4.(iv) Adverse events etc., observed in clinical studies"]

On the basis of the review below, PMDA considers that the adverse events that need particular cautions in treatment with dabrafenib are the following: secondary malignant tumor, cardiac disorders, hepatic impairment, pyrexia, and eye disorders.

In addition to these adverse events, attention should also be paid to the occurrence of hypertension, skin disorder, bone marrow depression, deep vein thrombosis, pulmonary embolism, cerebrovascular disorders, QT/QTc interval prolongation, and pancreatitis. With these premises, PMDA concluded that dabrafenib is well tolerated provided that adverse events are well monitored and managed and measures such as dose reduction, interruption, and discontinuation are taken appropriately by physicians with sufficient knowledge and experience of cancer chemotherapy. However, because of the extremely limited treatment experience with dabrafenib in Japanese patients, information should be continuously collected after the market launch, and new safety information should be provided appropriately to healthcare professionals in clinical settings.

4.(iii).B.(3).1) Safety profile of dabrafenib

(a) Safety profile in dabrafenib monotherapy

The applicant's explanation on the safety profile of dabrafenib monotherapy:
The following table summarizes the safety in the dabrafenib group and the DTIC group in the BREAK-3 study.

Summary of safety (BREAK-3 study)

	Number of patients (%)	
	Dabrafenib (n = 187)	DTIC (n = 59)
All adverse events	185 (98.9)	54 (91.5)
Grade ≥3 adverse events	63 (33.7)	25 (42.4)
Adverse events leading to death	1 (0.5)	0
Serious adverse events	43 (23.0)	13 (22.0)
Adverse events leading to treatment discontinuation	5 (2.7)	2 (3.4)
Adverse events leading to treatment interruption	51 (27.3)	16 (27.1)
Adverse events leading to dose reduction	34 (18.2)	10 (16.9)

Adverse events with an incidence ≥10% higher in the dabrafenib group than in the DTIC group were hyperkeratosis (36.9% in the dabrafenib group, 0% in the DTIC group), alopecia (21.9%, 1.7%), palmar-plantar erythrodysaesthesia syndrome (19.8%, 1.7%), rash (16.6%, 0%), pyrexia (27.8%, 10.2%), arthralgia (27.3%, 1.7%), headache (31.6%, 8.5%), skin papilloma (24.1%, 1.7%), and myalgia (10.7%, 0%). Grade ≥3 adverse events with an incidence ≥2% higher in the dabrafenib group than in the DTIC group were palmar-plantar erythrodysaesthesia syndrome (2.1%, 0%), pyrexia (3.2%, 0%), back pain (2.7%, 0%), and squamous cell carcinoma (3.2%, 0%). Serious adverse events with an incidence ≥2% higher in the dabrafenib group than in the DTIC group were pyrexia (3.7%, 0%) and squamous cell carcinoma (3.7%, 0%). There were no adverse events leading to treatment discontinuation with an incidence ≥2% higher. Adverse events leading to treatment interruption with an incidence ≥2% higher were pyrexia (10.7%, 0%), palmar-plantar erythrodysaesthesia syndrome (3.2%, 0%), and chills (2.7%, 0%). Adverse events leading to dose reduction with an incidence ≥2% higher were pyrexia (8.6%, 0%), palmar-plantar erythrodysaesthesia syndrome (3.2%, 0%), chills (2.7%, 0%), and fatigue (2.1%, 0%).

The applicant's explanation on the difference in the safety of dabrafenib monotherapy between Japanese and non-Japanese patients:
The following table summarizes the safety in (i) the dabrafenib group in Study BRF116056 in Japanese patients and (ii) the dabrafenib group in the BREAK-3 study in non-Japanese patients and the dabrafenib/placebo group in the COMBI-D study in non-Japanese patients.

Summary of safety in Japanese and non-Japanese patients (Study BRF116056, BREAK-3 study, and COMBI-D study)

	Number of patients (%)	
	Japanese patients (Study BRF116056)	Non-Japanese patients (BREAK-3 and COMBI-D studies)
	Dabrafenib (n = 12)	Dabrafenib and dabrafenib/placebo (n = 398)
All adverse events	12 (100)	390 (97.9)
Grade ≥3 adverse events	1 (8.3)	169 (42.4)
Adverse events leading to death	0	2 (0.5)*
Serious adverse events	2 (16.6)	121 (30.4)
Adverse events leading to treatment discontinuation	0	19 (4.7)
Adverse events leading to treatment interruption	2 (16.6)	129 (32.4)
Adverse events leading to dose reduction	0	63 (15.8)

*, Include 1 patient who was confirmed dead after data cut-off.

Adverse events with an incidence ≥20% higher in Japanese patients than in non-Japanese patients were alopecia (58.3% in Japanese patients, 25.1% in non-Japanese patients), alanine aminotransferase (ALT) increased (25.0%, 4.8%), aspartate aminotransferase (AST) increased (25.0%, 3.3%), blood alkaline phosphatase (ALP) increased (25.0%, 2.8%), arthralgia (50.0%, 29.4%), and leukopenia (50.0%, 0.5%). There were no Grade ≥3 adverse events with an incidence ≥10% higher in Japanese patients than in non-Japanese patients. All adverse events that were observed only in Japanese patients and not in non-Japanese patients (proteinuria, performance status decreased, haemorrhoids thrombosed, excessive granulation tissue, blood albumin decreased, nail discolouration/haemorrhage intracranial/excoriation, and myocardial ischaemia) were Grade 1 or 2 in severity.

Thus, some adverse events occurred more frequently after dabrafenib treatment in Japanese patients than in non-Japanese patients. However, they were mild in severity, suggesting that dabrafenib is well tolerated also in Japanese patients.

(b) Safety profile of dabrafenib/TRA combination therapy

The applicant's explanation on the safety profile of dabrafenib/TRA combination therapy:
The following table summarizes the safety in the COMBI-V and COMBI-D studies.

Summary of safety (COMBI-V and COMBI-D studies)

	Number of patients (%)			
	COMBI-V study		COMBI-D study	
	Dabrafenib/ TRA (n = 350)	Vem (n = 349)	Dabrafenib/ TRA (n = 209)	Dabrafenib/ placebo (n = 211)
All adverse events	343 (98.0)	345 (98.9)	203 (97.1)	205 (97.2)
Grade ≥3 adverse events	186 (53.1)	224 (64.2)	100 (47.8)	106 (50.2)
Adverse events leading to death	3 (0.9)	3 (0.9)	5 (2.4)	0
Serious adverse events	131 (37.4)	122 (35.0)	88 (42.1)	78 (37.0)
Adverse events leading to treatment discontinuation	44 (12.6)	41 (11.7)	24 (11.5)	14 (6.6)
Adverse events leading to treatment interruption	192 (54.9)	197 (56.4)	118 (56.5)	78 (37.0)
Adverse events leading to dose reduction	115 (32.9)	136 (39.0)	59 (28.2)	29 (13.7)

In the COMBI-V study, adverse events with an incidence ≥10% higher in the dabrafenib/TRA group than in the Vem group were pyrexia (52.6% in the dabrafenib/TRA group, 20.9% in the Vem group), chills (31.4%, 7.7%), and vomiting (28.9%, 15.2%), and Grade ≥3 adverse events with an incidence ≥2% higher in the dabrafenib/TRA group than in the Vem group were pyrexia (4.3%, 0.6%), hypertension (13.7%, 9.5%), neutropenia (4.9%, 0.9%), and ejection fraction decreased (3.7%, 0%). Serious adverse events with an incidence ≥2% higher in the dabrafenib/TRA group than in the Vem group were pyrexia (14.0%, 1.7%), ejection fraction decreased (6.9%, 0%), and chills (3.7%, 0%).

Adverse events leading to treatment discontinuation with an incidence ≥2% higher in the dabrafenib/TRA group than in the Vem group were pyrexia (3.4%, 0.3%) and ejection fraction decreased (2.9%, 0%). Adverse events leading to dose reduction with an incidence ≥2% higher were pyrexia (14.0%, 2.9%), ejection fraction decreased (3.7%, 0%), and chills (2.3%, 0%). Adverse events leading to treatment interruption with an incidence ≥2% higher were pyrexia (30.2%, 4.0%), chills (7.7%, 0.6%), ejection fraction decreased (5.7%, 0%), neutropenia (5.7%, 0.9%), vomiting (4.3%, 1.7%), dehydration (2.6%, 0.3%), urinary tract infection (2.3%, 0%), and malaise (2.0%, 0%).

In the COMBI-D study, adverse events with an incidence ≥10% higher in the dabrafenib/TRA group than in the dabrafenib/placebo group were pyrexia (56.9% in the dabrafenib/TRA group, 32.7% in the dabrafenib/placebo group), chills (30.6%, 16.6%), diarrhoea (30.1%, 15.6%), vomiting (24.9%, 14.2%), and oedema peripheral (21.1%, 9.0%), and Grade ≥3 adverse events with an incidence ≥2% higher were pyrexia (7.2%, 1.9%), neutropenia (3.3%, 0.5%), AST increased (3.3%, 0.9%), and hyperglycaemia (2.4%, 0%). Serious adverse events with an incidence ≥2% higher in the dabrafenib/TRA group than in the dabrafenib/placebo group were pyrexia (16.7%, 7.1%) and chills (4.3%, 1.4%). There were no adverse events leading to treatment discontinuation with an incidence ≥2% higher in the dabrafenib/TRA group than in the dabrafenib/placebo group. The adverse event leading to dose reduction with an incidence ≥2% higher was pyrexia (13.9%, 2.8%). Adverse events leading to treatment interruption with an incidence ≥2% higher were pyrexia (34.9%, 13.7%), chills (10.5%, 3.8%), vomiting (7.2%, 1.4%), nausea (5.3%, 1.9%), ejection fraction decreased (4.8%, 1.9%), diarrhoea (4.3%, 0.9%), headache (3.3%, 0.9%), dizziness (2.4%, 0%), influenza like illness (2.4%, 0%), and tremor (2.4%, 0%).

The applicant's explanation on the difference in the safety of dabrafenib/TRA combination therapy between Japanese and non-Japanese patients:
The following table summarizes the safety results obtained from Study MEK116885 in Japanese patients and from the pooled data of the dabrafenib/TRA groups in the COMBI-D and COMBI-V studies in non-Japanese patients.

Summary of safety in Japanese and non-Japanese patients (Study MEK116885, COMBI-D study, and COMBI-V study)

	Number of patients (%)	
	Japanese patients (Study MEK116885)	Non-Japanese patients (COMBI-D and COMBI-V studies)
	Dabrafenib/TRA (n = 12)	Dabrafenib/TRA (n = 559)
All adverse events	12 (100)	546 (97.7)
Grade ≥3 adverse events	7 (58.3)	286 (51.2)
Adverse events leading to death	0	8 (1.4)
Serious adverse events	1 (8.3)	219 (39.2)
Adverse events leading to treatment discontinuation	2 (16.6)	68 (12.2)
Adverse events leading to treatment interruption	3 (25.0)	310 (55.5)
Adverse events leading to dose reduction	2 (16.6)	174 (31.1)

Adverse events with an incidence ≥20% higher in Japanese patients than in non-Japanese patients were pyrexia (75.0% in Japanese patients, 54.2% in non-Japanese patients), AST increased (58.3%, 12.2%), oedema peripheral (50.0%, 15.4%), nasopharyngitis (50.0%, 11.8%), blood ALP increased (41.7%, 7.5%), stomatitis (41.7%, 2.1%), dermatitis acneiform (33.3%, 7.5%), erythema (33.3%, 8.6%) and rash maculo-papular (33.3%, 4.5%). The Grade ≥3 adverse event with an incidence ≥10% higher in Japanese patients than in non-Japanese patients was blood phosphorus decreased (16.7%, 0.7%). Adverse events that were observed only in Japanese patients and not in non-Japanese patients (dermatitis bullous and glucose urine present) were Grade 1 or 2 in severity.

Thus, some adverse events occurred more frequently after dabrafenib/TRA treatment in Japanese patients than in non-Japanese patients. However, they were mild in severity, suggesting that dabrafenib/TRA is well tolerated also in Japanese patients.

PMDA's view:
The above results (a) obtained from the BREAK-3 study showed that, compared with the DTIC group, the dabrafenib group did not show any clear tendency of higher incidence in all adverse events, Grade ≥3 adverse events, adverse events leading to death, or serious adverse events. Also, the above results (b)

obtained from the COMBI-D and COMBI-V studies showed that, compared with the control group, the dabrafenib/TRA group did not show any clear tendency of higher incidence in any of these adverse events. Consequently, PMDA considers that dabrafenib and dabrafenib/TRA are well tolerated when appropriate measures such as treatment interruption, dose reduction, and treatment discontinuation are taken as necessary.

Information on adverse events (hyperkeratosis, alopecia, palmar-plantar erythrodysaesthesia syndrome, rash, pyrexia, arthralgia, headache, skin papilloma, and myalgia) that occurred with a higher incidence in the dabrafenib group than in the DTIC group in the BREAK-3 study, should be provided appropriately to healthcare professionals in clinical settings through the package insert etc. In a similar manner, information on the occurrences of events (pyrexia, chills, vomiting, oedema peripheral, diarrhoea) observed at a higher incidence in the dabrafenib/TRA group than in the control groups in the COMBI-D and COMBI-V studies should also be provided appropriately to healthcare professionals in clinical settings through the package insert etc.

Since the number of Japanese patients treated with dabrafenib was extremely small, the safety profile can be compared between Japanese and non-Japanese patients only to a limited extent. However, the following events occurred more frequently in Japanese patients than in non-Japanese patients in the clinical studies: alopecia, pyrexia, arthralgia, leukopenia, ALT increased, AST increased, ALP increased, oedema peripheral, nasopharyngitis, and stomatitis. Information on the occurrences of adverse events in Japanese patients should also be appropriately provided to healthcare professionals in clinical settings through the package insert, etc.

In the following sections, PMDA evaluated adverse events by focusing on those with a higher incidence in the dabrafenib group or the dabrafenib/TRA group than in each control group, as well as those with a higher incidence in Japanese patients than in non-Japanese patients, and those in the caution list of drugs that have similar mechanism of action with dabrafenib, on the basis of the safety results obtained mainly from the BREAK-3 study, COMBI-D study, COMBI-V study, Study BRF116056, and Study MEK116885.

4.(iii).B.(3).2) Secondary malignant tumor

The applicant classified dabrafenib-induced malignant tumor into (a) cutaneous squamous cell carcinoma (cuSCC) and (b) non-cuSCC malignant tumor, and explained as follows:

(a) cuSCC

The following table shows the incidence of cuSCC* in patients receiving dabrafenib monotherapy, i.e., patients in the dabrafenib group of the BREAK-3 study and patients in the dabrafenib/placebo group of the COMBI-D study. No dabrafenib-induced cuSCC occurred in Study BRF116056.

*: Events corresponding to squamous cell carcinoma, cuSCC, or keratoacanthoma in preferred term of MedDRA 14.1/J14.1 in the BREAK-3 study; and events corresponding to squamous cell carcinoma, cuSCC, or keratoacanthoma, preferred terms of MedDRA 17.0/J17.0 in the COMBI-D study.

Incidences of cuSCC (BREAK-3 and COMBI-D studies)

Preferred term	Number of patients (%)					
	BREAK-3 study (MedDRA ver 14.1/J14.1)				COMBI-D study (MedDRA ver 17.0/J17.0)	
	Dabrafenib (n = 187)		DTIC (n = 59)		Dabrafenib/placebo (n = 211)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
cuSCC	14 (7.5)	8 (4.3)	0	0	22 (10.4)	22 (10.4)
Squamous cell carcinoma	7 (3.7)	6 (3.2)	0	0	9 (4.3)	9 (4.3)
cuSCC	3 (1.6)	3 (1.6)	0	0	11 (5.2)	11 (5.2)
Keratoacanthoma	5 (2.7)	0	0	0	4 (1.9)	4 (1.9)

In the dabrafenib group of the BREAK-3 study or in the dabrafenib/placebo group of the COMBI-D study, there were no patients with cuSCC that was fatal, or resulted in treatment discontinuation, treatment interruption, or dose reduction of dabrafenib treatment. Serious cuSCC was observed in 4.8% (9 of 187) of patients and 9.0% (19 of 211) of patients, respectively.

The following table shows the incidences of cuSCC* in patients receiving dabrafenib/TRA in the COMBI-V and COMBI-D studies. Dabrafenib/TRA-induced cuSCC was not observed in Study MEK116885.

*: Events corresponding to keratoacanthoma, squamous cell carcinoma, Bowen's disease, or cuSCC, preferred terms of MedDRA 17.0/J17.0.

Incidences of cuSCC (COMBI-V and COMBI-D studies)

	Number of patients (%)			
	COMBI-V study		COMBI-D study	
	Dabrafenib/ TRA (n = 350)	Vem (n = 349)	Dabrafenib/ TRA (n = 209)	Dabrafenib/ placebo (n = 211)
All adverse events	5 (1.4)	63 (18.1)	6 (2.9)	22 (10.4)
Grade ≥3 adverse events	5 (1.4)	62 (17.8)	6 (2.9)	22 (10.4)
Adverse events leading to death	0	0	0	0
Serious adverse events	5 (1.4)	55 (15.8)	5 (2.4)	19 (9.0)
Adverse events leading to treatment discontinuation	0	0	0	0
Adverse events leading to treatment interruption	0	1 (0.3)	0	0
Adverse events leading to dose reduction	0	0	0	0

Regarding the timing of the occurrence of cuSCC, the median days to the first onset (range) was 222 days (56-510 days) in the dabrafenib/TRA group of the COMBI-V or COMBI-D study.

(b) Non-cuSCC secondary malignant tumor

The following table shows the incidences of non-cuSCC secondary malignant tumor* following the treatment with dabrafenib monotherapy in the dabrafenib group of the BREAK-3 study or in the dabrafenib/placebo group of the COMBI-D study. There was no non-cuSCC secondary malignant tumor following the treatment with dabrafenib in Study BRF116056.

*: Events corresponding to malignant melanoma or mycosis fungoides stage I in preferred term of MedDRA 14.1/J14.1 in the BREAK-3 study; and events corresponding to malignant melanoma, malignant melanoma in situ, superficial spreading melanoma stage unspecified, adenocarcinoma gastric, bile duct adenocarcinoma, breast cancer, eyelid tumour, Hodgkin's disease, invasive ductal breast carcinoma, neoplasm, or transitional cell carcinoma、preferred terms of MedDRA 17.0/J17.0 in the COMBI-D study.

Incidences of non-cuSCC secondary malignant tumor (BREAK-3 and COMBI-D studies)

Preferred term	Number of patients (%)					
	BREAK-3 study (MedDRA ver 14.1/J14.1)				COMBI-D study (MedDRA ver 17.0/J17.0)	
	Dabrafenib (n = 187)		DTIC (n = 59)		Dabrafenib/placebo (n = 211)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Non-cuSCC secondary malignant tumor	4 (2.1)	2 (1.1)	0	0	11 (5.2)	5 (2.3)
Malignant melanoma	3 (1.6)	2 (1.1)	0	0	2 (1.0)	0
Mycosis fungoides stage I	1 (0.5)	0	0	0	0	0
Malignant melanoma in situ	0	0	0	0	1 (0.5)	0
Superficial spreading melanoma stage unspecified	0	0	0	0	1 (0.5)	1 (0.5)
Adenocarcinoma gastric	0	0	0	0	1 (0.5)	0
Bile duct adenocarcinoma	0	0	0	0	1 (0.5)	1 (0.5)
Breast cancer	0	0	0	0	1 (0.5)	1 (0.5)
Eyelid tumour	0	0	0	0	1 (0.5)	0
Hodgkin's disease	0	0	0	0	1 (0.5)	0
Invasive ductal breast carcinoma	0	0	0	0	1 (0.5)	1 (0.5)
Neoplasm	0	0	0	0	1 (0.5)	0
Transitional cell carcinoma	0	0	0	0	1 (0.5)	1 (0.5)

In the dabrafenib group of the BREAK-3 study or in the dabrafenib/placebo group of the COMBI-D study, there were no patients with non-cuSCC secondary malignant tumor that resulted in death or interruption. Serious non-cuSCC secondary malignant tumor occurred in 1.6% (3 of 187) of patients and 4.2% (9 of 211) of patients, respectively, in the dabrafenib group of the BREAK-3 study and in the dabrafenib/placebo group of the COMBI-D study; treatment discontinuation due to non-cuSCC secondary malignant tumor occurred in 0% and 0.9% (2 of 221) of patients; and dose reduction due to

non-cuSCC secondary malignant tumor occurred in 0% and 0.5% (1 of 211) of patients, respectively. None of these events occurred in Study BRF116056.

The table below shows the incidences of non-cuSCC secondary malignant tumor* following dabrafenib/TRA treatment in the COMBI-V and COMBI-D studies. In Study MEK116885, no onset of non-cuSCC secondary malignant tumor following dabrafenib/TRA treatment was noted.

*: Events corresponding to malignant melanoma, malignant melanoma in situ, superficial spreading melanoma stage III, acute myeloid leukaemia, ovarian neoplasm, papillary thyroid cancer, phaeochromocytoma malignant, prostate cancer, or lung adenocarcinoma, preferred terms of MedDRA 17.0/J17.0.

Incidences of non-cuSCC secondary malignant tumor (COMBI-V and COMBI-D studies)

	Number of patients (%)			
	COMBI-V study		COMBI-D study	
	Dabrafenib/ TRA (n = 350)	Vem (n = 349)	Dabrafenib/ TRA (n = 209)	Dabrafenib/ placebo (n = 211)
All adverse events	5 (1.4)	9 (2.6)	4 (1.9)	11 (5.2)
Grade ≥3 adverse events	5 (1.4)	8 (2.3)	3 (1.4)	5 (2.3)
Adverse events leading to death	0	0	0	0
Serious adverse events	4 (1.1)	9 (2.6)	4 (1.9)	9 (4.2)
Adverse events leading to treatment discontinuation	1 (0.3)	1 (0.3)	0	2 (0.9)
Adverse events leading to treatment interruption	1 (0.3)	0	1 (0.5)	1 (0.5)
Adverse events leading to dose reduction	0	0	0	0

The following table lists patients who experienced non-cuSCC secondary malignant tumor in the dabrafenib group of the BREAK-3 study, the dabrafenib/placebo group of the COMBI-D study, and the dabrafenib/TRA group of the COMBI-V and COMBI-D studies.

List of patients treated with dabrafenib who experienced non-cuSCC secondary malignant tumor

Treatment group	Age	Sex	Preferred term*	Grade	Day of onset	Duration (days)	Study drug	Treatment	Causal relationship with dabrafenib	Outcome
Dabrafenib in BREAK-3 study	40	F	Malignant melanoma	3	36	1	Unchanged	Excision	Yes	Recovered
	64	M	Malignant melanoma	3	65	1	Unchanged	Excision	Yes	Recovered
	64	M	Malignant melanoma	2	144	6	Unchanged	Excision	No	Recovered
	67	M	Mycosis fungoides	1	44	-	Unchanged	Unknown	Yes	Not recovered
Dabrafenib/placebo in COMBI-D study	58	M	Malignant melanoma	1	57	17	Unchanged	Excision	Yes	Recovered
	32	M	Malignant melanoma	2	56	29	Unchanged	Excision	Yes	Recovered
	47	M	Malignant melanoma	2	80	31	Unchanged	Excision	Yes	Recovered
	31	M	Superficial spreading melanoma stage unspecified	3	240	1	Unchanged	Excision	Yes	Recovered
	59	M	Adenocarcinoma gastric	1	53	17	Unchanged	Unknown	No	Recovered
	71	M	Bile duct adenocarcinoma	3	160	-	Discontinued	Unknown	Yes	Not recovered
	60	F	Breast cancer	3	504	52	Unchanged	Unknown	Yes	Recovered
	69	M	Eyelid tumour	1	112	37	Unchanged	Unknown	No	Recovered
			Neoplasm	1	448	23	Unchanged	Unknown	No	Recovered
	66	M	Hodgkin's disease	2	357	-	Discontinued	Unknown	No	Not recovered
	62	F	Invasive ductal breast carcinoma	3	145	53	Unchanged	Unknown	Yes	Recovered
Dabrafenib/TRA in COMBI-V study	53	M	Superficial spreading melanoma stage III	3	245	29	Unchanged	Excision	Yes	Recovered
	48	F	Malignant melanoma	3	323	1	Unchanged	Excision	No	Recovered
			Malignant melanoma	3	366	1	Unchanged	Excision	No	Recovered
	65	M	Acute myeloid leukaemia	4	320	-	Discontinued	Unknown	Yes	Not recovered
	72	M	Lung adenocarcinoma	3	239	-	Interrupted	Unknown	No	Not recovered
	40	F	Ovarian neoplasm	3	119	1	Unchanged	Unknown	No	Not recovered
Dabrafenib/TRA in COMBI-D study	76	M	Malignant melanoma	3	110	46	Interrupted	Excision	Yes	Recovered
	35	F	Phaeochromocytoma malignant	3	862	-	Unchanged	Unknown	No	Not recovered
	57	M	Papillary thyroid cancer	2	182	1	Unchanged	Unknown	Yes	Recovered
	66	M	Prostate cancer	3	330	-	Unchanged	Unknown	Yes	Not recovered

*, MedDRA 14.1/J14.1 in the BREAK-3 study, MedDRA 17.0/J17.0 in the COMBI-D and COMBI-V studies

PMDA's view:
Attention should be paid to occurrence of secondary malignant tumor associated with dabrafenib or dabrafenib/TRA treatment, taking account of the facts that (i) the incidence of secondary malignant tumor was higher in the dabrafenib group than in the DTIC group in the BREAK-3 study, that (ii) occurrence of serious secondary malignant tumor were noted, and that (iii) the results of nonclinical studies suggest the possibility that secondary malignant tumor may be caused by the activation of mitogen-activated protein kinase (MAPK) signal transduction pathway [see "3.(iii).A.(4) Carcinogenicity"]. Information on the incidences of secondary malignant tumor in clinical studies should be appropriately provided to healthcare professionals in clinical settings through the package insert etc. In addition, caution statements should be provided also to them through the package insert etc., so that patients should be monitored periodically during the treatment with dabrafenib, and if secondary malignant tumor occurs, appropriate measures should be taken.

4.(iii).B.(3).3) Cardiac disorders

The applicant's explanation on cardiac disorders associated with dabrafenib:
The following table shows the incidence of cardiac disorders* associated with dabrafenib monotherapy in the dabrafenib group of the BREAK-3 study and in the dabrafenib/placebo group of the COMBI-D study. In Study BRF116056, no cardiac disorders were observed after administration of dabrafenib.

*: In the BREAK-3 study, events corresponding to cardiac failure, ejection fraction decreased, or cardiac failure congestive, preferred terms of MedDRA 14.1/J14.1; in the COMBI-D study, events corresponding to cardiac failure or ejection fraction decreased, preferred terms of MedDRA 17.0/J17.0.

Incidence of cardiac disorders (BREAK-3 and COMBI-D studies)

Preferred term	Number of patients (%)					
	BREAK-3 study (MedDRA ver 14.1/J14.1)				COMBI-D study (MedDRA ver 17.0/J17.0)	
	Dabrafenib (n = 187)		DTIC (n = 59)		Dabrafenib/placebo (n = 211)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac disorders	5 (2.7)	2 (1.1)	0	0	10 (4.7)	4 (1.9)
Cardiac failure	1 (0.5)	0	0	0	3 (1.4)	0
Ejection fraction decreased	3 (1.6)	1 (0.5)	0	0	7 (3.3)	4 (1.9)
Cardiac failure congestive	1 (0.5)	1 (0.5)	0	0	0	0

In the dabrafenib group of the BREAK-3 study and in the dabrafenib/placebo group of the COMBI-D study, no fatal cardiac disorder was observed. Serious cardiac disorders were observed in 1.6% (3 of 187) of patients and 3.3% (7 of 211) of patients, respectively. Cardiac disorders resulted in treatment discontinuation in 0% and 0.9% (2 of 211) of patients, respectively; in treatment interruption in 0.5% (1 of 187) of patients and 2.8% (6 of 211) of patients; and in dose reduction in 0% and 0.9% (2 of 211) of patients.

The following table shows the incidence of dabrafenib/TRA-associated cardiac disorders* in Study MEK116885, COMBI-V study, and COMBI-D study.

*: Events corresponding to left ventricular dysfunction, cardiac failures, and ejection fraction decreased, preferred terms of MedDRA 17.0/J17.0.

Incidence of cardiac disorders (Study MEK116885, COMBI-V study, and COMBI-D study)

	Number of patients (%)				
	Study MEK116885	COMBI-V study		COMBI-D study	
	Dabrafenib/ TRA (n = 12)	Dabrafenib/ TRA (n = 350)	Vem (n = 349)	Dabrafenib/ TRA (n = 209)	Dabrafenib/ placebo (n = 211)
All adverse events	1 (8.3)	29 (8.3)	1 (0.3)	12 (5.7)	10 (4.7)
Grade ≥3 adverse events	0	13 (3.7)	0	3 (1.4)	4 (1.9)
Adverse events leading to death	0	0	0	0	0
Serious adverse events	0	24 (6.9)	0	9 (4.3)	7 (3.3)
Adverse events leading to treatment discontinuation	0	10 (2.9)	0	3 (1.4)	2 (0.9)
Adverse events leading to treatment interruption	1 (8.3)	21 (6.0)	0	10 (4.8)	6 (2.8)
Adverse events leading to dose reduction	0	13 (3.7)	0	4 (1.9)	3 (1.4)

The applicant's explanation on (a) time to onset of cardiac disorders, (b) method of monitoring cardiac disorders, and (c) risk factors of cardiac disorders in target patients, in clinical studies:

(a) Time to onset of cardiac disorders: In the dabrafenib/TRA group of the COMBI-V and COMBI-D studies, the median time to the first onset (range) was 145 days (15-758 days), showing no specific tendency in the time to the onset.

(b) Cardiac function was periodically assessed by cardiac ultrasonography.

(c) In clinical studies such as the COMBI-V study, patients with past or current cardiac disease (acute coronary syndrome, cardiac failure, poorly controlled hypertension, and cardiac valvulopathy, etc.) were excluded, and patients with history of heart-related disease (controllable hypertension, dyslipidaemia, arrhythmia, diabetes mellitus, and chronic obstructive pulmonary disease, etc.) were enrolled. In the COMBI-V study, 72.4% (21 of 29) of patients who showed decreased ejection fraction had a history of disease affecting the heart.

PMDA's view:

Attention should be paid to the onset of cardiac disorders in dabrafenib or dabrafenib/TRA treatment, taking account that (a) in the COMBI-V study, cardiac disorders occurred at a higher frequency in the dabrafenib/TRA group than in the Vem group, and most of them were serious and required dose adjustment, and that (b) in the COMBI-D study and Study BRF113220, myocardial ischaemia and ventricular arrhythmia occurred in 1 patient each, respectively, and resulted in death [see "4.(iii).A.(3).4)

Foreign phase III study" and "4.(iii).A.(1).2) Foreign phase I/II study"]. Information on the incidence of cardiac disorders in clinical studies should be appropriately provided to healthcare professionals in clinical settings through the package insert etc. In addition, caution statements should also be provided to them through the package insert etc., so that eligible patients should be carefully selected in the treatment with dabrafenib, that cardiac ultrasonography should be performed periodically and that appropriate measures should be taken if cardiac disorders occur.

4.(iii).B.(3).4) Hepatic dysfunction

The applicant's explanation on hepatic dysfunction associated with dabrafenib treatment:

The following table shows the incidence of hepatic dysfunction* associated with dabrafenib monotherapy in the dabrafenib group of Study BRF116056 and BREAK-3 study and in the dabrafenib/placebo group of the COMBI-D study.

*: In the BREAK-3 study, events corresponding to ALT increased, AST increased, blood ALP increased, hepatic pain, hyperbilirubinaemia, or gamma-glutamyltransferase increased, preferred terms of MedDRA 14.1/J14.1; in Study BRF116056 and COMBI-D study, events corresponding to ALT increased, AST increased, blood ALP increased, gamma-glutamyltransferase increased, hepatic pain, blood bilirubin increased, hepatic enzyme increased, ascites, liver function test abnormal, or hepatomegaly, preferred terms of MedDRA 17.0/J17.0.

Incidence of hepatic dysfunction (Study BRF116056, BREAK-3 study, and COMBI-D study)

Preferred term	Number of patients (%)							
	Study BRF116056 (MedDRA ver 17.0/J17.0)		BREAK-3 study (MedDRA ver 14.1/J14.1)				COMBI-D study (MedDRA ver 17.0/J17.0)	
	Dabrafenib (n = 12)		Dabrafenib (n = 187)		DTIC (n = 59)		Dabrafenib/ placebo (n = 211)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic dysfunction	6 (50.0)	0	14 (7.5)	6 (3.2)	4 (6.8)	2 (3.4)	25 (11.8)	4 (1.9)
ALT increased	3 (25.0)	0	7 (3.7)	3 (1.6)	0	0	12 (5.7)	1 (0.5)
AST increased	3 (25.0)	0	4 (2.1)	1 (0.5)	0	0	9 (4.3)	2 (1.0)
Blood ALP increased	3 (25.0)	0	3 (1.6)	0	2 (3.4)	0	8 (3.8)	0
γ-GTP increased	0	0	4 (2.1)	3 (1.6)	2 (3.4)	1 (1.7)	5 (2.4)	2 (1.0)
Hepatic pain	0	0	3 (1.6)	1 (0.5)	1 (1.7)	1 (1.7)	2 (1.0)	0
Blood bilirubin increased	0	0	0	0	0	0	1 (0.5)	0
Hepatic enzyme increased	0	0	0	0	0	0	3 (1.4)	0
Ascites	0	0	0	0	0	0	1 (0.5)	0
Liver function test abnormal	0	0	0	0	0	0	1 (0.5)	1 (0.5)
Hepatomegaly	0	0	0	0	0	0	1 (0.5)	0
Hyperbilirubinaemia	0	0	1 (0.5)	0	0	0	0	0

γ-GTP: Gamma-glutamyltransferase

In the dabrafenib group of the BREAK-3 study and in the dabrafenib/placebo group of the COMBI-D study, no fatal hepatic dysfunction was observed. Serious hepatic dysfunction was found in 0.5% (1 of 187) of patients and 0%, respectively. Hepatic dysfunction resulted in treatment discontinuation in 0.5% (1 of 187) of patients and 0%, respectively, in treatment interruption in 1.6% (3 of 187) of patients and 1.9% (4 of 211) of patients, respectively, and in dose reduction in 0.5% (1 of 187) of patients and 0.5% (1 of 211) of patients, respectively. None of these hepatic dysfunctions were observed in Study BRF116056.

The following table shows the incidence of dabrafenib/TRA-associated hepatic dysfunction* in Study MEK116885, COMBI-V study, and COMBI-D study.

*: Events corresponding to ALT increased, AST increased, bilirubin conjugated increased, blood ALP increased, blood bilirubin increased, cholestasis, gamma-glutamyltransferase increased, hepatic encephalopathy, hepatic enzyme increased, hepatic function abnormal, hepatocellular injury, hepatotoxicity, hypertransaminasaemia, liver function test abnormal, ascites, or transaminases increased, preferred terms of MedDRA 17.0/J17.0.

Incidence of hepatic dysfunction (Study MEK116885, COMBI-V study, and COMBI-D study)

	Number of patients (%)				
	Study MEK116885	COMBI-V study		COMBI-D study	
	Dabrafenib/ TRA (n = 12)	Dabrafenib/ TRA (n = 350)	Vem (n = 349)	Dabrafenib/ TRA (n = 209)	Dabrafenib/ placebo (n = 211)
All adverse events	10 (83.3)	92 (26.3)	110 (31.5)	39 (18.7)	25 (11.8)
Grade ≥3 adverse events	2 (16.7)	35 (10.0)	42 (12.0)	14 (6.7)	4 (1.9)
Adverse events leading to death	0	0	0	0	0
Serious adverse events	0	11 (3.1)	18 (5.2)	5 (2.4)	0
Adverse events leading to treatment discontinuation	1 (8.3)	7 (2.0)	14 (4.0)	2 (1.0)	0
Adverse events leading to treatment interruption	2 (16.7)	27 (7.7)	37 (10.6)	9 (4.3)	4 (1.9)
Adverse events leading to dose reduction	2 (16.7)	15 (4.3)	19 (5.4)	5 (2.4)	1 (0.5)

In the dabrafenib/TRA group of the COMBI-V and COMBI-D studies, the median time to the first onset (range) of hepatic dysfunction was 57 days (8-681 days), showing no specific tendency in the time to the onset.

In Study BRF116056, Study MEK116885, BREAK-3 study, COMBI-D study, or COMBI-V study, no patients experienced hepatic dysfunction meeting Hy's law criteria (defined based on Guidance for industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009).

PMDA's view:
Attention should be paid to the onset of hepatic dysfunction in dabrafenib or dabrafenib/TRA treatment, taking account that (a) the incidence was higher in Japanese patients than in non-Japanese patients, and that (b), in the COMBI-D study, hepatic dysfunction occurred at a higher frequency in the dabrafenib/TRA group than in the dabrafenib/placebo group, and serious hepatic dysfunction was observed. Information on the incidence of hepatic dysfunction in clinical studies should be appropriately provided to healthcare professionals in clinical settings through the package insert etc. In addition, caution statements should be provided also to them through the package insert etc., so that hepatic function test should be performed periodically during treatment with dabrafenib and appropriate measures should be taken if hepatic dysfunction occur.

4.(iii).B.(3).5) Pyrexia

The applicant's explanation on pyrexia-related events associated with dabrafenib treatment:
The following table shows the incidence of pyrexia-related events* associated with dabrafenib monotherapy in the dabrafenib group of Study BRF116056 and BREAK-3 study and in the dabrafenib/placebo group of the COMBI-D study.

*: In the BREAK-3 study, events corresponding to body temperature increased or pyrexia in preferred term of MedDRA 14.1/J14.1; in study BRF116056 and COMBI-D study, events corresponding to body temperature increased, influenza like illness, hyperthermia, or pyrexia, preferred terms of MedDRA 17.0/J17.0.

Incidence of pyrexia-related events (Study BRF116056, BREAK-3 study, and COMBI-D study)

Preferred term	Number of patients (%)							
	Study BRF116056 (MedDRA ver 17.0/J17.0)		BREAK-3 study (MedDRA ver 14.1/J14.1)				COMBI-D study (MedDRA ver 17.0/J17.0)	
	Dabrafenib (n = 12)		Dabrafenib (n = 187)		DTIC (n = 59)		Dabrafenib/placebo (n = 211)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Pyrexia-related events	6 (50.0)	0	53 (28.3)	6 (3.2)	6 (10.2)	0	79 (37.4)	4 (1.9)
Pyrexia	6 (50.0)	0	52 (27.8)	6 (3.2)	6 (10.2)	0	69 (32.7)	4 (1.9)
Influenza like illness	0	0	0	0	0	0	11 (5.2)	0
Hyperthermia	0	0	0	0	0	0	1 (0.5)	0
Body temperature increased	0	0	1 (0.5)	0	0	0	3 (1.4)	0

In the dabrafenib group of the BREAK-3 study and in the dabrafenib/placebo group of the COMBI-D study, serious pyrexia-related events occurred in 3.7% (7 of 187) of patients and 7.1% (15 of 211) of patients, respectively. Pyrexia-related events resulted in treatment discontinuation in 0% and 0.9% (2 of

211) of patients in the respective groups; in treatment interruption in 10.7% (20 of 187) of patients and 13.7% (29 of 211) of patients; and in dose reduction in 8.6% (16 of 187) of patients and 2.8% (6 of 211) of patients. In Study BRF116056, no patients experienced pyrexia-related events that were fatal, serious, or resulted in either treatment discontinuation or dose reduction, while 8.3% (1 of 12) of patients had pyrexia-related events that resulted in treatment interruption.

The following table shows the incidence of pyrexia-related events* associated with dabrafenib/TRA administration in Study MEK116885, COMBI-V study, and COMBI-D study.

*: Events corresponding to body temperature increased, hyperthermia, sweating fever, influenza like illness, or pyrexia, preferred terms of MedDRA 17.0/J17.0.

Incidence of pyrexia-related events (Study MEK116885, COMBI-V study, and COMBI-D study)

	Number of patients (%)				
	Study MEK116885	COMBI-V study		COMBI-D study	
	Dabrafenib/ TRA (n = 12)	Dabrafenib/ TRA (n = 350)	Vem (n = 349)	Dabrafenib/ TRA (n = 209)	Dabrafenib/ placebo (n = 211)
All adverse events	9 (75.0)	200 (57.1)	89 (25.5)	129 (61.7)	79 (37.4)
Grade ≥3 adverse events	0	21 (6.0)	2 (0.6)	16 (7.6)	4 (1.9)
Adverse events leading to death	0	0	0	0	0
Serious adverse events	0	51 (14.6)	6 (1.7)	36 (17.2)	15 (7.1)
Adverse events leading to treatment discontinuation	0	13 (3.7)	1 (0.3)	6 (2.9)	2 (0.9)
Adverse events leading to treatment interruption	0	110 (31.4)	16 (4.6)	74 (35.4)	29 (13.7)
Adverse events leading to dose reduction	0	53 (15.1)	10 (2.9)	29 (13.9)	6 (2.8)

In the dabrafenib/TRA group of the COMBI-V and COMBI-D studies, the median time to the first onset (range) of pyrexia-related events was 31 days (1-774 days), showing no specific tendency in the time to the onset.

PMDA's view:
Attention should be paid to the onset of pyrexia in dabrafenib or dabrafenib/TRA treatment, taking account that (a) the incidence of pyrexia was higher in the dabrafenib group than in the DTIC group in the BREAK-3 study, and that (b) the incidence of all-Grade pyrexia and serious pyrexia was higher in the dabrafenib/TRA group than in the control group in the COMBI-V and COMBI-D studies. Information on the incidence of pyrexia in clinical studies should be appropriately provided to healthcare professionals in clinical settings through the package insert etc. In addition, caution statements should be provided also to them through the package insert etc., so that patients should be monitored periodically during treatment with dabrafenib and appropriate measures should be taken if pyrexia occurs.

4.(iii).B.(3).6) Hypertension

The applicant's explanation on hypertension associated with dabrafenib treatment:
The following table shows the incidence of hypertension* associated with dabrafenib monotherapy in the dabrafenib group of the BREAK-3 study and in the dabrafenib/placebo group of the COMBI-D study. No dabrafenib/TRA-associated hypertension developed in Study BRF116056.

*: In the BREAK-3 study, events corresponding to blood pressure increased or hypertension in preferred term of MedDRA 14.1/J14.1; in the COMBI-D study, events corresponding to blood pressure diastolic increased, blood pressure increased, hypertension, or diastolic hypertension, preferred terms of MedDRA 17.0/J17.0.

Incidence of hypertension (BREAK-3 and COMBI-D studies)

Preferred term	Number of patients (%)					
	BREAK-3 study (MedDRA ver 14.1/J14.1)				COMBI-D study (MedDRA ver 17.0/J17.0)	
	Dabrafenib (n = 187)		DTIC (n = 59)		Dabrafenib/placebo (n = 211)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypertension	7 (3.7)	2 (1.1)	2 (3.4)	1 (1.7)	36 (17.1)	13 (6.2)
Blood pressure increased	1 (0.5)	1 (0.5)	0	0	1 (0.5)	0
Hypertension	6 (3.2)	1 (0.5)	2 (3.4)	1 (1.7)	33 (15.6)	13 (6.2)
Blood pressure diastolic increased	0	0	0	0	1 (0.5)	0
Diastolic hypertension	0	0	0	0	1 (0.5)	0

In the dabrafenib group of the BREAK-3 study and in the dabrafenib/placebo group of the COMBI-D study, no patients experienced hypertension that was serious or resulted in treatment discontinuation, treatment interruption, or dose reduction.

The following table shows the incidence of hypertension* associated with dabrafenib/TRA treatment in Study MEK116885, COMBI-V study, and COMBI-D study.

*: Events corresponding to blood pressure diastolic increased, blood pressure increased, hypertension, blood pressure systolic increased, or diastolic hypertension, preferred terms of MedDRA 17.0/J17.0.

Incidence of hypertension (Study MEK116885, COMBI-V study, and COMBI-D study)

	Number of patients (%)				
	Study MEK116885	COMBI-V study		COMBI-D study	
	Dabrafenib/ TRA (n = 12)	Dabrafenib/ TRA (n = 350)	Vem (n = 349)	Dabrafenib/ TRA (n = 209)	Dabrafenib/ placebo (n = 211)
All adverse events	1 (8.3)	94 (26.8)	90 (25.8)	54 (25.8)	36 (17.1)
Grade ≥3 adverse events	0	49 (14.0)	34 (9.7)	12 (5.7)	13 (6.2)
Adverse events leading to death	0	0	0	0	0
Serious adverse events	0	0	2 (0.6)	1 (0.5)	0
Adverse events leading to treatment discontinuation	0	0	2 (0.6)	0	0
Adverse events leading to treatment interruption	0	6 (1.7)	3 (0.9)	2 (0.9)	0
Adverse events leading to dose reduction	0	5 (1.4)	2 (0.6)	2 (0.9)	0

PMDA's view:

In clinical studies, serious hypertension associated with dabrafenib treatment occurred only infrequently. However, in the COMBI-V study, the incidence of Grade ≥3 hypertension was higher in the dabrafenib/TRA group than in the Vem group, suggesting that caution against the occurrence of hypertension is necessary in dabrafenib or dabrafenib/TRA treatment. Information on the incidence of hypertension in clinical studies should be appropriately provided to healthcare professionals in clinical settings through the package insert etc. Moreover, information on dabrafenib-associated hypertension should be continuously collected after the market launch to determine whether further caution to alert physicians is necessary.

4.(iii).B.(3).7) Skin disorders

The applicant's explanation on skin disorder associated with dabrafenib treatment:

The following table shows the incidences of skin disorder* associated with dabrafenib monotherapy in the dabrafenib group of Study BRF116056 and BREAK-3 study and in the dabrafenib/placebo group of the COMBI-D study.

*: In the BREAK-3 study, events corresponding to palmar-plantar erythrodysaesthesia syndrome, rash, rash maculo-papular, dermatitis bullous, erythema, dermatitis acneiform, rash papular, skin exfoliation, blister, rash erythematous, rash generalised, rash macular, seborrhoeic dermatitis, skin reaction, rash pustular, or mouth ulceration, preferred terms of MedDRA 14.1/J14.1; in Study BRF116056 and COMBI-D study, events corresponding to palmar-plantar erythrodysaesthesia syndrome, rash, rash maculo-papular, dermatitis bullous, erythema, dermatitis acneiform, rash papular, skin exfoliation, blister, rash erythematous, rash generalised, rash macular, rash pustular, acne, rash pruritic, palmoplantar keratoderma, erythema multiforme, or rash vesicular, preferred terms of MedDRA 17.0/J17.0.

Incidence of skin disorders (Study BRF116056, BREAK-3 study, and COMBI-D study)

Preferred term	Number of patients (%)							
	Study BRF116056 (MedDRA ver 17.0/J17.0)		BREAK-3 study (MedDRA ver 14.1/J14.1)				COMBI-D study (MedDRA ver 17.0/J17.0)	
	Dabrafenib (n = 12)		Dabrafenib (n = 187)		DTIC (n = 59)		Dabrafenib/placebo (n = 211)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin disorder	5 (41.7)	0	82 (43.9)	4 (2.1)	3 (5.1)	0	112 (53.1)	4 (1.9)
PPES	2 (16.7)	0	37 (19.8)	4 (2.1)	1 (1.7)	0	39 (18.5)	1 (0.5)
Rash	2 (16.7)	0	31 (16.6)	0	0	0	46 (21.8)	2 (1.0)
Rash maculo-papular	2 (16.7)	0	2 (1.1)	0	0	0	8 (3.8)	1 (0.5)
Dermatitis bullous	1 (8.3)	0	1 (0.5)	0	0	0	0	0
Erythema	1 (8.3)	0	14 (7.5)	0	1 (1.7)	0	16 (7.6)	0
Dermatitis acneiform	0	0	3 (1.6)	0	0	0	8 (3.8)	0
Rash papular	0	0	3 (1.6)	0	0	0	3 (1.4)	0
Skin exfoliation	0	0	3 (1.6)	0	0	0	4 (1.9)	0
Blister	0	0	2 (1.1)	0	0	0	4 (1.9)	0
Rash erythematous	0	0	2 (1.1)	0	0	0	2 (1.0)	0
Rash generalised	0	0	1 (0.5)	0	0	0	1 (0.5)	0
Rash macular	0	0	1 (0.5)	0	0	0	1 (0.5)	0
Seborrhoeic dermatitis	0	0	1 (0.5)	0	0	0	0	0
Skin reaction	0	0	1 (0.5)	0	0	0	0	0
Rash pustular	0	0	7 (3.7)	0	0	0	5 (2.4)	0
Mouth ulceration	0	0	3 (1.6)	0	0	0	0	0
Acne	0	0	0	0	0	0	3 (1.4)	0
Rash pruritic	0	0	0	0	0	0	2 (1.0)	0
Palmoplantar keratoderma	0	0	0	0	0	0	25 (11.8)	0
Erythema multiforme	0	0	0	0	0	0	1 (0.5)	0
Rash vesicular	0	0	0	0	0	0	1 (0.5)	0

PPES: Palmar-plantar erythrodysaesthesia syndrome

In the dabrafenib group of the BREAK-3 study and in the dabrafenib/placebo group of the COMBI-D study, no patients experienced skin disorder that was serious or resulted in treatment discontinuation, whereas skin disorder resulted in treatment interruption in 3.2% (6 of 187) of patients and 5.7% (12 of 211) of patients, respectively, and in dose reduction in 3.2% (6 of 187) of patients and 5.2% (11 of 211) of patients, respectively. Neither of these disorders was observed in Study BRF116056.

The following table shows the incidence of skin disorder* associated with dabrafenib/TRA treatment in Study MEK116885, COMBI-V study, and COMBI-D study.

*: Events corresponding to acne, hand dermatitis, blister, mouth ulceration, rash papular, dermatitis, dermatitis acneiform, rash pruritic, dermatitis bullous, palmar-plantar erythrodysaesthesia syndrome, rash pustular, dermatitis exfoliative, palmoplantar keratoderma, rash, rash erythematous, rash follicular, seborrhoeic dermatitis, erythema, rash generalised, skin exfoliation, erythema multiforme, rash macular, or rash maculo-papular, preferred terms of MedDRA 17.0/J17.0.

Incidence of skin disorders (Study MEK116885, COMBI-V study, and COMBI-D study)

	Number of patients (%)				
	Study MEK116885	COMBI-V study		COMBI-D study	
	Dabrafenib/ TRA (n = 12)	Dabrafenib/ TRA (n = 350)	Vem (n = 349)	Dabrafenib/ TRA (n = 209)	Dabrafenib/ placebo (n = 211)
All adverse events	7 (58.3)	157 (44.9)	267 (76.5)	101 (48.3)	112 (53.1)
Grade ≥3 adverse events	0	7 (2.0)	57 (34.9)	1 (0.5)	4 (1.9)
Adverse events leading to death	0	0	0	0	0
Serious adverse events	0	4 (1.1)	8 (2.3)	0	0
Adverse events leading to treatment discontinuation	0	0	4 (1.1)	0	0
Adverse events leading to treatment interruption	0	16 (4.6)	85 (24.4)	7 (3.3)	12 (5.7)
Adverse events leading to dose reduction	0	8 (2.3)	66 (18.9)	8 (3.8)	11 (5.2)

The phototoxicity study suggested the possible phototoxicity of dabrafenib [see "3.(iii).A.(6).1) Phototoxicity studies"]. Therefore, the protocol in clinical studies of dabrafenib required that unnecessary exposure to sunlight be avoided, and dabrafenib was well tolerated accordingly.

PMDA's view:
In clinical studies, serious skin disorders associated with dabrafenib treatment occurred only infrequently. However, in the BREAK-3 study, the incidence was higher in the dabrafenib group than in the DTIC group, suggesting that caution against the occurrence of skin disorders is necessary in dabrafenib or dabrafenib/TRA treatment. Information on the incidence of skin disorders in clinical studies should be appropriately provided to healthcare professionals in clinical settings through the package insert etc. In addition, information on dabrafenib-associated skin disorders should be continuously collected after the market launch to determine whether further caution to alert physicians is necessary.

4.(iii).B.(3).8) Bone marrow depression

The applicant's explanation on dabrafenib-associated bone marrow depression:
The following table shows the incidence of bone marrow depression* associated with dabrafenib monotherapy in the dabrafenib group of Study BRF116056 and BREAK-3 study and in the dabrafenib/placebo group of the COMBI-D study.

*: In the BREAK-3 study, events corresponding to lymphopenia, haemoglobin decreased, anaemia, neutropenia, leukopenia, or thrombocytopenia, preferred terms of MedDRA 14.1/J14.1; in Study BRF116056 and COMBI-D study, events corresponding to leukopenia, lymphopenia, white blood cell count decreased, febrile neutropenia, thrombocytopenia, platelet count decreased, lymphocyte count decreased, haemoglobin decreased, anaemia, or neutropenia, preferred terms of MedDRA 17.0/J17.0.

Incidence of bone marrow depression (Study BRF116056, BREAK-3 study, and COMBI-D study)

Preferred term	Number of patients (%)							
	Study BRF116056 (MedDRA ver 17.0/J17.0)		BREAK-3 study (MedDRA ver 14.1/J14.1)				COMBI-D study (MedDRA ver 17.0/J17.0)	
	Dabrafenib (n = 12)		Dabrafenib (n = 187)		DTIC (n = 59)		Dabrafenib/placebo (n = 211)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Bone marrow depression	8 (66.7)	1 (8.3)	11 (5.9)	4 (2.1)	18 (30.5)	11 (18.6)	37 (17.5)	19 (9.0)
Leukopenia	6 (50.0)	0	1 (0.5)	0	6 (10.2)	2 (3.4)	1 (0.5)	0
Lymphopenia	2 (16.7)	1 (8.3)	1 (0.5)	1 (0.5)	1 (1.7)	0	4 (1.9)	3 (1.4)
White blood cell count decreased	0	0	0	0	2 (3.4)	1 (1.7)	2 (1.0)	0
Febrile neutropenia	0	0	0	0	1 (1.7)	1 (1.7)	2 (1.0)	2 (1.0)
Thrombocytopenia	2 (16.7)	0	1 (0.5)	1 (0.5)	5 (8.5)	3 (5.1)	3 (1.4)	1 (0.5)
Platelet count decreased	0	0	0	0	5 (8.5)	0	4 (1.9)	0
Lymphocyte count decreased	0	0	0	0	3 (5.1)	0	5 (2.4)	4 (1.9)
Haemoglobin decreased	1 (8.3)	0	1 (0.5)	0	0	0	1 (0.5)	0
Anaemia	1 (8.3)	0	7 (3.7)	1 (0.5)	7 (11.9)	2 (3.4)	20 (9.5)	9 (4.3)
Neutropenia	1 (8.3)	0	2 (1.1)	1 (0.5)	10 (16.9)	8 (13.6)	4 (1.9)	1 (0.5)

In the dabrafenib group of the BREAK-3 study and in the dabrafenib/placebo group of the COMBI-D study, no fatal bone marrow suppression developed. Serious bone marrow depression was observed in 0.5% (1 of 187) of patients and 2.4% (5 of 211) of patients, respectively. Bone marrow depression resulted in treatment discontinuation in 0% and 0.5% (1 of 211) of patients, respectively, in treatment interruption in 1.1% (2 of 187) of patients and 5.7% (12 of 211) of patients, respectively, and in dose reduction in 0% and 2.4% (5 of 211) of patients, respectively. None of these were observed in Study BRF116056.

The following table shows the incidence of bone marrow depression* associated with dabrafenib/TRA treatment in Study MEK116885, COMBI-V study, and COMBI-D study.

*: Events corresponding to neutrophil count decreased, haemoglobin decreased, platelet count decreased, white blood cell count decreased, haematocrit decreased, lymphocyte count decreased, red blood cell count decreased, anaemia, neutropenia, leukopenia, thrombocytopenia, lymphopenia, febrile neutropenia, neutropenic sepsis, or pancytopenia, preferred terms of MedDRA 17.0/J17.0.

Incidence of bone marrow depression (Study MEK116885, COMBI-V study, and COMBI-D study)

	Number of patients (%)				
	Study MEK116885	COMBI-V study		COMBI-D study	
	Dabrafenib/ TRA (n = 12)	Dabrafenib/ TRA (n = 350)	Vem (n = 349)	Dabrafenib/ TRA (n = 209)	Dabrafenib/ placebo (n = 211)
All adverse events	6 (50.0)	81 (23.1)	42 (12.0)	53 (25.4)	37 (17.5)
Grade ≥3 adverse events	2 (16.7)	34 (9.7)	16 (4.6)	21 (10.0)	19 (9.0)
Adverse events leading to death	0	0	0	0	0
Serious adverse events	0	7 (1.1)	3 (0.9)	8 (1.9)	5 (2.4)
Adverse events leading to treatment discontinuation	0	1 (0.3)	1 (0.3)	1 (0.5)	1 (0.5)
Adverse events leading to treatment interruption	0	30 (8.6)	8 (2.3)	11 (5.3)	12 (5.7)
Adverse events leading to dose reduction	0	15 (4.3)	4 (1.1)	6 (2.9)	5 (2.4)

PMDA's view:
In clinical studies, serious bone marrow depression associated with dabrafenib treatment occurred only infrequently. However, taking account that the incidence was higher in Japanese patients than in non-Japanese patients, and that the incidence of Grade ≥3 bone marrow depression was higher in the dabrafenib/TRA group than in the Vem group in the COMBI-V study, attention should be paid to occurrence of bone marrow depression in dabrafenib or dabrafenib/TRA treatment. Information on the incidences of bone marrow depression in clinical studies should be appropriately provided to healthcare professionals in clinical settings through the package insert etc. In addition, information on dabrafenib-associated bone marrow depression should be continuously collected after the market launch to determine whether further caution to alert physicians is necessary.

4.(iii).B.(3).9) Others
The applicant's explanation on adverse events that resulted in death in multiple patients in clinical studies and those mentioned in foreign package inserts to alert physicians, as shown in (a) through (g) below.

(a) Deep vein thrombosis and pulmonary embolism*
*: In the BREAK-3 study, events corresponding to pulmonary embolism, venous thrombosis, or venous thrombosis limb, preferred terms of MedDRA 14.1/J14.1; in other clinical studies, events corresponding to deep vein thrombosis, pulmonary embolism, or venous thrombosis, preferred terms of MedDRA 17.0/J17.0.

In the BREAK-3 and COMBI-D studies, deep vein thrombosis or pulmonary embolism associated with dabrafenib monotherapy occurred in 1.6% (3 of 187) of patients and 0.9% (2 of 211) of patients, respectively. The events were Grade ≥3 in 0.5% (1 of 187) of patients in the BREAK-3 study and in 0.5% (1 of 211) of patients in the COMBI-D study; and were serious in 0.5% (1 of 187) of patients in the BREAK-3 study and in 0.9% (2 of 211) of patients in the COMBI-D study.

In the COMBI-V and COMBI-D studies, deep vein thrombosis or pulmonary embolism associated with dabrafenib/TRA treatment occurred in 2.3% (8 of 350) of patients and 2.9% (6 of 209) of patients, respectively. Of these, 2.0% (7 of 350) of patients in the COMBI-V study and in 1.9% (4 of 209) of patients in the COMBI-D study were Grade ≥3; and 1.1% (4 of 350) of patients in the COMBI-V study and in 1.9% (4 of 209) of patients in the COMBI-D study were serious.

In phase I and II parts of Study BRF113220, fatal pulmonary embolism was noted in 1 patient each [see "4.(iii).A. (3).1) Foreign phase I/II study" and "4.(iii).A. (1).2) Foreign phase I/II study"].

(b) Cerebrovascular disorders*
*: In the BREAK-3 study, events corresponding to carotid artery stenosis or transient ischaemic attack, preferred terms of MedDRA 14.1/J14.1; in other clinical studies, events corresponding to cerebral haemorrhage, brain stem haemorrhage, cerebrovascular accident, carotid artery stenosis, subdural haematoma, haemorrhage intracranial, transient ischaemic attack, cerebral infarction, or subarachnoid haemorrhage, preferred terms of MedDRA 17.0/J17.0.

In Study BRF116056, BREAK-3 study, and COMBI-D study, cerebrovascular disorders associated with dabrafenib monotherapy occurred in 8.3% (1 of 12) of patients, 1.1% (2 of 187) of patients, and 0.9% (2 of 211) of patients, respectively, but no Grade ≥3 events were noted.

In the COMBI-V and COMBI-D studies, cerebrovascular disorders associated with dabrafenib/TRA treatment occurred in 1.4% (5 of 350) of patients and 1.9% (4 of 209) of patients, respectively. Three of 350 patients (0.9%) in the COMBI-V study and 3 of 209 patients (1.4%) in the COMBI-D study died of cerebrovascular disorders [see "4.(iii).A.(3).3) Foreign phase III study" and "4.(iii).A.(3).4) Foreign phase III study"].

(c) Eye disorders*

*: In the BREAK-3 study, events corresponding to vitreous floaters, vision blurred, iritis, photophobia, visual acuity reduced, or diplopia, preferred terms of MedDRA 14.1/J14.1; in other studies, events corresponding to blindness, chorioretinal disorder, chorioretinopathy, cystoid macular oedema, eye disorder, iridocyclitis, photophobia, photopsia, retinal detachment, retinal exudates, retinal tear, retinopathy, uveitis, vision blurred, visual acuity reduced, diplopia, visual field defect, visual impairment, vitreous detachment, retinal haemorrhage, dry eye, or vitreous floaters, preferred terms of MedDRA 17.0/J17.0.

In Study BRF116056, BREAK-3 study, and COMBI-D study, eye disorders associated with dabrafenib monotherapy occurred in 8.3% (1 of 12) of patients, 2.7% (5 of 187) of patients, and 10.9% (23 of 211) of patients, respectively. All events were Grade ≤2, while events were assessed serious in 1.4% (3 of 211) of patients in the COMBI-D study.

In MEK116885, COMBI-V, and COMBI-D studies, eye disorders associated with dabrafenib/TRA treatment occurred in 25.0% (3 of 12) of patients, 11.1% (39 of 350) of patients, and 12.9% (27 of 209) of patients, respectively. The events were Grade ≥3 in 8.3% (1 of 12) of patients in Study MEK116885, 0.6% (2 of 350) of patients in the COMBI-V study, and 1.4% (3 of 209) of patients in the COMBI-D study, and were assessed serious in 0.9% (3 of 350) of patients in the COMBI-V study and 1.4% (3 of 209) of patients in the COMBI-D study.

In the dabrafenib/TRA group of the COMBI-V and COMBI-D studies, the median time to the first onset (range) of eye disorders was 85 days (1-701 days), showing no specific tendency in the time to the onset.

(d) QT/QTc interval prolongation*

*: Events corresponding to electrocardiogram repolarisation abnormality or electrocardiogram QT prolonged, preferred terms of MedDRA 17.0/J17.0.

In Study BRF116056 and COMBI-D study, QT/QTc interval prolongation associated with dabrafenib monotherapy was noted in 8.3% (1 of 12) of patients and 2.4% (5 of 211) of patients, respectively. The severity was Grade ≥3 in 0.9% (2 of 211) of patients in the COMBI-D study but were assessed as non-serious events.

In Study MEK116885 and COMBI-V study, QT/QTc interval prolongation associated with dabrafenib/TRA treatment was observed in 8.3% (1 of 12) of patients and 1.7% (6 of 350) of patients, respectively, and the severity was Grade ≥3 in 0.6% (2 of 350) of patients in the COMBI-V study.

(e) Pancreatitis*

*: In the BREAK-3 study, events corresponding to pancreatitis, lipase increased, or hyperlipasaemia, preferred terms of MedDRA 14.1/J14.1; in other clinical studies, events corresponding to amylase increased, pancreatitis, or lipase increased, preferred terms of MedDRA 17.0/J17.0.

In the BREAK-3 and COMBI-D studies, pancreatitis associated with dabrafenib monotherapy occurred in 1.1% (2 of 187) of patients and 0.5% (1 of 211) of patients, respectively. All events were Grade ≥3, and those in 1.1% (2 of 187) of patients in the BREAK-3 study were assessed as serious events.

In the COMBI-V and COMBI-D studies, pancreatitis associated with dabrafenib/TRA treatment occurred in 0.6% (2 of 350) of patients and 0.5% (1 of 209) of patients, respectively. The events were Grade ≥3 in 0.6% (2 of 350) of patients in the COMBI-V study, but all of them were assessed as non-serious.

(f) Haemorrhage*

*: In the BREAK-3 study, events corresponding to epistaxis, haemoglobin decreased, mouth haemorrhage, menometrorrhagia, or contusion, preferred terms of MedDRA 14.1/J14.1; in other clinical studies, events corresponding to activated partial thromboplastin time prolonged, gingival bleeding, anal haemorrhage, haematochezia, haematocrit decreased, haematuria, haematoma, post procedural haematoma, haemoglobin decreased, haemoptysis, haemorrhage, purpura, rectal haemorrhage, red blood cell count decreased, haemorrhoidal haemorrhage, hepatic haematoma, brain stem haemorrhage, hyphaema, increased tendency to bruise, cerebral haemorrhage, international normalised ratio increased, intra-abdominal haematoma, subcutaneous haematoma, subdural haematoma, melaena, menorrhagia, conjunctival haemorrhage, contusion, metrorrhagia, traumatic haematoma, muscle haemorrhage, duodenal ulcer haemorrhage, ear haemorrhage, nipple exudate bloody, ecchymosis, epistaxis, vaginal haemorrhage, fibrin D dimer increased, vascular rupture, vessel puncture site

haematoma, gastritis haemorrhagic, bone contusion, haematospermia, wound haemorrhage, haemorrhagic ovarian cyst, haemothorax, laryngeal haemorrhage, peritoneal haemorrhage, pulmonary haemorrhage, haematoma infection, blood urine present, haemarthrosis, haemorrhage subcutaneous, or haematuria, preferred terms of MedDRA 17.0/J17.0.

In Study BRF116056, BREAK-3 study, and COMBI-D study, haemorrhage associated with dabrafenib monotherapy occurred in 25.0% (3 of 12) of patients, 6.4% (12 of 187) of patients, and 15.2% (32 of 211) of patients, respectively. The events were Grade ≥3 in 0.5% (1 of 187) of patients in the BREAK-3 study and in 1.9% (4 of 211) of patients in the COMBI-D study, and were assessed as serious events in 1.1% (2 of 187) of patients in the BREAK-3 study and in 1.9% (4 of 211) of patients in the COMBI-D study.

In the COMBI-V and COMBI-D studies, haemorrhage associated with dabrafenib/TRA treatment occurred in 17.7% (62 of 350) of patients and 19.1% (40 of 209) of patients, respectively. The events were Grade ≥3 in 2.9% (10 of 350) of patients in the COMBI-V study and 2.9% (6 of 209) of patients in the COMBI-D study, and were assessed as serious in 3.1% (11 of 350) of patients in the COMBI-V study and 2.9% (6 of 209) of patients in the COMBI-D study.

(g) Hyperglycaemia*

*: In the BREAK-3 study, events corresponding to hyperglycaemia, diabetes mellitus, diabetes mellitus inadequate control, or blood glucose increased, preferred terms of MedDRA 14.1/J14.1; in other clinical studies, events corresponding to hyperglycaemia, blood glucose increased, diabetes mellitus, type 2 diabetes mellitus, or glucose urine present, preferred terms of MedDRA 17.0/J17.0.

In the BREAK-3 and COMBI-D studies, hyperglycaemia associated with dabrafenib monotherapy occurred in 5.3% (10 of 187) of patients and 3.3% (7 of 211) of patients, respectively. The events were Grade ≥3 in 2.7% (5 of 187) of patients in the BREAK-3 study and in 0.5% (1 of 211) of patients in the COMBI-D study, and were assessed as serious events in 1.1% (2 of 187) of patients in the BREAK-3 study and in 0.9% (1 of 211) of patients in the COMBI-D study.

In Study MEK116885, COMBI-V study, and COMBI-D study, hyperglycaemia associated with dabrafenib/TRA treatment occurred in 16.7% (2 of 12) of patients, 6.6% (23 of 350) of patients, and 7.2% (15 of 209) of patients, respectively. The events were Grade ≥3 in 2.6% (9 of 350) of patients in the COMBI-V study and 2.9% (6 of 209) of patients in the COMBI-D study, and were assessed as serious events in 0.3% (1 of 350) of patients in the COMBI-V study and 0.5% (1 of 209) of patients in the COMBI-D study.

PMDA's view:
Information of the above events (a) to (e) in clinical studies should be appropriately provided to healthcare professionals in clinical settings through the package insert, for the following reasons. Although adverse events (f) and (g) occurred only infrequently in clinical studies, some of them were serious haemorrhage and, in the BREAK-3 study, the incidence of hyperglycaemia tended to be higher in the dabrafenib group than in the DTIC group. Therefore, information on haemorrhage and hyperglycaemia associated with dabrafenib treatment should be continuously collected after market launch to determine whether further caution to alert physicians is necessary.

(a) In Study BRF113220, some patients experienced fatal pulmonary embolism. Therefore, the onset of deep vein thrombosis and pulmonary embolism should be carefully monitored in dabrafenib or dabrafenib/TRA treatment.

(b) In the COMBI-V study, COMBI-D study, and Study BRF113220, there were multiple events of fatal cerebrovascular disorders. Thus, the onset of cerebrovascular disorders should be carefully monitored in dabrafenib or dabrafenib/TRA treatment.

(c) Since serious eye disorders were found in clinical studies, attention should be paid to the onset of eye disorders in dabrafenib or dabrafenib/TRA treatment. In addition, caution statements should be provided to healthcare professionals in clinical settings through the package insert and other materials so that patients are periodically monitored for ocular abnormalities during treatment with dabrafenib and, if any abnormality is noted, appropriate measures should be taken.

(d) Although dabrafenib-associated QT/QTc prolongation occurred only infrequently in clinical studies, there were cases of QT/QTc interval prolongation that resulted in treatment discontinuation in the COMBI-V study. Thus, possible onset of QT/QTc interval prolongation should be carefully

monitored during treatment with dabrafenib or dabrafenib/TRA.

(e) Although pancreatitis occurred only infrequently in clinical studies, some patients experienced serious pancreatitis in the BREAK-3 study. Thus, the onset of pancreatitis should be carefully monitored in dabrafenib or dabrafenib/TRA treatment.

4.(iii).B.(4) Clinical positioning

In Japanese and foreign clinical practice guidelines and leading clinical oncology textbooks, descriptions on dabrafenib in the treatment of unresectable malignant melanoma with BRAF V600 mutations are as shown below.

[Clinical practice guidelines]

- NCCN Guideline (v.3.2015): Dabrafenib and dabrafenib/TRA are recommended for patients with unresectable malignant melanoma with BRAF V600 mutations (category 1*)
  *: Based on high-level evidence with uniform NCCN consensus that the intervention is appropriate.

- US National Cancer Institute Physician Data Query (NCI-PDQ) (published on July 14, 2015): Dabrafenib and dabrafenib/TRA are recommended for patients with unresectable malignant melanoma with BRAF V600 mutations.

- Japanese Skin Cancer Society, Japanese Dermatological Association, eds. *Clinical Practice Guideline for malignant skin tumor*, 2nd ed. Kanehara & Co., Ltd., 2015: A phase III study was conducted to compare the efficacy and safety of dabrafenib and DTIC, and the results showed improved life expectancy in the dabrafenib group.

[Textbooks]

- *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology.* 10th ed. PA, USA: Lippincott Williams & Wilkins; 2015: Dabrafenib brought about a statistically significant increase in PFS compared with DTIC in patients with unresectable malignant melanoma with BRAF V600 mutations.

- Japanese Society of Medical Oncology, eds. *New Clinical Oncology*. 4th ed. Nankodo Co., Ltd., 2015: Dabrafenib brought about a statistically significant increase in PFS compared with DTIC in patients with unresectable malignant melanoma with BRAF V600 mutations.

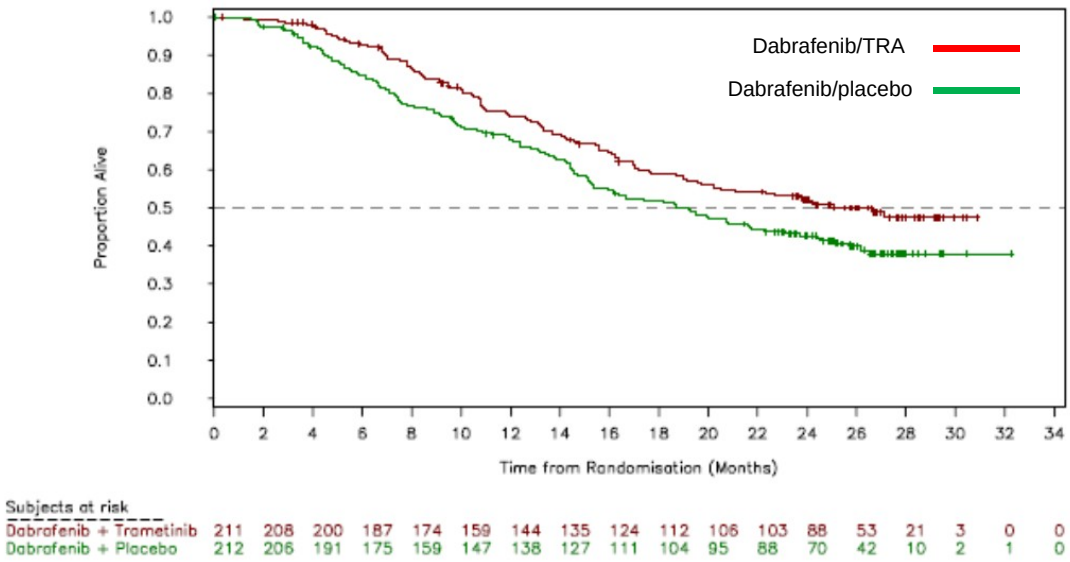
The applicant's explanation on the clinical positioning of dabrafenib monotherapy and dabrafenib/TRA:
Results of BREAK-3 and COMBI-V studies have demonstrated the clinical usefulness of dabrafenib and dabrafenib/TRA in patients with unresectable malignant melanoma with BRAF V600 mutations. Therefore, dabrafenib and dabrafenib/TRA can be positioned as treatment options for this patient group.

The applicant's explanation on the choice between dabrafenib monotherapy and dabrafenib/TRA:
In the COMBI-D study which investigated the efficacy and safety between dabrafenib/TRA and dabrafenib/placebo in patients with unresectable malignant melanoma with BRAF V600 mutations, the superiority of dabrafenib/TRA to dabrafenib/placebo was demonstrated in the primary endpoint, i.e., PFS assessed by the investigator [see "4.(iii).A.(3).4) Foreign phase III study"]. In addition, OS, one of secondary endpoints, and its Kaplan-Meier curves were as shown in the following table and figure, respectively, indicating a statistically significant prolongation of OS in the dabrafenib/TRA group compared with the dabrafenib/placebo group.

Final analysis of OS (ITT population; data cut-off, January 12, 2015)

	Dabrafenib/TRA	Dabrafenib/placebo
Number of patients	211	212
Number of deaths (%)	99 (46.9)	123 (58.0)
Median [95% CI] (months)	25.1 [19.2, NE]	18.7 [15.2, 23.7]
Hazard ratio [95% CI]*1	0.71 [0.55, 0.92]	
P value (two-sided)*2	0.011	

NE, Not estimable; *1, Pike's estimate; *2, Stratified log-rank test (stratified by LDH level and by *BRAF* mutation type); significance level (two-sided) 0.0496



Kaplan-Meier curves of OS (ITT population; data cut-off, January 12, 2015)

From the safety point of view, although noteworthy adverse events occur in association with dabrafenib/TRA treatment, dabrafenib/TRA can be well tolerated provided that adverse events are monitored and controlled and appropriate measures such as treatment interruption are taken by the physician with sufficient knowledge and experience of cancer chemotherapy [see "4.(iii).B.(3) Safety"].

Consequently, dabrafenib/TRA combination therapy is recommended over dabrafenib monotherapy in patients with unresectable malignant melanoma with BRAF V600 mutations. On the other hand, in patients for whom dabrafenib/TRA is not recommended, such as those with low tolerance to TRA, dabrafenib may be considered as a treatment choice for the following reasons:

- The BREAK-3 study showed the superiority of dabrafenib to DTIC in the primary endpoint, i.e., PFS assessed by the investigator [see "4.(iii).A.(3).2) Foreign phase III study"].
- Study BRF116056 showed that 54.5% (6 of 11) of Japanese patients of malignant melanoma with BRAF mutations responded to dabrafenib, and dabrafenib monotherapy may possibly be well tolerated.

PMDA accepted the applicant's explanation.

4.(iii).B.(5) Indication

The proposed indication of dabrafenib was "Malignant melanoma with BRAF V600 gene mutation." The Precautions for Indications section included the following description:

- Dabrafenib should be administered to patients with known BRAF V600 mutations through tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic should be used in the test.

- Since the efficacy and safety of dabrafenib in patients with wild-type BRAF have not been established, dabrafenib should not be administered to patients with wild-type BRAF.

- The physician should be thoroughly versed in the content of the "Clinical Studies" section and fully understand the efficacy and safety of dabrafenib before selecting the patients to be treated.

- The efficacy and safety of dabrafenib in the adjuvant chemotherapy have not been established.

Upon examining "4.(iii).B.(2) Efficacy," "4.(iii).B.(3) Safety," "4.(iii).B.(4) Clinical positioning," and the following discussion in this section, PMDA concluded that the indication of dabrafenib should be "unresectable malignant melanoma with BRAF mutations." PMDA also concluded that information on BRAF testing kits used in Study MEK116885, COMBI-V study, COMBI-D study, and other studies,

and on the types of BRAF mutations in patients enrolled in these studies should be provided in the Clinical Studies section of the package insert, and that the proposed Precautions for indications should be modified as shown below.

- Dabrafenib should be administered to patients who are confirmed to be *BRAF* mutation-positive through tests performed by a thoroughly experienced pathologist or testing institutions. An approved *in vitro* diagnostic should be used in the test.

- The physician should be thoroughly versed in the content of the "Clinical Studies" section and fully understand the efficacy and safety of dabrafenib before selecting the patients to be treated.

- The efficacy and safety of dabrafenib in the adjuvant chemotherapy have not been established.

4.(iii).B.(5).1) The target patients and indication of dabrafenib

PMDA asked the applicant to explain dabrafenib treatment in patient population not included in COMBI-V or other studies, namely patients with resectable malignant melanoma and patients with wild-type BRAF malignant melanoma.

The applicant' response:

Since surgical removal is recommended for patients with resectable malignant melanoma, dabrafenib treatment in these patients is not recommended.

Similarly, dabrafenib treatment in patients with wild-type BRAF malignant melanoma is not recommended for reasons including the following: (a) No clinical data are available on the efficacy and safety of dabrafenib in this patient population, and (b) dabrafenib has a lower inhibitory effect on BRAF wild-type melanoma than BRAF mutated melanoma [see "3.(i).A.(1).1) Inhibitory effects on phosphorylation of kinases such as v-raf murine sarcoma viral oncogene product homolog B1 (BRAF)"]. Of 287 patients who were enrolled in the BREAK-3 study and were positive for BRAF V600 mutations by PCR, 280 patients were found positive by THxID BRAF mutation test; and, of 256 patients who were negative for BRAF V600 mutations by PCR, 247 patients were found negative by THxID BRAF test.

On the above basis, patients to be treated with dabrafenib should be limited to those with known *BRAF* mutations through an appropriate test. Therefore, the proposed indication was determined to be "malignant melanoma with BRAF V600 mutations," and the Clinical Studies section in the proposed package insert included information on the types of *BRAF* mutations in patients enrolled in Study MEK116885, COMBI-D study, and COMBI-V study and the Precautions for Indications section, included caution stating that dabrafenib should be administered to patients with known *BRAF* mutations.

PMDA's view:

The applicant's explanation is basically acceptable, but the indication should be "unresectable malignant melanoma with *BRAF* mutations" for the following reasons.

- Patients enrolled in the Study MEK116885, COMBI-V study, or COMBI-D study were those with unresectable malignant melanoma with *BRAF* mutations.
- In Study MEK116885, COMBI-V study, and COMBI-D study, patients were selected by THxID BRAF Kit, and the efficacy and safety of dabrafenib in these patients were confirmed. Therefore, this kit is recommended as the companion diagnostic for dabrafenib in selecting patients eligible to be treated with dabrafenib in clinical settings.

4.(iii).B.(5).2) Efficacy and safety as adjuvant chemotherapy

The applicant's explanation:

Since there are no clinical data on the efficacy and safety of dabrafenib in adjuvant chemotherapy, caution would be provided to that effect in the Precautions for Indications section of the package insert.

PMDA accepted the applicant's explanation.

4.(iii).B.(6) Dosage and administration

The proposed dosage regimen was "The usual adult dosage is 150 mg of dabrafenib administered orally twice daily." The Precautions for Dosage and Administration section included the following.

- See the "Clinical Studies" section and the package insert of TRA before dabrafenib treatment.
- Postprandial administration of dabrafenib was reported to decrease C_{max} and AUC. In order to avoid food effect, dabrafenib should be administered either ≥1 hour before meal or ≥2 hours after meal.
- Criteria for dabrafenib dose adjustment
- Patients should be instructed to receive dabrafenib only if the next scheduled dose is ≥6 hours away in case of a missed dose.
- When adverse drug reactions are sufficiently controlled by appropriate measures, the dose may be increased in the reverse process of dose reduction. The dose of dabrafenib should not exceed 150 mg orally twice daily.

The result of evaluation in "4.(i).B.(1) Food effect" and "4.(iii).B.(4) Clinical positioning" and the following section, PMDA concluded that the dosage and administration of dabrafenib should be "The usual adult dosage is 150 mg of dabrafenib administered orally twice daily under fasted conditions," and that the following should be included in the Precautions for Dosage and Administration section.

- The efficacy and safety of concomitant treatment with antineoplastic agents other than TRA have not been established.
- Postprandial administration of dabrafenib was reported to decrease C_{max} and AUC. It is desirable to refrain from receiving dabrafenib from 1 hour before meal to 2 hours after meal to avoid food effect.
- If an adverse drug reaction occurs after administration of dabrafenib, dabrafenib treatment should be interrupted, discontinued, or continued at a reduced dose with reference to the following criteria. If cuSCC or new primary malignant melanoma occurs, dabrafenib may be continued without interruption or dose reduction after surgical resection or other appropriate actions are given.

Criteria for interruption, dose reduction, and discontinuation

NCI-CTCAE*-assessed Grade	Action
Intolerable Grade 2 or Grade 3	Interruption After improvement to Grade ≤1, resume administration at a dose 1 level lower.
Grade 4	In principle, administration should be discontinued.

* Grade assessed by NCI-CTCAE v4.0

Guide for dose adjustment

Dose adjustment level*	Dose
Usual dose	150 mg/dose (twice daily)
1-level dose reduction	100 mg/dose (twice daily)
2-level dose reduction	75 mg/dose (twice daily)
3-level dose reduction	50 mg/dose (twice daily)
4-level dose reduction	Discontinue

*: If adverse drug reactions are sufficiently controlled by appropriate measures, the dose may be increased in the reverse process of dose reduction.

4.(iii).B.(6).1) Dabrafenib monotherapy and concomitant use with antineoplastic agents other than TRA

PMDA asked the applicant to explain the efficacy and safety of dabrafenib monotherapy and of concomitant use with antineoplastic agents other than TRA.

The applicant's response:

On the basis of the results of the BREAK-3 study etc., dabrafenib monotherapy is recommended to be a treatment option in patients with unresectable malignant melanoma with BRAF V600 mutations [see "4.(iii).B.(4) Clinical positioning"]. In contrast, there are no clinical data on the efficacy and safety of concomitant use of dabrafenib with antineoplastic agents other than TRA in patients with unresectable malignant melanoma with BRAF V600 mutations. Therefore, concomitant administration of dabrafenib with antineoplastic agents other than TRA is not recommended.

PMDA's view:
The applicant's explanation is basically acceptable, but the Clinical Studies section of the package insert should include the results of the COMBI-D study and others which showed a greater prolongation of PFS in the dabrafenib/TRA group compared with the dabrafenib/placebo group among patients with unresectable malignant melanoma with BRAF V600 mutations. The Precautions for Dosage and Administration section of the package insert should include the following caution statement.

- The efficacy and safety of concomitant treatment with antineoplastic agents other than TRA have not been established.

4.(iii).B.(6).2) Dosage and administration of dabrafenib

The applicant's explanation on the rationale for the proposed dosage and administration of dabrafenib in dabrafenib monotherapy and in dabrafenib/TRA treatment:
During the dose escalation phase in the foreign phase I study (Study BRF112680) in patients with solid tumors, DLT was observed in 1 of 6 patients in the dabrafenib 200 mg BID group (syncope) and in 1 of 6 patients in the dabrafenib 300 mg BID group (hyponatraemia), but MTD was not reached. The response rate in the dabrafenib 150 and 200 mg BID groups was 50.0% (8 of 16) of patients and 37.5% (6 of 16) of patients, respectively. Consequently, the recommended dosage and administration in dabrafenib monotherapy in subsequent clinical studies was determined to be 150 mg BID. This dosage regimen was employed in the BREAK-3 study and the results demonstrated the efficacy and safety of dabrafenib in patients with unresectable malignant melanoma with BRAF V600 mutations.

Meanwhile, the results of Study BRF113220 suggested the efficacy and safety of dabrafenib or TRA monotherapy at the recommended dose (dabrafenib 150 mg BID and TRA 2 mg QD) [see 4.(iii).A.(3).1) Foreign phase I/II study"]. This dosage regimen was employed in the COMBI-D and COMBI-V studies, and the results demonstrated the clinical usefulness of dabrafenib/TRA in patients with unresectable malignant melanoma with BRAF V600 mutations. Therefore, the proposed dosage and administration of dabrafenib in dabrafenib/TRA combination therapy was determined accordingly on the basis of the dosage regimen employed in the above studies.

PMDA accepted the applicant's explanation.

4.(iii).B.(6).3) Dose adjustment, etc.

The applicant's explanation on the dose adjustment of dabrafenib:
In the COMBI-V study, COMBI-D study, and Study MEK116885, the criteria for dose adjustment of dabrafenib were specified according to factors such as severity of adverse events observed, and dabrafenib was tolerated when administered in compliance with the criteria. Therefore, the dose adjustment criteria were determined in the Precautions for Dosage and Administration section by referring to these criteria. Since left ventricular ejection fraction decreased, retinal vein occlusion, detachment of retinal pigment epithelium, and interstitial pneumonia/pneumonitis are adverse events specific to TRA, the dose adjustment of dabrafenib is considered unnecessary even if these events occur. On the other hand, since pyrexia of ≥38°C and uveitis are adverse events unique to dabrafenib, dose adjustment of TRA is considered unnecessary in the case of these events. Adverse drug reactions that require dose adjustment of either dabrafenib or TRA only are listed in the Precautions for Dosage and Administration section to call for attention (the table below).

Adverse drug reactions requiring interruption, dose reduction, or discontinuation of either dabrafenib or TRA only

Interruption, dose reduction, or discontinuation of dabrafenib only	Pyrexia of ≥38°C, uveitis
Interruption, dose reduction, or discontinuation of TRA only	Left ventricular ejection fraction decreased, retinal vein occlusion, detachment of retinal pigment epithelium, interstitial pneumonia, pneumonitis

PMDA's view:
The applicant's explanation is largely acceptable. However, it has not been sufficiently justified for the above tabulated adverse drug reactions to require dose adjustment of either dabrafenib or TRA only when the following results are taken into account. PMDA therefore concludes that setting the above requirements for interruption, dose reduction, or discontinuation is not appropriate.

- In the METRIC study, some patients experienced pyrexia after administration of TRA alone, resulting in dose adjustment.
- In the COMBI-V and COMBI-D studies, some patients experienced pyrexia or uveitis after administration of dabrafenib/TRA, resulting in dose adjustment for both dabrafenib and TRA.
- In the COMBI-V and COMBI-D studies, some patients experienced ventricular ejection fraction decreased, detachment of retinal pigment epithelium, or interstitial pneumonia and pneumonitis, resulting in dose adjustment for both dabrafenib and TRA.

4.(iii).B.(7) Post-marketing investigations

The applicant's explanation on the plan for the post-marketing surveillance:
In order to evaluate the safety etc., of dabrafenib in routine clinical use after market launch, a post-marketing surveillance in all patients treated with dabrafenib (the surveillance) will be conducted.

Since dabrafenib/TRA is to be recommended and is expected to be administered to most of the patients, the following priority survey items in this surveillance were determined on the basis of the incidence of adverse drug reactions in clinical studies in and out of Japan in which dabrafenib/TRA was administered: Squamous cell carcinoma of skin, new primary malignant melanoma, non-cutaneous malignant tumor, prerenal or renal parenchymal failure, pancreatitis, neutropenia, and haemorrhage.

The target number of patients to be surveyed was 200 receiving dabrafenib/TRA, based on the incidence of the planned priority survey items (selected adverse events) observed in the COMBI-V and COMBI-D studies.

The follow-up period was set at 1 year, taking account of the time to onset (median, 50-284 days) of the planned priority survey items, observed in the COMBI-V and COMBI-D studies.

PMDA's view:
Extremely limited information is available regarding the safety of dabrafenib administered to Japanese patients with unresectable malignant melanoma with *BRAF* mutations. Therefore, a post-marketing surveillance covering all patients treated with dabrafenib to collect safety information in a prompt and unbiased manner, and thereby to provide the safety information obtained to healthcare professionals in clinical settings immediately.

On the basis of the incidence of adverse drug reactions in clinical studies in and out of Japan, the following adverse events are considered to require particular caution in dabrafenib/TRA treatment, and should be included in the priority items in the surveillance: Cardiac disorder, hepatic dysfunction, pyrexia, eye disorders, spinocellular carcinoma, secondary malignant tumor other than spinocellular carcinoma, and rhabdomyolysis.

The number of patients to be surveyed and the follow-up period should be reconsidered by taking account of the nature of the priority items.

Since dabrafenib and TRA are expected to be used in combination in most cases [see "4.(iii).B.(4) Clinical positioning" and "4.(iii).B.(6) Dosage and administration"], a survey plan that allows investigation of safety etc., in concomitant use of dabrafenib with TRA should be designed.

4.(iv) Adverse events etc., observed in clinical studies

Deaths reported in clinical data submitted for safety evaluation are described in "4.(iii) Summary of clinical efficacy and safety." Major adverse events other than death are shown in the following table.

4.(iv).(1) Japanese phase I study (Study BRF116056)

Adverse events in 100% (3 of 3) of patients in the 75 mg group, 100% (3 of 3) of patients in the 100 mg group, and 100% (6 of 6) of patients in the 150 mg group; a causal relationship to the study drug could not be ruled out for all events in the all groups. Those with an incidence of ≥40% in any group were as shown in the following table.

Adverse events with an incidence of ≥40% in any group

System organ class Preferred term (MedDRA/J ver17.0)	Number of patients (%)					
	75 mg (n = 3)		100 mg (n = 3)		150 mg (n = 6)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	0	3 (100)	0	6 (100)	1 (17)
General disorders and administration site conditions						
Pyrexia	1 (33)	0	1 (33)	0	4 (67)	0
Fatigue	3 (100)	0	0	0	0	0
Skin and subcutaneous tissue disorders						
Alopecia	2 (67)	0	2 (67)	0	3 (50)	0
Hyperkeratosis	2 (67)	0	0	0	2 (33)	0
Palmar-plantar erythrodysaesthesia syndrome	0	0	2 (67)	0	0	0
Investigations						
ALT increased	2 (67)	0	1 (33)	0	0	0
AST increased	1 (33)	0	2 (67)	0	0	0
Blood ALP increased	0	0	2 (67)	0	1 (17)	0
Musculoskeletal and connective tissue disorders						
Arthralgia	0	0	3 (100)	0	3 (50)	0
Blood and lymphatic system disorders						
Leukopenia	2 (67)	0	2 (67)	0	2 (33)	0
Gastrointestinal disorders						
Nausea	3 (100)	0	0	0	1 (17)	0
Constipation	2 (67)	0	0	0	1 (17)	0

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase

Serious adverse events were noted in 33% (1 of 3) of patients in the 100 mg group and 17% (1 of 6) of patients in the 150 mg group: bronchitis in 1 patient and myocardial ischaemia in 1 patient in the respective groups. Of these, a causal relationship to the study drug could not be ruled out for myocardial ischaemia in 1 patient in the 150 mg group.

There were no adverse events leading to study discontinuation.

4.(iv).(2) Japanese phase I/II study (Study MEK116885)

4.(iv).(2).1) Phase I part

Adverse events were noted in all 6 patients; a causal relationship to the study drug could not be ruled out for the events in all patients. Those with an incidence of ≥40% were as shown in the following table.

Adverse events with an incidence of ≥40%

System organ class Preferred term (MedDRA/J ver17.0)	Number of patients (%) Dabrafenib (n = 6)	
	All Grades	Grade ≥3
All adverse events	6 (100)	4 (67)
General disorders and administration site conditions		
Pyrexia	5 (83)	0
Investigations		
AST increased	4 (67)	0
Blood ALP increased	3 (50)	1 (17)
Skin and subcutaneous tissue disorders		
Dermatitis acneiform	3 (50)	0
Erythema	4 (67)	0
Rash maculo-papular	4 (67)	0
Alopecia	3 (50)	0
Infections and infestations		
Nasopharyngitis	4 (67)	0
Nervous system disorders		
Headache	3 (50)	0
Metabolism and nutrition disorders		
Decreased appetite	3 (50)	0

AST, Aspartate aminotransferase; ALP, Alkaline phosphatase

A serious adverse event, pneumonitis, occurred in 17% (1 of 6) of patients, its causal relationship to the study drug could not be ruled out.

An adverse event leading to study discontinuation, blood ALP increased, was observed in 17% (1 of 6) of patients; its causal relationship to the study drug could not be ruled out.

4.(iv).(2).2) Phase II part

Adverse events were found in all 6 patients; a causal relationship to the study drug could not be ruled out for the events in all patients.

Adverse events with an incidence of ≥40% were pyrexia and oedema peripheral in 67% (4 of 6) of patients each and AST increased and stomatitis in 50% (3 of 6) of patients each. None of them were Grade ≥3.

No serious adverse events were reported.

An adverse event leading to study discontinuation, uveitis, occurred in 17% (1 of 6) of patients; its causal relationship to the study drug could not be ruled out.

4.(iv).(3) Foreign phase I study (Study BRF113479)

Adverse events occurred in 75% (3 of 4) of patients; a causal relationship to the study drug could not be ruled out for all the events.

The observed adverse events were flushing in 2 patients (50%), abdominal pain, fatigue, upper respiratory tract infection, and hyperhidrosis in 1 patient (25%) each. There were no Grade ≥3 events.

No serious adverse events occurred.

There were no adverse events leading to study discontinuation.

4.(iv).(4) Foreign phase I study (Study BRF113468)

Adverse events occurred in 79% (11 of 14) of patients in Cohort 1 (study of the effect of particle size) and in 79% (11 of 14) of patients in Cohort 2 (study of food effect); a causal relationship to the study drug could not be ruled out for the events in 64% (9 of 14) of patients and 36% (5 of 14) of patients in the respective cohorts. Those with an incidence of ≥10% in either cohort were as shown in the following table.

Adverse events with an incidence of ≥10% in either cohort

System organ class Preferred term (MedDRA/J ver14.0)	Number of patients (%)			
	Cohort 1 (n = 14)		Cohort 2 (n = 14)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	11 (79)	0	11 (79)	2 (14)
Gastrointestinal disorders				
Vomiting	3 (21)	0	0	0
Diarrhoea	2 (14)	0	0	0
Nausea	2 (14)	0	1 (7)	0
Abdominal pain	1 (7)	0	2 (14)	0
Skin and subcutaneous tissue disorders				
Dry skin	2 (14)	0	0	0
Rash	2 (14)	0	1 (7)	0
General disorders and administration site conditions				
Pyrexia	2 (14)	0	4 (29)	0
Fatigue	1 (7)	0	2 (14)	0
Musculoskeletal and connective tissue disorders				
Back pain	2 (14)	0	0	0
Nervous system disorders				
Dysgeusia	2 (14)	0	0	0

Serious adverse events occurred in 0% (0 of 14) of patients in Cohort 1 and 7% (1 of 14) of patients in Cohort 2: abdominal pain and anaemia in Cohort 2. A causal relationship to the study drug was ruled out for both events.

There were no adverse events leading to study discontinuation.

4.(iv).(5) Foreign phase I study (Study BRF113463)

Adverse events occurred in all 4 patients; a causal relationship to the study drug could not be ruled out for the events in 25% (1 of 4) of patients.

The adverse events noted were diarrhoea in 2 patients (50%) and post-tussive vomiting, fatigue, pharyngitis, dehydration, headache, nasal congestion, and rash in 1 patient (25%) each. The severity of dehydration was Grade ≥3.

No serious adverse events occurred.

There were no adverse events leading to study discontinuation.

4.(iv).(6) Foreign phase I study (Study BRF113771)

4.(iv).(6).1) Part A (study on interaction with warfarin)

Adverse events occurred in 86% (12 of 14) of patients; a causal relationship to the study drug could not be ruled out for the events in 79% (11 of 14) of patients.

Adverse events with an incidence of ≥10% were rash in 7 patients (50%), arthralgia in 4 patients (29%), headache and flushing in 3 patients (21%) each, and pruritus, abdominal pain upper, dry mouth, nausea, vomiting, chills, fatigue, oedema peripheral, pyrexia, back pain, hyperglycaemia, and skin papilloma in 2 patients (14%) each. Of these, hyperglycaemia in 2 patients and headache and skin papilloma in 1 patient each were Grade ≥3.

A serious adverse event, pneumonia, occurred in 7% (1 of 14) of patients, and its causal relationship to the study drug was ruled out.

There were no adverse events leading to study discontinuation.

4.(iv).(6).2) Part B (study on interaction with ketoconazole)

Adverse events occurred in 88% (14 of 16) of patients; a causal relationship to the study drug could not be ruled out for the events in 75% (12 of 16) of patients.

Adverse events with an incidence of ≥10% were pyrexia and skin papilloma in 5 patients (31%) each, diarrhoea, nausea, rash, and headache in 4 patients (25%) each, fatigue and pain in extremity in 3 patients (19%) each, dyspepsia, myalgia, cough, nasopharyngitis, hot flush, and hypokalaemia in 2 patients (13%) each. None of the events were Grade ≥3.

Serious adverse events occurred in 13% (2 of 16) of patients: lower gastrointestinal haemorrhage, sepsis, and pericardial effusion in 1 patient (6%) each. Of these, a causal relationship to the study drug could not be ruled out for sepsis.

An adverse event leading to study discontinuation, sepsis, occurred in 6% (1 of 16) of patients, and its causal relationship to the study drug could not be ruled out.

4.(iv).(6).3) Part C (study on interaction with gemfibrozil)
Adverse events occurred in 88% (15 of 17) of patients; a causal relationship to the study drug could not be ruled out for the events in 59% (10 of 17) of patients.

Adverse events with an incidence of ≥10% were skin papilloma in 4 patients (24%), fatigue in 3 patients (18%), arthralgia, myalgia, abdominal pain, nausea, vomiting, oedema peripheral, acrocodon, seborrhoeic keratosis, rash, and insomnia in 2 patients (12%) each. Of these, fatigue in 1 patient was Grade ≥3.

Serious adverse events were observed in 12% (2 of 17) of patients: dyspnoea and pyrexia in 1 patient (6%) each. Of these, a causal relationship to the study drug could not be ruled out for pyrexia.

There were no adverse events leading to study discontinuation.

4.(iv).(6).4) Part D (study on pharmacokinetics in multiple administration of HPMC capsules)
Adverse events occurred in all 13 patients; a causal relationship to the study drug could not be ruled out for the events in 85% (11 of 13) of patients.

Adverse events with an incidence of ≥10% were as shown in the following table.

Adverse events with an incidence of ≥10%

System organ class Preferred term (MedDRA/J ver15.1)	Number of patients (%) Dabrafenib (HPMC capsule) (n = 13)	
	All Grades	Grade ≥3
All adverse events	13 (100)	2(15)
Skin and subcutaneous tissue disorders		
Palmar-plantar erythrodysaesthesia syndrome	4 (31)	0
Rash	4 (31)	0
Pruritus	3 (23)	0
Pain of skin	2 (15)	0
Gastrointestinal disorders		
Nausea	3 (23)	0
Vomiting	3 (23)	0
Diarrhoea	2 (15)	0
General disorders and administration site conditions		
Chills	2 (15)	0
Fatigue	2 (15)	0
Pyrexia	2 (15)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	4 (31)	0
Myalgia	3 (23)	0
Back pain	2 (15)	0
Musculoskeletal pain	2 (15)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Skin papilloma	7 (54)	0
Nervous system disorders		
Headache	2 (15)	0

Serious adverse events occurred in 15% (2 of 13) of patients: small intestinal obstruction and atrial flutter in 1 patient (8%) each. Of these, a causal relationship to the study drug could not be ruled out for atrial flutter.

An adverse event leading to study discontinuation, small intestinal obstruction, occurred in 8% (1 of 13) of patients, and its causal relationship to the study drug was ruled out.

4.(iv).(7) Foreign phase I/II study (Study BRF113220) (phase II part)

Adverse events occurred in 100% (53 of 53) of patients in the dabrafenib alone group, 98% (53 of 54) of patients in the dabrafenib/TRA 1 mg combination group, and 100% (55 of 55) of patients in the dabrafenib/TRA 2 mg combination group. A causal relationship to the study drug could not be ruled out for the events in 96% (51 of 53) of patients, 96% (52 of 54) of patients, and 100% (55 of 55) of patients in the respective groups. Those with an incidence of ≥30% in any group were as shown in the following table.

Adverse events with an incidence of ≥30% in any group

System organ class Preferred term (MedDRA/J ver16.1)	Number of patients (%)					
	Dabrafenib (n = 53)		Dabrafenib/TRA 1 mg (n = 54)		Dabrafenib/TRA 2 mg (n = 55)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	53 (100)	25 (47)	53 (98)	30 (56)	55 (100)	39 (71)
General disorders and administration site conditions						
Pyrexia	14 (26)	0	39 (72)	6 (11)	38 (69)	4 (7)
Chills	9 (17)	0	28 (52)	1 (2)	33 (60)	1 (2)
Fatigue	22 (42)	4 (8)	35 (65)	1 (2)	32 (58)	2 (4)
Skin and subcutaneous tissue disorders						
Rash	19 (36)	0	13 (24)	0	17 (31)	0
Hyperkeratosis	16 (30)	0	4 (7)	0	8 (15)	0
Alopecia	18 (34)	0	7 (13)	0	3 (5)	0
Gastrointestinal disorders						
Diarrhoea	15 (28)	0	17 (31)	2 (4)	26 (47)	1 (2)
Nausea	11 (21)	0	30 (56)	3 (6)	26 (47)	1 (2)
Vomiting	8 (15)	0	23 (43)	3 (6)	26 (47)	1 (2)
Musculoskeletal and connective tissue disorders						
Arthralgia	18 (34)	0	28 (52)	0	17 (31)	0
Myalgia	12 (23)	1 (2)	16 (30)	0	13 (24)	1 (2)
Nervous system disorders						
Headache	17 (32)	0	25 (46)	1 (2)	17 (31)	0
Respiratory, thoracic and mediastinal disorders						
Cough	11 (21)	0	10 (19)	0	18 (33)	0
Metabolism and nutrition disorders						
Decreased appetite	11 (21)	0	18 (33)	0	16 (29)	0

Serious adverse events occurred in 26% (14 of 53) of patients in the dabrafenib group, 43% (23 of 54) of patients in the dabrafenib/TRA 1 mg group, and 69% (38 of 55) of patients in the dabrafenib/TRA 2 mg group. Those reported by ≥2 patients in any group were squamous cell carcinoma of skin in 5 patients (9%) and squamous cell carcinoma in 4 patients (8%) in the dabrafenib group; pyrexia in 10 patients (19%), chills in 7 patients (13%), ejection fraction decreased in 4 patients (7%), vomiting in 3 patients (6%), anaemia and nausea in 2 patients (4%) each in the dabrafenib/TRA 1 mg group; and pyrexia in 16 patients (29%), chills in 12 patients (22%), ejection fraction decreased and pneumonia in 3 patients (5%) each, dehydration, gastrointestinal haemorrhage, neutropenia, pulmonary embolism, renal failure acute, squamous cell carcinoma, and squamous cell carcinoma of skin in 2 patients (4%) each in the dabrafenib/TRA 2 mg group. Of these, a causal relationship to the study drug could not be ruled out for squamous cell carcinoma of skin in 5 patients and squamous cell carcinoma in 4 patients in the dabrafenib group; pyrexia in 9 patients, chills in 6 patients, ejection fraction decreased in 4 patients, nausea and vomiting in 2 patients each, and anaemia in 1 patient in the dabrafenib/TRA 1 mg group; and pyrexia in 15 patients, chills in 11 patients, neutropenia, pneumonia, renal failure acute, squamous cell carcinoma, and squamous cell carcinoma of skin in 2 patients each, and ejection fraction decreased in 1 patient in the dabrafenib/TRA 2 mg group.

Adverse events leading to study discontinuation occurred in 2% (1 of 53) of patients in the dabrafenib group, 6% (3 of 54) of patients in the dabrafenib/TRA 1 mg group, and 15% (8 of 55) of patients in the dabrafenib/TRA 2 mg group: blood creatinine increased in 1 patient (2%); pyrexia, chills, colitis, pain in extremity, and sepsis in 1 patient (2%) each; and pyrexia in 2 patients (4%), cerebral haemorrhage, dyspnoea, ejection fraction decreased, fatigue, haemorrhage intracranial, nausea, pulmonary embolism, and renal failure in 1 patient (2%) each in the respective groups. Of these, a causal relationship to the study drug could not be ruled out for blood creatinine increased in 1 patient; pyrexia, chills, and pain in extremity in 1 patient each; and pyrexia in 2 patients, fatigue, nausea and renal failure in 1 patient each in the respective groups.

4.(iv).(8) Foreign phase III study (Study BRF113683)

Adverse events occurred in 99% (185 of 187) of patients in the dabrafenib group and 92% (54 of 59) of patients in the dacarbazine group; a causal relationship to the study drug could not be ruled out for the events in 88% (164 of 187) of patients and 73% (43 of 59) of patients in the respective groups. Those with an incidence of ≥10% in either group were as shown in the following table.

Adverse events with an incidence of ≥10% in either group

System organ class Preferred term (MedDRA/J ver14.1)	Number of patients (%)			
	Dabrafenib (n = 187)		Dacarbazine (n = 59)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	185 (99)	63 (34)	54 (92)	25 (42)
Skin and subcutaneous tissue disorders				
Hyperkeratosis	69 (37)	2 (1)	0	0
Alopecia	41 (22)	0	1 (2)	0
Palmar-plantar erythrodysaesthesia syndrome	37 (20)	4 (2)	1 (2)	0
Rash	31 (17)	0	0	0
General disorders and administration site conditions				
Pyrexia	52 (28)	6 (3)	6 (10)	0
Fatigue	36 (19)	2 (1)	14 (24)	0
Asthenia	33 (18)	1 (<1)	9 (15)	1 (2)
Gastrointestinal disorders				
Nausea	35 (19)	1 (<1)	30 (51)	0
Vomiting	23 (12)	2 (1)	15 (25)	0
Constipation	21 (11)	3 (2)	8 (14)	0
Diarrhoea	20 (11)	1 (<1)	7 (12)	0
Abdominal pain	7 (4)	1 (<1)	8 (14)	1 (2)
Musculoskeletal and connective tissue disorders				
Arthralgia	51 (27)	2 (1)	1 (2)	0
Back pain	22 (12)	5 (3)	4 (7)	0
Myalgia	20 (11)	0	0	0
Pain in extremity	16 (9)	1 (<1)	7 (12)	0
Nervous system disorders				
Headache	59 (32)	0	5 (8)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Skin papilloma	45 (24)	0	1 (2)	0
Infections and infestations				
Nasopharyngitis	19 (10)	0	2 (3)	0
Respiratory, thoracic and mediastinal disorders				
Cough	23 (12)	0	3 (5)	0
Blood and lymphatic system disorders				
Anaemia	7 (4)	1 (<1)	7 (12)	2 (3)
Neutropenia	2 (1)	1 (<1)	10 (17)	8 (14)
Leukopenia	1 (<1)	0	6 (10)	2 (3)

Serious adverse events occurred in 23% (43 of 187) of patients in the dabrafenib group and 22% (13 of 59) of patients in the dacarbazine group. Those with an incidence of ≥1% in either group were pyrexia and squamous cell carcinoma in 7 patients (4%) each, squamous cell carcinoma of skin and malignant melanoma in 3 patients (2%) each, vomiting, atrial fibrillation, ejection fraction decreased, and hypotension in 2 patients (1%) each in the dabrafenib group; and abdominal pain in 2 patients (3%), vomiting, anaemia, constipation, hepatic pain, nausea, pulmonary embolism, angina pectoris, depression, eyelid oedema, febrile neutropenia, gastrointestinal infection, haematuria, hyperhidrosis, lethargy, neutropenia, pain, sepsis, splenic rupture, and white blood cell count decreased in 1 patient (2%) each

in the dacarbazine group. Of these, a causal relationship to the study drug could not be ruled out for squamous cell carcinoma in 7 patients, pyrexia in 5 patients, squamous cell carcinoma of skin in 3 patients, ejection fraction decreased and malignant melanoma in 2 patients each, vomiting, atrial fibrillation, and hypotension in 1 patient each in the dabrafenib group; and nausea, vomiting, lethargy, neutropenia, and white blood cell count decreased in 1 patient each in the dacarbazine group.

Adverse events leading to study discontinuation occurred in 3% (5 of 187) of patients in the dabrafenib group and 3% (2 of 59) of patients in the dacarbazine group: hepatic pain, constipation, mitral valve disease, muscular weakness, myocardial infarction, and tricuspid valve disease in 1 patient (<1%) each; and hepatic pain, abdominal pain, haematuria, and subileus in 1 patient (2%) each in the respective groups. Of these, a causal relationship to the study drug could not be ruled out for mitral valve disease, muscular weakness, myocardial infarction, and tricuspid valve disease in 1 patient each in the dabrafenib group.

4.(iv).(9) Foreign phase III study (Study MEK115306)

Adverse events occurred in 97% (203 of 209) of patients in the dabrafenib/TRA group and 97% (205 of 211) of patients in the dabrafenib/placebo group. A causal relationship to the study drug could not be ruled out for the events in 87% (181 of 209) of patients and 90% (189 of 211) of patients in the respective groups. Those with an incidence of ≥15% in either group were as shown in the following table.

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

System organ class Preferred term (MedDRA/J ver17.0)	Number of patients (%)			
	Dabrafenib/TRA (n = 209)		Dabrafenib/placebo (n = 211)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	203 (97)	100 (48)	205 (97)	106 (50)
General disorders and administration site conditions				
Pyrexia	119 (57)	15 (7)	69 (33)	4 (2)
Fatigue	81 (39)	5 (2)	79 (37)	3 (1)
Chills	64 (31)	0	35 (17)	1 (<1)
Oedema peripheral	44 (21)	2 (<1)	19 (9)	1 (<1)
Skin and subcutaneous tissue disorders				
Rash	56 (27)	0	46 (22)	2 (<1)
Dry skin	26 (12)	0	34 (16)	0
Alopecia	18 (9)	0	59 (28)	0
Hyperkeratosis	15 (7)	0	74 (35)	1 (<1)
Palmar-plantar erythrodysaesthesia syndrome	11 (5)	1 (<1)	39 (18)	1 (<1)
Gastrointestinal disorders				
Nausea	72 (34)	1 (<1)	56 (27)	3 (1)
Diarrhoea	63 (30)	3 (1)	33 (16)	2 (<1)
Vomiting	52 (25)	2 (<1)	30 (14)	1 (<1)
Musculoskeletal and connective tissue disorders				
Arthralgia	54 (26)	2 (<1)	66 (31)	0
Pain in extremity	32 (15)	3 (1)	36 (17)	2 (<1)
Back pain	26 (12)	2 (<1)	34 (16)	5 (2)
Nervous system disorders				
Headache	69 (33)	1 (<1)	63 (30)	3 (1)
Respiratory, thoracic and mediastinal disorders				
Cough	44 (21)	0	44 (21)	0
Vascular disorders				
Hypertension	52 (25)	12 (6)	33 (16)	13 (6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Skin papilloma	4 (2)	0	46 (22)	0

Serious adverse events occurred in 42% (88 of 209) of patients in the dabrafenib/TRA group and in 37% (78 of 211) of patients in the dabrafenib/placebo group. Those reported by ≥3 patients in either group were pyrexia in 35 patients (17%), chills in 9 patients (4%), ejection fraction decreased in 9 patients (4%), basal cell carcinoma in 7 patients (3%), hypotension and pneumonia in 6 patients (3%) each, abdominal pain, ALT increased, confusional state, fatigue, pulmonary embolism, squamous cell carcinoma, syncope, and vomiting in 3 patients (1%) each in the dabrafenib/TRA group; and pyrexia in 15 patients (7%), basal cell carcinoma in 13 patients (6%), squamous cell carcinoma of skin in 11 patients (5%), squamous cell carcinoma in 9 patients (4%), ejection fraction decreased in 5 patients (2%),

chills and anaemia in 3 patients (1%) each in the dabrafenib/placebo group. Of these, a causal relationship to the study drug could not be ruled out for pyrexia in 35 patients, chills in 9 patients, ejection fraction decreased in 7 patients, basal cell carcinoma in 6 patients, confusional state, hypotension, and squamous cell carcinoma in 3 patients each, and abdominal pain, ALT increased, fatigue, syncope, and vomiting in 2 patients each in the dabrafenib/TRA group; and pyrexia in 14 patients, basal cell carcinoma in 10 patients, squamous cell carcinoma and squamous cell carcinoma of skin in 9 patients each, ejection fraction decreased in 5 patients, and chills in 3 patients in the dabrafenib/placebo group.

Adverse events leading to study discontinuation occurred in 11% (24 of 209) of patients in the dabrafenib/TRA group and in 7% (14 of 211) of patients in the dabrafenib/placebo group. Those reported by ≥3 patients in either group were pyrexia in 5 patients (2%) and ejection fraction decreased in 3 patients (1%) in the dabrafenib/TRA group and ejection fraction decreased in 3 patients (1%) in the dabrafenib/placebo group, and a causal relationship to the study drug could not be ruled out for all of these events.

4.(iv).(10) Foreign phase III study (Study MEK116513)

Adverse events occurred in 98% (343 of 350) of patients in the dabrafenib/TRA group and in 99% (345 of 349) of patients in the Vem group; a causal relationship to the study drug could not be ruled out for the events in 91% (320 of 350) of patients and 98% (342 of 349) of patients in the respective groups. Those with an incidence of ≥15% in either group were as shown in the following table.

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

System organ class Preferred term (MedDRA/J ver17.0)	Number of patients (%)			
	Dabrafenib/TRA (n = 350)		Vem (n = 349)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	343 (98)	186 (53)	345 (99)	224 (64)
General disorders and administration site conditions				
Pyrexia	184 (53)	15 (4)	73 (21)	2 (<1)
Chills	110 (31)	3 (<1)	27 (8)	0
Fatigue	101 (29)	4 (1)	115 (33)	6 (2)
Asthenia	55 (16)	5 (1)	57 (16)	4 (1)
Gastrointestinal disorders				
Nausea	121 (35)	1 (<1)	125 (36)	2 (<1)
Diarrhoea	112 (32)	4 (1)	131 (38)	1 (<1)
Vomiting	101 (29)	4 (1)	53 (15)	3 (<1)
Nervous system disorders				
Headache	101 (29)	4 (1)	77 (22)	2 (<1)
Vascular disorders				
Hypertension	92 (26)	48 (14)	84 (24)	33 (9)
Musculoskeletal and connective tissue disorders				
Arthralgia	84 (24)	3 (<1)	178 (51)	15 (4)
Myalgia	58 (17)	0	51 (15)	4 (1)
Skin and subcutaneous tissue disorders				
Rash	76 (22)	4 (1)	149 (43)	30 (9)
Pruritus	30 (9)	0	75 (21)	3 (<1)
Dry skin	29 (8)	0	62 (18)	1 (<1)
Alopecia	20 (6)	0	137 (39)	1 (<1)
Hyperkeratosis	15 (4)	0	86 (25)	2 (<1)
Photosensitivity reaction	13 (4)	0	78 (22)	1 (<1)
Palmar-plantar erythrodysaesthesia syndrome	8 (2)	0	55 (16)	1 (<1)
Respiratory, thoracic and mediastinal disorders				
Cough	69 (20)	0	34 (10)	0
Investigations				
ALT increased	48 (14)	9 (3)	61 (17)	15 (4)
Metabolism and nutrition disorders				
Decreased appetite	42 (12)	2 (<1)	70 (20)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Skin papilloma	6 (2)	0	80 (23)	2 (<1)

ALT: Alanine aminotransferase

Serious adverse events were observed in 37% (131 of 350) of patients in the dabrafenib/TRA group and in 35% (122 of 349) of patients in the Vem group. Those reported by ≥4 patients in either group were pyrexia in 49 patients (14%), ejection fraction decreased in 24 patients (7%), chills in 13 patients (4%), dehydration in 8 patients (2%), vomiting in 7 patients (2%), urinary tract infection in 6 patients (2%), ALT increased, hyponatraemia, and hypotension in 5 patients (1%) each, erysipelas, hepatic enzyme increased, nausea, pulmonary embolism, and renal failure in 4 patients (1%) each in the dabrafenib/TRA group; and squamous cell carcinoma in 33 patients (9%), keratoacanthoma in 21 patients (6%), squamous cell carcinoma of skin in 17 patients (5%), ALT increased in 8 patients (2%), pyrexia, blood bilirubin increased, and hepatic enzyme increased in 6 patients (2%) each, AST increased in 5 patients (1%), atrial fibrillation, malignant melanoma, pericarditis, and pneumonia in 4 patients (1%) each in the Vem group. Of these, a causal relationship to the study drug could not be ruled out for pyrexia in 47 patients, ejection fraction decreased in 21 patients, chills in 12 patients, dehydration in 8 patients, vomiting in 6 patients, hypotension in 5 patients, ALT increased and hyponatraemia in 4 patients each, hepatic enzyme increased, nausea, and renal failure in 3 patients each, and urinary tract infection in 2 patients in the dabrafenib/TRA group; and squamous cell carcinoma in 33 patients, keratoacanthoma in 21 patients, squamous cell carcinoma of skin in 16 patients, ALT increased in 7 patients, blood bilirubin increased in 6 patients, pyrexia, AST increased, and hepatic enzyme increased in 5 patients each, and atrial fibrillation and malignant melanoma in 3 patients each in the Vem group.

Adverse events leading to study discontinuation occurred in 13% (44 of 350) of patients in the dabrafenib/TRA group and in 12% (41 of 349) of patients in the Vem group. Those reported by ≥4 patients in either group were pyrexia in 12 patients (3%) and ejection fraction decreased in 10 patients (3%) in the dabrafenib/TRA group; and arthralgia in 7 patients (2%), AST increased in 5 patients (1%), and ALT increased in 4 patients (1%) in the Vem group. A causal relationship to the study drug could not be ruled out for all events.

4.(iv).(11) Foreign phase I study (Study BRF112680)

4.(iv).(11).1) Dose escalation phase

Adverse events occurred in 100% (5 of 5) of patients in Cohort 1/2 (dabrafenib 12 or 35 mg QD), 100% (9 of 9) of patients in Cohort 3 (dabrafenib 35 mg BID), 100% (14 of 14) of patients in Cohort 4 (dabrafenib 70 mg BID), 90% (9 of 10) of patients in Cohort 5 (dabrafenib 100 mg BID), 100% (20 of 20) of patients in Cohort 6 (dabrafenib 100 mg TID), 100% (20 of 20) of patients in Cohort 7 (dabrafenib 150 mg BID), 100% (20 of 20) of patients in Cohort 8 (dabrafenib 200 mg BID), 100% (10 of 10) of patients in Cohort 9 (dabrafenib 300 mg BID), and 83% (5 of 6) of patients in Cohort 10 (dabrafenib 75/150 mg BID). A causal relationship to the study drug could not be ruled out were for the events in 80% (4 of 5) of patients, 78% (7 of 9) of patients, 93% (13 of 14) of patients, 90% (9 of 10) of patients, 90% (18 of 20) of patients, 85% (17 of 20) of patients, 90% (18 of 20) of patients, 100% (10 of 10) of patients, and 83% (5 of 6) of patients in the respective groups.

Serious adverse events were observed in 60% (3 of 5) of patients in Cohort 1/2, 22% (2 of 9) of patients in Cohort 3, 50% (7 of 14) of patients in Cohort 4, 10% (1 of 10) of patients in Cohort 5, 30% (6 of 20) of patients in Cohort 6, 40% (8 of 20) of patients in Cohort 7, 50% (10 of 20) of patients in Cohort 8, 80% (8 of 10) of patients in Cohort 9, and 33% (2 of 6) of patients in Cohort 10. Those reported by ≥2 patients in any cohort were squamous cell carcinoma in 2 patients (14%) in Cohort 4, squamous cell carcinoma in 5 patients (25%) and pneumonia in 2 patients (10%) in Cohort 6, squamous cell carcinoma in 3 patients (15%) and pyrexia in 3 patients (15%) in Cohort 7, squamous cell carcinoma in 4 patients (20%) and pyrexia in 2 patients (10%) in Cohort 8, and squamous cell carcinoma in 2 patients (20%) in Cohort 9. Of these, a causal relationship to the study drug could not be ruled out for squamous cell carcinoma in 2 patients in Cohort 4, squamous cell carcinoma in 5 patients in Cohort 6, squamous cell carcinoma in 3 patients and pyrexia in 2 patients in Cohort 7, squamous cell carcinoma in 4 patients and pyrexia in 2 patients in Cohort 8, and squamous cell carcinoma in 2 patients in Cohort 9.

There were no adverse events leading to study discontinuation.

4.(iv).(11).2) Cohort expansion phase

Adverse events occurred in 100% (30 of 30) of patients in Cohort A (patients with malignant melanoma treated with dabrafenib 150 mg BID), 100% (20 of 20) of patients in Cohort B (patients with solid

tumors other than malignant melanoma treated with dabrafenib 150 mg BID), and 100% (20 of 20) of patients in Cohort C (patients with malignant melanoma treated with dabrafenib 50 mg BID). A causal relationship to the study drug could not be ruled out for the events in 100% (30 of 30) of patients, 85% (17 of 20) of patients, and 90% (18 of 20) of patients in the respective groups.

Serious adverse events occurred in 23% (7 of 30) of patients in Cohort A, 35% (7 of 20) of patients in Cohort B, and 25% (5 of 20) of patients in Cohort C. Those reported by ≥2 patients in any cohort were pyrexia in 3 patients (10%), fatigue, dehydration, and syncope in 2 patients (7%) each in Cohort A, and squamous cell carcinoma in 2 patients (10%) in Cohort C. Of these, a causal relationship to the study drug could not be ruled out for pyrexia in 3 patients and fatigue in 1 patient in Cohort A and squamous cell carcinoma in 2 patients in Cohort C.

There were no adverse events leading to study discontinuation.

4.(iv).(12) Foreign phase I/II study (Study BRF113220) (phase I part)
4.(iv).(12).1) Part A
Adverse events occurred in all 8 patients; a causal relationship to the study drug could not be ruled out for the events in all patients.

Adverse events with an incidence of ≥30% were rash in 6 patients (75%), nausea, vomiting and fatigue in 5 patients (63%), decreased appetite in 4 patients (50%), diarrhoea, chills, pyrexia, cough, and skin papilloma in 3 patients (38%) each. Of these, nausea in 1 patient was Grade ≥3.

Serious adverse events occurred in 63% (5 of 8) of patients. They were nausea in 2 patients (25%), cellulitis, convulsion, diplopia, dysphagia, haemorrhage intracranial, headache, neck pain, pericarditis, rectal haemorrhage, squamous cell carcinoma, upper airway obstruction, vision blurred, vomiting, and wound infection in 1 patient (13%) each. Of these, a causal relationship to the study drug could not be ruled out for squamous cell carcinoma in 1 patient.

An adverse event leading to study discontinuation, convulsion, occurred in 13% (1 of 8) of patients, and its causal relationship to the study drug was ruled out.

4.(iv).(12).2) Part B
Adverse events occurred in all patients (6 patients in the dabrafenib 75 mg BID/TRA 1 mg QD group [B-1 group], 23 patients in the dabrafenib 150 mg BID/TRA 1 mg QD group [B-2 group], 27 patients in the dabrafenib 150 mg BID/TRA 1.5 mg QD group [B-3 group], and 79 patients in the dabrafenib 150 mg BID/TRA 2 mg QD group [B-4 group]). A causal relationship to the study drug could not be ruled out for the events in 100% (6 of 6) of patients, 96% (22 of 23) of patients, 100% (27 of 27) of patients, and 91% (72 of 79) of patients in the respective groups. Those with an incidence of ≥40% in any group were as shown in the following table.

Adverse events with an incidence of ≥40% in any group

System organ class Preferred term (MedDRA/J ver15.0)	Number of patients (%)							
	B-1 (n = 6)		B-2 (n = 23)		B-3 (n = 27)		B-4 (n = 79)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	6 (100)	3 (50)	23 (100)	14 (61)	27 (100)	12 (44)	79 (100)	50 (63)
General disorders and administration site conditions								
Pyrexia	4 (67)	0	12 (52)	1 (4)	14 (52)	1 (4)	55 (70)	6 (8)
Fatigue	4 (67)	0	13 (57)	2 (9)	12 (44)	2 (7)	39 (49)	5 (6)
Chills	3 (50)	1 (17)	10 (43)	1 (4)	11 (41)	0	38 (48)	1 (1)
Gastrointestinal disorders								
Nausea	2 (33)	0	10 (43)	1 (4)	11 (41)	0	39 (49)	1 (1)
Nervous system disorders								
Headache	3 (50)	0	10 (43)	0	8 (30)	0	25 (32)	0
Respiratory, thoracic and mediastinal disorders								
Cough	3 (50)	0	3 (13)	0	9 (33)	0	20 (25)	0
Metabolism and nutrition disorders								
Decreased appetite	3 (50)	0	1 (4)	0	4 (15)	0	19 (24)	1 (1)

Serious adverse events occurred in 52% (12 of 23) of patients in the B-2 group; 44% (12 of 27) of patients in the B-3 group; and 56% (44 of 79) of patients in the B-4 group. Those reported by ≥2 patients in any group were pyrexia in 4 patients (17%), squamous cell carcinoma of skin and asthenia in 2 patients (9%) each in the B-2 group; pyrexia in 6 patients (22%), chills, hypotension, dehydration, squamous cell carcinoma of skin, confusional state, convulsion, and dizziness in 2 patients (7%) each in the B-3 group; and pyrexia in 19 patients (24%), chills in 13 patients (16%), hypotension in 5 patients (6%), dehydration in 4 patients (5%), ejection fraction decreased in 4 patients (5%), basal cell carcinoma in 3 patients (4%), anaemia, dyspnoea, failure to thrive, hyperbilirubinaemia, partial seizures, and pulmonary embolism in 2 patients (3%) each in the B-4 group. Of these, a causal relationship to the study drug could not be ruled out for pyrexia and squamous cell carcinoma of skin in 2 patients each and asthenia in 1 patient in the B-2 group; pyrexia in 5 patients, chills and dizziness in 2 patients each, and hypotension, dehydration, and squamous cell carcinoma of skin in 1 patient each in the B-3 group; and pyrexia in 18 patients, chills in 13 patients, ejection fraction decreased in 3 patients, dehydration and hyperbilirubinaemia in 2 patients each, and basal cell carcinoma in 1 patient in the B-4 group.

Adverse events leading to study discontinuation were noted in 8% (6 of 79) of patients in the B-4 group. Those reported by ≥2 patients were nausea and vomiting in 2 patients (3%) each, and a causal relationship to the study drug could not be ruled out for either event.

4.(iv).(12).3) Part D

Adverse events occurred in 100% (15 of 15) of patients in the dabrafenib 75 mg BID group (D-1 group), 100% (15 of 15) of patients in the dabrafenib 150 mg BID group (D-2 group), 100% (41 of 41) of patients in the dabrafenib 75 mg BID/TRA 2 mg QD group (D-3 group), and 97% (38 of 39) of patients in the dabrafenib 150 mg BID/TRA 2 mg QD group (D-4 group). A causal relationship to the study drug could not be ruled out for the events in 100% (15 of 15) of patients, 100% (15 of 15) of patients, 95% (39 of 41) of patients, and 95% (37 of 39) of patients, respectively. Those with an incidence of ≥30% in any group were as shown in the following table.

Adverse events with ≥30% incidence in any group

System organ class Preferred term (MedDRA/J ver15.0)	Number of patients (%)							
	D-1 (n = 15)		D-2 (n = 15)		D-3 (n = 41)		D-4 (n = 39)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	15 (100)	4 (27)	15 (100)	11 (73)	41 (100)	22 (54)	38 (97)	21 (54)
General disorders and administration site conditions								
Pyrexia	10 (67)	2 (13)	8 (53)	2 (13)	19 (46)	1 (2)	22 (56)	2 (5)
Chills	7 (47)	0	8 (53)	0	13 (32)	0	20 (51)	1 (3)
Fatigue	7 (47)	0	3 (20)	0	21 (51)	2 (5)	13 (33)	0
Gastrointestinal disorders								
Nausea	5 (33)	0	8 (53)	0	23 (56)	1 (2)	19 (49)	1 (3)
Vomiting	2 (13)	0	6 (40)	0	20 (49)	1 (2)	17 (44)	0
Diarrhoea	4 (27)	0	5 (33)	0	15 (37)	0	7 (18)	1 (3)
Abdominal pain	5 (33)	0	2 (13)	0	5 (12)	0	1 (3)	0
Musculoskeletal and connective tissue disorders								
Arthralgia	9 (60)	0	7 (47)	0	14 (34)	0	14 (36)	0
Skin and subcutaneous tissue disorders								
Rash	5 (33)	0	5 (33)	0	12 (29)	0	15 (38)	0
Rash macular	5 (33)	0	0	0	3 (7)	0	1 (3)	0
Nervous system disorders								
Headache	5 (33)	0	3 (20)	0	7 (17)	1 (2)	14 (36)	0
Blood and lymphatic system disorders								
Anaemia	0	0	6 (40)	1 (7)	7 (17)	1 (2)	7 (18)	1 (3)

Serious adverse events occurred in 47% (7 of 15) of patients in the D-1 group, 80% (12 of 15) of patients in the D-2 group, 54% (22 of 41) of patients in the D-3 group, and 64% (25 of 39) of patients in the D-4 group. Those reported by ≥3 patients in any group were pyrexia and chills in 6 patients (40%) each and ALT increased, AST increased, and blood ALP increased in 3 patients (20%) each in the D-1 group; pyrexia in 5 patients (33%) and chills in 4 patients (27%) in the D-2 group; pyrexia in 12 patients (29%) and chills in 5 patients (12%) in the D-3 group; and pyrexia in 16 patients (41%), chills in 15 patients (38%), cytokine release syndrome in 4 patients (10%), and hypotension in 3 patients (8%) in the D-4 group. Of these, a causal relationship to the study drug could not be ruled out for pyrexia and chills in 6 patients each, ALT increased, AST increased, and blood ALP increased in 2 patients each in the D-1 group; pyrexia and chills in 4 patients each in the D-2 group; pyrexia in 11 patients and chills in 4 patients in the D-3 group; and pyrexia in 16 patients, chills in 15 patients, and cytokine release syndrome in 4 patients in the D-4 group.

Adverse events leading to study discontinuation occurred in 27% (4 of 15) of patients in the D-2 group, 10% (4 of 41) of patients in the D-3 group, and 10% (4 of 39) of patients in the D-4 group. They were pulmonary embolism, colorectal cancer, completed suicide, and optic ischaemic neuropathy in 1 patient (7%) each in the D-2 group; pulmonary embolism in 2 patients (5%), fatigue and mental disorder in 1 patient (2%) each in the D-3 group; and glioblastoma, headache, influenza like illness, liver function test abnormal, nausea, uveitis, and vomiting in 1 patient (3%) each in the D-4 group. Of these, a causal relationship to the study drug could not be ruled out for colorectal cancer and optic ischaemic neuropathy in 1 patient each in the D-2 group; fatigue in 1 patient in the D-3 group; and glioblastoma, headache, influenza like illness, liver function test abnormal, nausea, uveitis, and vomiting in 1 patient each in the D-4 group.

4.(iv).(13) Foreign phase II study (Study BRF113929)

Adverse events occurred in 91% (81 of 89) of patients in Cohort A (patients without history of local treatment for brain metastasis) and in 95% (79 of 83) of patients in Cohort B (patients with history of local treatment for brain metastasis). A causal relationship to the study drug could not be ruled out for the events in 82% (73 of 89) of patients and 82% (68 of 83) of patients, respectively. Those with an incidence of ≥20% in either cohort were as shown in the following table.

Adverse events with an incidence of ≥20% in either cohort

System organ class Preferred term (MedDRA/J ver16.0)	Number of patients (%)			
	Cohort A (n = 89)		Cohort B (n = 83)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	81 (91)	38 (43)	79 (95)	43 (52)
Skin and subcutaneous tissue disorders				
Hyperkeratosis	24 (27)	0	23 (28)	1 (1)
Rash	18 (20)	0	16 (19)	0
General disorders and administration site conditions				
Pyrexia	26 (29)	0	23 (28)	1 (1)
Fatigue	19 (21)	0	27 (33)	2 (2)
Nervous system disorders				
Headache	30 (34)	2 (2)	23 (28)	1 (1)
Gastrointestinal disorders				
Nausea	19 (21)	2 (2)	27 (33)	2 (2)
Vomiting	20 (22)	1 (1)	18 (22)	3 (4)
Musculoskeletal and connective tissue disorders				
Arthralgia	18 (20)	0	14 (17)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Skin papilloma	18 (20)	0	11 (13)	0

Serious adverse events occurred in 29% (26 of 89) of patients in Cohort A and in 37% (31 of 83) of patients in Cohort B. Those reported by ≥2 patients in either cohort were squamous cell carcinoma in 6 patients (7%), pyrexia in 4 patients (4%), ejection fraction decreased in 3 patients (3%), haemorrhage intracranial, headache, cerebral haemorrhage, atrial fibrillation, neutropenia, and pulmonary embolism in 2 patients (2%) each in Cohort A; and pyrexia in 9 patients (11%), squamous cell carcinoma in 7 patients (8%), haemorrhage intracranial and hypotension in 3 patients (4%) each, and headache, chills, convulsion, fatigue, pancytopenia, and vomiting in 2 patients (2%) each in Cohort B. Of these, a causal relationship to the study drug could not be ruled out for squamous cell carcinoma in 6 patients, pyrexia in 3 patients, ejection fraction decreased in 2 patients, headache and neutropenia in 1 patient each in Cohort A; and squamous cell carcinoma and pyrexia in 7 patients, chills, hypotension, pancytopenia, and vomiting in 2 patients each, and convulsion and fatigue in 1 patient each in Cohort B.

Adverse events leading to study discontinuation occurred in 3% (3 of 89) of patients in Cohort A and in 4% (3 of 83) of patients in Cohort B. They were cerebral haemorrhage, ejection fraction decreased, and epilepsy in 1 patient (1%) each in Cohort A; and pancytopenia, intracranial tumour haemorrhage, and lymphopenia in 1 patient (1%) each in Cohort B. Of these, a causal relationship to the study drug could not be ruled out for ejection fraction decreased in 1 patient in Cohort A and in pancytopenia and lymphopenia in 1 patient each in Cohort B.

4.(iv).(14) Foreign phase II study (Study BRF113710)

Adverse events occurred in 93% (86 of 92) of patients, and a causal relationship to the study drug could not be ruled out for the events in 86% (79 of 92) of patients. Those with an incidence of ≥15% were as shown in the following table.

Adverse events with an incidence of ≥15%

System organ class Preferred term (MedDRA/J ver14.0)	Number of patients (%) Dabrafenib group (n = 92)	
	All Grades	Grade ≥3
All adverse events	86 (93)	33 (36)
Skin and subcutaneous tissue disorders		
Hyperkeratosis	25 (27)	1 (1)
Musculoskeletal and connective tissue disorders		
Arthralgia	30 (33)	1 (1)
General disorders and administration site conditions		
Pyrexia	22 (24)	0
Fatigue	20 (22)	1 (1)
Gastrointestinal disorders		
Nausea	18 (20)	1 (1)
Vomiting	14 (15)	1 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Skin papilloma	14 (15)	0
Nervous system disorders		
Headache	19 (21)	2 (2)

Serious adverse events occurred in 27% (25 of 92) of patients. Those reported by ≥2 patients were basal cell carcinoma in 4 patients (4%), squamous cell carcinoma in 4 patients (4%), squamous cell carcinoma of skin in 4 patients (4%), anaemia and pyrexia in 3 patients (3%) each, non-cardiac chest pain and vomiting in 2 patients (2%) each. Of these, a causal relationship to the study drug could not be ruled out for basal cell carcinoma, squamous cell carcinoma, and squamous cell carcinoma of skin in 4 patients each, and anaemia, pyrexia, and non-cardiac chest pain in 1 patient each.

An adverse event leading to study discontinuation, pancytopenia, occurred in 1% (1 of 92) of patients and its causal relationship to the study drug was ruled out.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted 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 for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted 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 for the data submitted in the new drug application (5.3.5.2: MEK116885). PMDA concluded that the conducted clinical studies were generally in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted application documents. The following was noted during the investigations carried out by some of the participating medical institutions although they did not significantly affect the overall evaluation of the study. These were notified to the head of the pertinent medical institutions for improvement.

Matters to be improved

Medical institutions

- Protocol deviations (blood sampling for blood biomarker test not performed, blood sampling for PK analysis not performed in patients who showed abnormal vision)

IV. Overall Evaluation

On the basis of the submitted data, the efficacy of dabrafenib in the treatment of patients with unresectable malignant melanoma with a mutation in v-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene has been demonstrated and its safety is acceptable in view of its observed benefits. Dabrafenib is a drug product containing a new active ingredient that inhibits tumor growth by inhibiting serine/threonine kinase of BRAF V600 mutations, and thus have a clinical significance as a treatment option for unresectable malignant melanoma with *BRAF* mutations. Dosage and administration, post-marketing investigations, etc., will be further discussed at the Expert Discussion.

This application may be approved if dabrafenib is not considered to have particular problems based on comments from the Expert Discussion.

Review Report (2)

January 19, 2016

I. Product Submitted for Registration

[Brand name]	Tafinlar Capsules 50 mg
	Tafinlar Capsules 75 mg
[Non-proprietary name]	Dabrafenib Mesilate
[Applicant]	Novartis Pharma K.K.
[Date of application]	April 27, 2015

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, 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) Efficacy

As a result of its review in "4.(iii).B.(2) Efficacy" of the Review Report (1), PMDA concluded that dabrafenib mesilate (hereinafter referred to as dabrafenib) monotherapy and concomitant use of dabrafenib with trametinib dimethyl sulfoxide (TRA) (dabrafenib/TRA) are both effective in patients with unresectable malignant melanoma with v-raf murine sarcoma viral oncogene homolog B1 (BRAF) with mutations in valine-encoding codon 600 (BRAF V600 mutations), as demonstrated by the results of the following 2 foreign phase III studies, etc.

- Study BRF113683 (BRAKE-3 study):
  The study was conducted to compare the efficacy and safety between dabrafenib and dacarbazine (DTIC) in patients with unresectable malignant melanoma with BRAF V600 mutations. The results showed the superiority of dabrafenib to DTIC in the progression-free survival (PFS) assessed by the investigator, the primary endpoint.

- Study MEK116513 (COMBI-V study):
  The study was conducted to compare the efficacy and safety between dabrafenib/TRA and vemurafenib (Vem) in patients with unresectable malignant melanoma with BRAF V600 mutations. The results showed the superiority of dabrafenib/TRA to Vem in the overall survival (OS), the primary endpoint.

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

(2) Safety

In the review of "4.(iii).B.(3) Safety" of the Review Report (1) PMDA concluded that adverse events requiring particular caution in dabrafenib treatment are secondary malignant tumor, cardiac disorders, hepatic impairment, pyrexia, and eye disorders, and that particular caution should be exercised against possible occurrence of these adverse events in dabrafenib treatment.

With these premises, PMDA has concluded that dabrafenib is well tolerated provided that adverse events are monitored and controlled, and dose reduction, interruption, discontinuation, and other actions are appropriately taken by a physician with sufficient knowledge and experience of cancer chemotherapy.

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

(3) Clinical positioning

In the review of "4.(iii).B.(4) Clinical positioning" of the Review Report (1), PMDA concluded that dabrafenib and dabrafenib/TRA may be positioned as treatment options for patients with unresectable

malignant melanoma with BRAF V600 mutations. As for the choice between dabrafenib and dabrafenib/TRA, PMDA concluded that dabrafenib/TRA treatment is recommended in preference to dabrafenib monotherapy in patients with unresectable malignant melanoma with BRAF V600 mutations, based on the results of the foreign phase III study (Study MEK115306 [COMBI-D study]) which compared the efficacy and safety between dabrafenib and dabrafenib/TRA in the patient population with the same disease.

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

(4) Indication

In the review of "4.(iii).B.(5) Indication" of the Review Report (1), PMDA concluded that the indication should be "unresectable malignant melanoma with *BRAF* mutations," the Clinical Studies section of the package insert should include the types of *BRAF* mutations in patients investigated in the COMBI-V study, etc., and the Precautions for Indications section should include the following cautions.

[Precautions for Indications]

- Dabrafenib should be administered to patients who are confirmed to have *BRAF* mutations through tests performed by a well-experienced pathologist or testing laboratory. An approved *in vitro* diagnostic should be used for the test.

- The physician should thoroughly understand the description in the "Clinical Studies" section and be fully aware of the efficacy and safety of dabrafenib before selecting patients appropriate to be treated.

- The efficacy and safety of dabrafenib as adjuvant chemotherapy have not been established.

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

On the above basis, PMDA instructed the applicant to describe the indication as above and provide the above caution statement in Indications and Precautions for Indications sections, to which the applicant agreed.

(5) Dosage and administration

In the review of "4.(iii).B.(6) Dosage and administration" of the Review Report (1), PMDA concluded that the dosage and administration and Precautions for Dosage and Administration sections should include the following description.

[Dosage and administration]

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.

[Precautions for Dosage and Administration]

- The efficacy and safety of dabrafenib in concomitant use with antineoplastic agents other than TRA have not been established.

- Postprandial administration of dabrafenib has been reported to cause a decrease in C_{max} and AUC. Taking dabrafenib during the time range from 1 hour before up to 2 hours after meals should be refrained in order to avoid food effect.

- If adverse drug reaction occurs after the use of dabrafenib, dabrafenib should be interrupted, discontinued, or continued at a reduced dose with reference to the following criteria. If spinocellular carcinoma (squamous cell carcinoma of skin) or new primary malignant melanoma occurs, dabrafenib may be continued without interruption or dose reduction after appropriate actions such as surgical resection.

Criteria for interruption, dose reduction, and discontinuation

NCI-CTCAE*-assessed Grade	Action
Intolerable Grade 2, or Grade 3	Interruption After improvement to Grade ≤1, resume administration at a dose 1 level lower.
Grade 4	In principle, administration should be discontinued. If deemed desirable for the patient, administration may be resumed at a dose 1 level lower after improvement to Grade ≤1.

*: Grade assessed by NCI-CTCAE v4.0

Guide for dose adjustment

Dose adjustment level	Dose
Usual dose	150 mg/dose (twice daily)
1-level dose reduction	100 mg/dose (twice daily)
2-level dose reduction	75 mg/dose (twice daily)
3-level dose reduction	50 mg/dose (twice daily)
4-level dose reduction	Discontinue

*: If adverse drug reactions are sufficiently controlled by appropriate measures, the dose may be increased by the reverse process of dose reduction.

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

On the above basis, PMDA instructed the applicant to describe the indication as above and provide the caution statement in the Dosage and Administration and Precautions for Dosage and Administration sections. The applicant agreed.

(6) Risk management plan (draft)

In order to investigate the safety, etc., of dabrafenib in routine clinical use after market launch, the applicant plans to conduct an all-case post-marketing surveillance covering all patients treated with dabrafenib/TRA, with the planned sample size of 200 patients and 1-year follow-up period.

In the review of "4.(iii).B.(7) Post-marketing investigations" of the Review Report (1), PMDA concluded that, because of the extremely limited safety information currently available for Japanese patients treated with dabrafenib, a post-marketing surveillance should be conducted in all patients treated with dabrafenib in order to collect safety information promptly and without bias, and thereby to provide the safety information obtained to healthcare professionals in clinical settings as soon as possible.

On the basis of incidence of adverse drug reactions in clinical studies in and out of Japan, PMDA considers that the following adverse events requiring particular caution in dabrafenib/TRA treatment should be included in the priority items of the surveillance: Cardiac disorders, hepatic dysfunction, pyrexia, eye disorders, spinocellular carcinoma, secondary malignant tumor other than spinocellular carcinoma, and rhabdomyolysis. The number of patients to be surveyed and the follow-up period should be reconsidered in light of the nature of the priority items.

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

On the basis of the above review, PMDA asked the applicant to re-examine the surveillance plan.

The applicant's response:

- Cardiac disorders, hepatic dysfunction, pyrexia, eye disorders, spinocellular carcinoma, secondary malignant tumor other than spinocellular carcinoma, and rhabdomyolysis will be described as the primary survey items.
- The surveillance will be performed in 200 patients (those treated with dabrafenib/TRA), a similar sample size as that of the dabrafenib/TRA group in the foreign clinical study.
- In light of the time of onset of adverse events (those described as primary items) in the foreign clinical study, the follow-up period should be 1 year.

PMDA's view:
PMDA accepted the applicant's response regarding the surveillance plan (draft). However, if there are additional matters requiring investigation during the surveillance, the necessity of changing the sample size and additional surveys should be considered.

Also, on the basis of the above discussions, PMDA concluded that the current draft risk management plan should include safety specifications and efficacy specifications and that additional pharmacovigilance activities and risk minimization activities should be conducted as described in the following tables.

Safety and efficacy specifications in the proposed risk management plan

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Spinocellular carcinoma • Secondary malignant tumor other than spinocellular 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		
• Efficacy in routine clinical use		

Outline of additional pharmacovigilance activities and risk minimization activities in the proposed risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey	• Provide information based on the early post-marketing phase vigilance • Prepare and distribute materials for healthcare professionals • Prepare and supply materials for patients

Outline of the proposed specified use-results survey plan

Objective	Investigate the safety etc., of dabrafenib in routine clinical use
Method	All-case surveillance by central registration method
Patients population	All patients treated with dabrafenib
Follow-up period	1 year
Planned sample size	200 patients treated with dabrafenib/TRA
Main investigation items	Priority investigation items: Cardiac disorder, hepatic dysfunction, pyrexia, eye disorder, spinocellular carcinoma, secondary malignant tumor other than spinocellular carcinoma, and rhabdomyolysis Other investigation items: Patient characteristics, use status of dabrafenib and TRA, concomitant drugs and therapies, adverse events (including changes in laboratory values)

III. Overall Evaluation

As a result of the above review, PMDA has concluded that this product may be approved after modifying the indication as well as the dosage and administration as shown below with the following conditions for approval, on the premise that (i) cautions are provided in the package insert and information concerning the proper use of dabrafenib is provided appropriately after market launch, and (ii) the proper use of dabrafenib is ensured under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions capable to deal with emergencies appropriately. Since dabrafenib is an orphan drug, the re-examination period is 10 years. The drug substance and the drug product are both classified as a powerful drug. The drug product is not classified as a biological product or as a specified biological product.

[Indication] Unresectable malignant melanoma with *BRAF* mutations

[Dosage and administration] 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.

[Conditions for approval] The applicant is required to:

1. Develop and appropriately implement a risk management plan; and

2. Conduct a drug use-results survey covering all Japanese patients treated with the product after market launch until data from a certain number of patients have been accumulated to identify 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, since an extremely limited number of patients participated in the Japanese clinical study of the product.

[Warnings]

Dabrafenib should be administered only to patients who require chemotherapy of dabrafenib and only under the supervision of a physician with sufficient knowledge and experience in cancer chemotherapy at a medical institution where adequate facilities for the management of emergencies are available. Before initiating treatment with dabrafenib, the attending physician should fully explain the efficacy and risks of dabrafenib to the patient or the family members, and obtain informed consent from them.

[Contraindications]

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]

1. Dabrafenib should be administered to patients who are confirmed to have *BRAF* mutations through tests performed by a well experienced pathologist or testing laboratory. An approved *in vitro* diagnostic should be used for the test.

2. The physician should thoroughly understand the description in the "Clinical Studies" section and be fully aware of the efficacy and safety of Tafinlar before selecting patients to be treated with dabrafenib.

3. The efficacy and safety of dabrafenib as adjuvant chemotherapy have not been established.

[Precautions for Dosage and Administration]

1. The efficacy and safety of dabrafenib in concomitant use with antineoplastic agents other than trametinib have not been established.

2. Postprandial administration of dabrafenib has been reported to cause a decrease in C_{max} and AUC. Taking dabrafenib during the time range from 1 hour before up to 2 hours after meal should be refrained in order 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. If spinocellular carcinoma (squamous cell carcinoma of skin) or new primary malignant melanoma occurs, dabrafenib may be continued without interruption or dose reduction after appropriate actions such as surgical resection are taken.

Criteria for interruption, dose reduction, and discontinuation

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

1) Grade assessed by NCI-CTCAE v4.0

Guide for dose adjustment

Dose adjustment level[2)]	Dose
Usual dose	150 mg/dose (twice daily)
1-level dose reduction	100 mg/dose (twice daily)
2-level dose reduction	75 mg/dose (twice daily)
3-level dose reduction	50 mg/dose (twice daily)
4-level dose reduction	Discontinue

2) If adverse drug reactions are sufficiently controlled by appropriate measures, the dose may be increased by the reverse process of dose reduction.