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]	Mekinist Tablets 0.5 mg Mekinist Tablets 2 mg
[Non-proprietary name]	Trametinib Dimethyl Sulfoxide (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 is classified as a poisonous drug and the drug product is classified as a powerful drug. 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

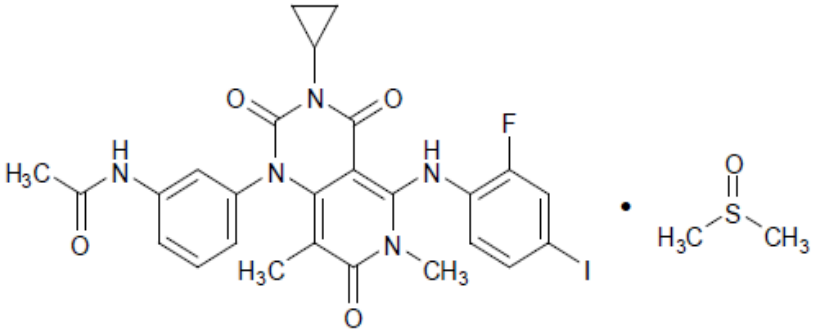
January 21, 2016

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]	Mekinist Tablets 0.5 mg Mekinist Tablets 2 mg
[Non-proprietary name]	Trametinib Dimethyl Sulfoxide
[Applicant]	Novartis Pharma K.K.
[Date of application]	April 27, 2015
[Dosage form/Strength]	Tablets, each containing 0.5635 or 2.254 mg of Trametinib Dimethyl Sulfoxide (equivalent to 0.5 or 2 mg of trametinib, respectively).
[Application classification]	Prescription drug, (1) Drugs with a new active ingredient

[Chemical structure]



Molecular formula: $C_{26}H_{23}FIN_5O_4 \bullet C_2H_6OS$
Molecular weight: 693.53
Chemical name:

N-(3-{3-Cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl}phenyl)acetamide—(methylsulfinyl)methane (1:1)

[Items warranting special mention]

Orphan drug (Designation No. 317 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]	Mekinist Tablets 0.5 mg Mekinist Tablets 2 mg
[Non-proprietary name]	Trametinib Dimethyl Sulfoxide
[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 performed on cardiac disorders, hepatic dysfunction, pyrexia, eye disorders, and rhabdomyolysis 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 2 mg of trametinib administered orally once daily under fasted conditions in combination with dabrafenib. 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 using 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.

Review Report (1)

November 13, 2015

I. Product Submitted for Registration

[Brand name]	Mekinist Tablets 0.5 mg Mekinist Tablets 2 mg
[Non-proprietary name]	Trametinib Dimethyl Sulfoxide
[Applicant]	Novartis Pharma K.K.
[Date of application]	April 27, 2015
[Dosage form/Strength]	Tablets, each containing 0.5635 or 2.254 mg of Trametinib Dimethyl Sulfoxide (equivalent to 0.5 or 2 mg of trametinib, respectively).
[Proposed indication]	Malignant melanoma with BRAF V600 mutations
[Proposed dosage and administration]	The usual adult dosage is 2 mg of trametinib administered orally once 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.

Trametinib dimethyl sulfoxide (hereinafter referred to as trametinib) is a low molecular weight compound discovered by Japan Tobacco Inc., and is considered to suppress the growth of tumors with BRAF V600 mutations, by inhibiting phosphorylation of MEK1 and MEK2.

1.(2) Development history etc.

A phase I clinical study (Study MEK111054) of trametinib monotherapy in patients with advanced solid tumors or lymphoma was initiated by GlaxoSmithKline (UK) in July 2008. Subsequently, a phase III study (Study MEK114267) was initiated to compare trametinib monotherapy with dacarbazine or paclitaxel monotherapy in patients with unresectable malignant melanoma with BRAF V600 mutations in November 2010.

Also, a phase I/II study (Study BRF113220) of a combination therapy of trametinib and dabrafenib mesilate (DAB) (trametinib/DAB) in patients with advanced solid tumors 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 trametinib/DAB combination therapy and DAB monotherapy in May 2012; and Study MEK116513 comparing trametinib/DAB combination therapy and vemurafenib monotherapy in June 2012.

An application for trametinib monotherapy was submitted in the US and EU in August 2012 and February 2013, respectively, with the results of Study MEK114267 as the pivotal data. Trametinib monotherapy was approved in the US in May 2013 for the following indication: “MEKINIST 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." It was also approved in the EU in June 2014 for the following indication: "Trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy."

An application for trametinib/DAB was submitted in the US in July 2013 with the results of Study BRF113220 as the pivotal data, and approved in January 2014 with the following indication: "MEKINIST, in combination with dabrafenib, 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 MEKINIST in combination with dabrafenib." In the EU, an application for trametinib/DAB was submitted in February 2013 simultaneously with the application for trametinib 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 trametinib/DAB combination was withdrawn in March 2014. Subsequently, with the results of Study MEK116513 made available, an application for trametinib/DAB was submitted in April 2015 and was approved in August 2015 after the indication was changed to "Trametinib as monotherapy or in combination with dabrafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy."

As of September 2015, trametinib is approved in 35 countries or regions for the indication of malignant melanoma.

In Japan, a phase I study (Study MEK114784) of trametinib monotherapy in patients with advanced solid tumors was initiated by the applicant in January 2011. Also, a phase I/II study (Study MEK116885) of trametinib/DAB in patients with advanced solid tumors or unresectable malignant melanoma, both with BRAF V600 mutations, was initiated in August 2013.

Recently, an application for trametinib has been submitted with the results of Studies MEK114267, MEK115306, MEK116513, and MEK116885 as the pivotal data.

Trametinib was designated as an orphan drug in April 2015 with the expected indication of "malignant melanoma with $BRAF^{V600}$ mutations" (Designation No. 17 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 crystalline powder. The general properties of the drug substance including description, solubility, hygroscopicity, melting point, thermal analysis, pH, dissociation constant, partition coefficient, crystalline polymorphism, and particle size, were determined. The drug substance is a dimethyl sulfoxide adduct, for which only 1 crystalline form is confirmed. Trametinib is confirmed to form solvates with solvents other than dimethyl sulfoxide and, under specific conditions, to form [redacted]. However, during [redacted] in the manufacturing process of the drug substance, no solvate-forming solvents other than dimethyl sulfoxide are used, and only dimethyl sulfoxide adduct is formed in commercial process.

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

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

The drug substance is synthesized using [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

*1: [redacted]

*2: [redacted]

*3: [redacted]

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

*1: [redacted]

*2: [redacted]

*3: [redacted]

*4: [redacted]

*5: [redacted]

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

The proposed specifications for the drug substance consist of content, description, identification (IR), purity (related substance [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 photolabile.

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 (double-layered, with desiccant*1) + aluminum bag + polyethylene container*2	48 months
Accelerated	3 commercial-scale batches	40°C	75%RH		6 months

*1: Desiccant was placed between the double layers of polyethylene bag.
*2: Packaged in a polyethylene container in order to protect from impacts during storage and transport.

On the basis of study results above, a retest period of [redacted] months has been proposed for the drug substance when stored at room temperature and protected from light in a double-layered polyethylene bag (with desiccant between the double layers of polyethylene bag) in an aluminum bag. The long-term testing will be continued up to [redacted] months.

2.A.(2) Drug product

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

The drug product is film-coated tablets, each containing 0.5635 or 2.254 mg of the drug substance (0.5 or 2 mg trametinib, respectively). The drug product contains, as excipients, D-mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, sodium lauryl sulfate, light anhydrous silicic acid, magnesium stearate, [redacted] (only in Mekinist Tablets 0.5 mg), and [redacted] (only in Mekinist Tablets 2 mg).

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

The drug product is manufactured through processes comprising blending, tableting, film-coating, and packaging/labeling.

Mainly the following were investigated using a QbD approach.

- [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] were identified 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] and [redacted] are defined as the critical process steps, and process control parameters and control limits are defined for each of them.

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 (content uniformity test [HPLC]), purity (related substances [HPLC]), [redacted] ([redacted]), water content, dissolution (HPLC), 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 photolabile.

Stability studies of drug product

Study	Primary batch	Temperature	Humidity	Storage configuration	Storage period
Long-term	3 commercial-scale batches	5°C	-	High-density polyethylene bottle/polypropylene cap with aluminum-laminated film (with desiccant)	24 months
Accelerated	3 commercial-scale batches	25°C	60%RH		24 months

On the above basis, the shelf life of 24 months has been proposed for the drug product when stored at 5 ± 3°C together with the desiccant in the high-density polyethylene bottle stoppered with a polypropylene cap with aluminum-laminated film and thus protected from light. The long-term testing will be continued up to [redacted] months.

2.B Outline of the review by PMDA

Based on the submitted data and on the results of the following reviews, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

Control of [redacted] of the drug substance in the drug product

The applicant's explanation on [redacted]:

[redacted].

[redacted]

*: [redacted]

PMDA asked the applicant to explain the reason for considering [redacted].

The applicant's response:

[redacted]

PMDA accepted the applicant's explanation.

3. Non-clinical data

In non-clinical studies, trametinib dimethyl sulfoxide (hereinafter referred to as trametinib), its free base (trametinib [free base]), and trametinib acetic acid (trametinib [acetic acid]) were used. The dose and concentration of trametinib and trametinib (acetic acid) are expressed as free-base equivalents.

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 mitogen-activated protein kinase/extracellular signal-regulated kinase kinase (Reports UH2008/00021/00, UH2008/00046/00 [Reference data], UH2008/00047/00 [Reference data], UH2008/00051/03, and UH2007/00097/02)

The inactive forms of mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) kinase (MEK1 and MEK2), are activated when phosphorylated by v-raf murine sarcoma viral oncogene product homolog B1 (BRAF), and subsequently phosphorylates ERK. The protein encoded by *BRAF* gene is a serine/threonine kinase, and the inhibitory effects of trametinib on phosphorylation (activation) of MEK1 and MEK2 (recombinant proteins) by a mutant type BRAF V600E, a mutation of BRAF at codon 600 originally coding for valine (BRAF V600 mutation), were determined based on the transfer of ^{33}P-labeled adenosine triphosphate (ATP). Also, the inhibitory effects of trametinib on ERK phosphorylation by activated forms of MEK1 and MEK2 were investigated in a similar manner. The IC_{50} values of trametinib are shown in the following table.

Inhibitory effects of trametinib on phosphorylation of MEK

Kinase	n	IC_{50} (nmol/L)
Inactive MEK1*	19	0.7
Inactive MEK2*	2	0.97, 0.77
Activated MEK1	20	13.2
Activated MEK2	2	12.4, 9.3

Mean (individual values for n = 2) *: Activated by BRAF V600E mutation

Phosphorylation of serine residues at 218 and 222 (S218 and S222) is essential in the kinase activity of MEK1 *(J Biol Chem*. 1994;269:19067-19073). The phosphorylation site of MEK1 that is inhibited by trametinib was investigated by mass spectrometry. The result showed that trametinib inhibited phosphorylation of S218, but not S222.

The inhibitory effects of trametinib and trametinib (free base) on phosphorylation of kinases were investigated in panels of 43 and 171 types of kinases, respectively by time-resolved fluorescence/fluorescence resonance energy transfer etc. Trametinib at 10 μmol/L did not inhibit any of the kinases tested by >50%.

3.(i).A.(1).2) Effects on MEK (Report UH2008/00021/00)

Binding of trametinib (free base) to the inactive MEK1 was investigated by surface plasmon resonance analysis (Biacore). The dissociation constant (Kd) of trametinib and the inactivated MEK1 was 0.019 nmol/L.

The inhibitory effect of trametinib on ERK-phosphorylation activity of the activated MEK1 was determined based on the transfer of ^{33}P-labeled ATP. The relationship between the inhibitory activity and ATP concentration showed that trametinib inhibits the activated MEK1 by an allosteric mechanism noncompetitive with respect to ATP.

3.(i).A.(1).3) Inhibitory effects on phosphorylation of ERK and MEK5 (Reports UH2007/00097/02 and UH2008/00051/03)

MEK5 is highly homologous with MEK1 and MEK2 in the kinase domain and the ATP-binding site. The inhibitory effect of trametinib on ERK5 phosphorylation by platelet-derived growth factor (PDGF)-stimulated MEK5 was determined by Western blotting in mouse embryonic skin-derived cell line NIH3T3 based on the amount of phosphorylation of ERK5. The results showed that trametinib had no inhibitory effect.

The inhibitory effect of trametinib on phosphorylation of ERK in tumor tissue was determined by Western blotting in athymic mice (nude mice) subcutaneously transplanted with human malignant melanoma-derived cell line A375P F11 expressing a BRAF V600 mutation. The animals were orally given a single dose of trametinib (1, 3 mg/kg), and the results showed the inhibitory effect of trametinib.

3.(i).A.(1).4) Cell cycle arrest and apoptosis induction (Report UH2008/00045/00 [Reference data])

The effects of trametinib (free base) on cell cycle were analyzed by flow cytometry in human colon cancer-derived cell lines HT29 and Colo205, both expressing BRAF V600E mutation. Trametinib (free base) arrested the cell cycle of both cell lines at G0/G1 phase.

The effects of trametinib (free base) on the expression levels of cell cycle-related proteins (cyclin A1, cyclin D1, and cyclin D2, c-Myc, p15, and p27) and on phosphorylation of retinoblastoma (RB) protein were determined in HT29 cell line by Western blotting. Trametinib (free base) decreased the protein levels of cell cycle activators (cyclin A1, cyclin D1, and cyclin D2, and c-Myc), increased the protein levels of cell cycle inhibitors (p15 and p27), and decreased the amount of phosphate in RB protein.

The apoptosis-inducing effect of trametinib (free base) was evaluated in HT29 and Colo205 cell lines based on DNA fragmentation, caspase 3, caspase 7, and caspase 9 activation, and PARP activation. The results showed that trametinib had apoptosis-inducing activity.

3.(i).A.(1).5) Studies of cell growth-inhibitory effects of trametinib and on related factors (Reports UH2007/00097/02 and 2014N205857_00)

The relationship between ERK phosphorylation and the tumor growth-inhibitory effects of trametinib was determined in 21 cell lines derived from human malignant tumor by Western blotting. Trametinib inhibited the growth of 4 of 5 strains in the highest quartile of ERK phosphorylation among the 21 cell lines tested.

The relationship between the expression level of mRNA in dual specificity phosphatase 6 (DUSP6), which inactivates ERK by dephosphorylation (*FEBS J*. 2013;280:489-504), and the growth-inhibitory effects of trametinib was investigated in 218 cell lines derived from human malignant tumor. Trametinib inhibited the growth of most cell lines expressing DUSP6 mRNA, showing a correlation between the expression of DUSP6 mRNA and the growth-inhibitory effects of trametinib.

The growth-inhibitory effects of trametinib were determined in 272 cell lines derived from human malignant tumor expressing (i) wild-type BRAF and RAS, (ii) mutated BRAF, or (iii) mutated RAS by measuring intracellular ATP levels or counting viable cells after nuclear staining. The growth-inhibitory effects of trametinib were observed in 28% (46/167*) of cell lines expressing wild-type BRAF and RAS, in 88% (35/40*) of cell lines expressing mutated BRAF, and in 72% (47/65*) of cell lines expressing mutated RAS.

*: Number of cell lines inhibited/total number of cell lines tested

3.(i).A.(1).6) Growth-inhibitory effects on BRAF V600 mutant cell lines derived from human malignant melanoma (Reports UH2007/00097/02, 2011N116395_00, 2011N116394_00, and UH2008/00051/03)

i) *In vitro*

(a) Human malignant melanoma-derived cell lines

The growth-inhibitory effects of trametinib were determined in 17 BRAF V600 mutant cell lines derived from human malignant melanoma by measuring intracellular ATP levels. The IC_{50} values of trametinib are shown in the following table.

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

Cell line derived from malignant melanoma	BRAF mutation	n	IC_{50} (nmol/L)
UACC-257	V600E	8	1.4 ± 0.3
SK-MEL-1		5	2.5 ± 0.7
COLO-829		11	4.2 ± 1.7
A101D		8	5.6 ± 2.0
SK-MEL-24		4	9.5 ± 8.9
SK-MEL-5		6	4.0 ± 1.8
SK-MEL-3		7	>1000
A2058		9	>1000
SK-MEL-28		4	1.7 ± 0.5
UACC-62		9	2.4 ± 2.1
A375P F11		9	6.7 ± 4.2
WW165	V600K	4	0.3 ± 0.0
IGR-1		7	62.3 ± 43.8
YUMAC		4	0.5 ± 0.1
YULAC		4	0.8 ± 0.4
YUSIT1		4	0.7 ± 0.2
WM-115	V600D	4	9.3 ± 6.7

Mean ± standard deviation (SD)

(b) Human malignant melanoma-derived cell lines that have acquired resistance to dabrafenib mesilate

A375P F11 and YUSIT1 cell lines were cultured in the presence of a BRAF inhibitor dabrafenib mesilate (DAB), and cell lines that had acquired resistance to DAB were isolated. The growth-inhibitory effects of trametinib were determined in these resistant cell lines, by measuring intracellular ATP levels. The growth-inhibitory effects of trametinib on DAB-resistant A375P F11 and YUSIT1 cell lines were ≤1/10 and approximately 1/7 to 1/3 those on their respective parent cell lines.

ii) *In vivo*

The tumor growth-inhibitory effect of trametinib was investigated in nude mice subcutaneously transplanted with A375P F11 cell line. Starting 15th day post-transplantation when the tumor volume reached approximately 120 to 450 mm^3, trametinib (1, 3, 10 mg/kg) was administered orally once daily (QD) for 14 consecutive days, and tumor volume was measured on Day 13 of trametinib treatment. Compared with the vehicle control group (0.5% hydroxypropyl methylcellulose [HPMC] and 0.2% polyoxyethylene sorbitan monooleate [Tween 80]), the trametinib 1 and 3 mg/kg groups showed a statistically significant inhibition of tumor growth (the table below).

Tumor growth-inhibitory effect of trametinib

Group	Tumor volume*1 (mm^3)	Median tumor volume (mm^3)	Rate of tumor growth inhibition (%)	*P* value in ANCOVA	*P* value in step-down Bonferroni method
Vehicle	705.3 ± 363.0	486	0	-	-
Trametinib 1 mg/kg	215.9 ± 162.2	245	49.6	0.0033	0.0066
Trametinib 3 mg/kg	113.4 ± 81.3	108	77.8	<0.0001	0.0006
Nogitecan 10 mg/kg*2	22.1 ± 11.7	23	95.4	-	-

n = 7; -, Not applicable or not performed; *1, Mean ± SD; *2, Positive control, administered intraperitoneally every 4 days, 4 times in total

3.(i).A.(1).7) Pharmacological effects of trametinib metabolites (Reports 2012N139081_00 and 2012N148387_00)

Pharmacological effects of M5 (deacetylation of trametinib) and M7 (oxygenation of M5), the major trametinib metabolites in human plasma, were examined, and the following results were obtained.

- The inhibitory effects of trametinib and M5 on BRAF V600E-catalyzed phosphorylation of the inactive MEK1 and on activated MEK1-catalyzed phosphorylation of ERK2 were determined based on ^{33}P-labeled ATP transfer. The inhibitory effects of M5 on inactive MEK1 and on activated MEK1 were comparable to those observed with trametinib.

- The inhibitory effects of trametinib and M5 on phosphorylation of ERK and the growth-inhibitory effects of trametinib and M5 were determined in SK-MEL-28 cell line by Western blotting and by measuring intracellular ATP levels, respectively. The ERK phosphorylation-inhibiting effect and growth-inhibitory effect of M5 were comparable to those observed with trametinib.

- The inhibitory effects of trametinib and M7 on activated MEK1-catalyzed phosphorylation of ERK2 were determined based on ^{33}P-labeled ATP transfer. The inhibitory activity of M7 on activated MEK1-catalyzed ERK2 phosphorylation was approximately 1/10 that of trametinib.

3.(i).A.(2) Secondary pharmacodynamics (Reports CD2007/01300/00 [Reference data], UH2007/00097/02, UH2008/00021/00, and UH2008/00047/00 [Reference data])

The inhibitory effects of trametinib (10 μmol/L) on the binding of ligands to 30 different types of receptors, channels, and enzymes were investigated. An inhibitory effect >50% to any of the receptors etc., was not observed in trametinib.

The growth-inhibitory effects of trametinib were determined by measuring intracellular ATP levels in human umbilical vein endothelial cells (HUVEC) in the presence and absence of vascular endothelial growth factor (VEGF). Trametinib had no growth-inhibitory effect (IC_{50}: 10,000 nmol/L) on HUVEC growth in the absence of VEGF, but exhibited a growth-inhibitory effect (IC_{50}: 4 nmol/L) in the presence of VEGF.

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

3.(i).A.(3).1) Effects on central nervous system (Report CD2007/01303/00 [non-GLP, Reference data])

A single oral dose of trametinib (100 mg/kg) was administered to rats (n = 4), and the effects of trametinib on clinical signs and neurobehavior were investigated. Reduced body weight gain, decreased locomotor activity, prone position, eyelid ptosis, diarrhoea, piloerection, and mydriasis were noted.

The applicant's explanation:
The findings observed in this study were considered to be caused by the aggravation of clinical signs. Since the dose of trametinib administered to these animals (100 mg/kg) corresponds to 2500 times the clinical dose (2 mg) administered to a patient weighing 50 kg, trametinib is unlikely to pose safety problems related to the above findings in clinical use.

3.(i).A.(3).2) Effects on cardiovascular system

i) Effects on human *ether-a-go-go*-related gene potassium current (Report FD2007/00151/00)

The effects of trametinib on human *ether-a-go-go*-related gene (hERG) potassium current was investigated in human embryonic kidney-derived cell line HEK293 transfected with hERG. Trametinib inhibited hERG potassium current with IC_{50} of 1.54 μmol/L (947.7 ng/mL).

ii) Effects on cardiovascular system of dogs (Reports CD2007/01301/00 [non-GLP, Reference data] and CD2007/00962/00)

Trametinib (1 mg/kg) was administered intravenously over 10 minutes to dogs (n = 3) in a crossover manner, and the effects of trametinib on electrocardiogram (PR interval, QRS duration, RR interval, QT interval, and QTc interval), blood pressure, and heart rate were investigated. Trametinib had no effects on these parameters.

A single oral dose of trametinib (0.025, 0.038, 0.075 mg/kg) was administered to dogs (n = 4) in a Latin square design, and the effects on electrocardiogram (PR interval, QRS duration, RR interval, and QT interval), arterial pressure, heart rate, and body temperature were assessed. Trametinib had no effects on electrocardiogram, arterial pressure, heart rate, or body temperature.

iii) Effects on left ventricular coronary perfusion preparation of rabbits (Report UH2007/00108/00 [non-GLP])

The effects of trametinib (0.3, 1, 10, 30 μmol/L) on QT interval and transmural dispersion of repolarization or Tp-e interval were investigated in left ventricular coronary perfusion preparation of rabbits (n = 4). Trametinib had no effects on QT interval. Isometric contraction force in rabbits given trametinib 10 and 30μmol/L decreased by 16.3% and 64.8%, respectively, and, Tp-e interval decreased in rabbits given 30 μmol/L.

The applicant's explanation:
Inhibition of hERG potassium current, decreased isometric contraction force, and decreased Tp-e interval are unlikely to be related to heart-related events observed in clinical studies, given the following findings: (a) Effects on hERG potassium current was observed at 1.54 μmol/L (947.7 ng/mL), and effects on isometric contractive force and on Tp-e interval in left ventricular coronary perfusion preparation of rabbits were observed at 10 μmol/L (6154 ng/mL), (b) following multiple administrations of trametinib 2 mg QD to Japanese patients with solid tumors, C_{max} was 25.5 ng/mL [see "4.(ii).A.(1) Japanese clinical studies"], and (c) protein non-binding rate of trametinib is <4% [see "3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells"].

Trametinib-induced risk of cardiac disorders will be described in "4.(iii).B.(3).2) Cardiac disorder," on the basis of clinical study results etc.

3.(i).A.(3).3) Effects on respiratory system (Report CD2007/00963/00)

A single oral dose of trametinib (0.016, 0.0625, 0.125 mg/kg) was administered to rats (n = 4/group) in a Latin square design, and the effects of trametinib on respiratory rate, tidal volume, minute ventilation, airway resistance, and body temperature were evaluated. Trametinib at 0.125 mg/kg caused a mild transient decrease in body temperature. Trametinib had no effects on other parameters tested.

Since decreased body temperature observed in rats was mild and transient, the applicant explained that trametinib is unlikely to pose safety problems related to decreased body temperature in clinical use.

3.(i).A.(4) Pharmacodynamic and pharmacokinetic 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 trametinib alone, DAB alone, and their combination (trametinib/DAB) were determined by measuring 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

trametinib/DAB are shown in the following table. The applicant explained that the results demonstrated the enhancement of growth inhibition (CI <1.1) by trametinib/DAB in 13 of 17 cell lines.

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

Malignant melanoma-derived tumor cell line	BRAF mutation	n	IC_{50} (nmol/L)			CI
			DAB	Trametinib	Trametinib/ DAB[*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 DAB when trametinib and DAB were coadministered in a molar ratio of 1:10; *2, Mean

The apoptosis-inducing effects of trametinib/DAB (molar ratio 1:10) were investigated in A101D, A2058, A375P F11, SK-MEL-1, SK-MEL-3, UACC-62, UACC-257, and YUMAC cell lines. No enhanced induction of apoptosis was observed in the treatment with trametinib/DAB compared with the treatment with trametinib or DAB alone.

ii) ***In vivo***

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

The tumor growth-inhibitory effect of trametinib/DAB was evaluated in nude mice subcutaneously transplanted with A375P F11 cell line. Starting 4th week post-transplantation when tumor volume reached 100 to 300 mm^3, animals orally received trametinib (0.3 mg/kg) alone, DAB (30, 300 mg/kg) alone, or trametinib/DAB (0.3 mg/kg + 30 mg/kg) QD for 90 days, and then, tumor volume was measured. The applicant explained that tumor growth-inhibitory effect was enhanced in the trametinib/DAB group compared with the trametinib or DAB alone group, 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 trametinib, DAB, or any DAB metabolites (hydroxylated form, carboxylated form, demethylated form [3 DAB 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 trametinib, DAB, or 3 DAB metabolites did not increase cytokine concentrations.

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

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

Mechanism of action and efficacy of trametinib
The applicant's explanation for the mechanism of action of trametinib against BRAF V600 mutation-positive malignant melanoma:
With the BRAF mutations, serine/threonine kinase is constitutively activated, resulting in the constitutive 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 trametinib inhibits MEK1 and MEK2 phosphorylation (i.e., activation) by a BRAF V600 mutation and ERK phosphorylation by MEK1 and MEK2 [see "3.(i).A.(1).1) Inhibitory effects on phosphorylation of kinases such as mitogen-activated protein kinase/extracellular signal-regulated kinase kinase"], leading to inhibition of the growth of BRAF V600 mutant cell lines derived from human malignant melanoma [see "3.(i).A.(1).6) Growth-inhibitory effects on BRAF V600 mutant cell lines derived from human malignant melanoma"]. 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 trametinib against BRAF V600 mutation-positive malignant melanoma can be expected.

The applicant's explanation of the efficacy of trametinib/DAB in patients with malignant melanoma with BRAF V600 mutations:
Rapidly acquired resistance to BRAF inhibitor (DAB and vemurafenib) monotherapies is of a clinical concern. Re-activation of MAP pathway by mutations in RAS and MEK is suspected to be the mechanism of the acquired resistance to BRAF inhibitors (*Nature*. 2011;468:968-972, *N Engl J Med.* 2011;364:772-774, etc.). Trametinib inhibits MEK, and trametinib/DAB demonstrated, compared with each monotherapy, enhanced growth inhibition of BRAF V600 mutation-positive malignant melanoma cell lines [see "3.(i).A.(4).1) Growth-inhibitory effects on BRAF V600 mutant cell lines derived from human malignant melanoma"].

Therefore, the applicant expects that trametinib/DAB is effective on BRAF V600 mutation-positive malignant melanoma.

PMDA accepted the applicant's explanation.

3.(ii) Summary of pharmacokinetic studies

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

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

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

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

Female mice received under fed conditions a single oral dose of trametinib acetic acid adduct 0.3, 1, 3 mg/kg or a single intravenous dose of trametinib free base 1 mg/kg, and plasma concentration of unchanged trametinib was determined (the table below). Bioavailability (BA) after oral administration of trametinib acetic acid adduct 1 mg/kg was 95%. C_{max} and AUC_{inf} of unchanged trametinib after oral administration increased more than dose-proportionally between 0.3 and 1 mg/kg groups, and almost dose-proportionally between 1 and 3 mg/kg groups. The applicant's explanation of the reason of these observations:
At low doses, metabolism of unchanged trametinib is saturated, whereas at high doses, solubility of trametinib acetic acid adduct decreases, resulting in decreased absorption rate, leading to unsaturated metabolism.

Male rats received under fed conditions a single oral dose of unpulverized trametinib 3 mg/kg, a single oral dose of trametinib acetic acid 0.1, 0.3, 1, 3 mg/kg, or a single intravenous dose of trametinib free base 1 mg/kg, and plasma concentration of unchanged trametinib was determined (the table below). BA of trametinib after oral administration of trametinib acetic acid 1 mg/kg was 29%. C_{max} and AUC_{inf} of unchanged trametinib after oral administration of trametinib acetic acid increased more than

proportionally to dose over the dose range tested. The applicant explained that these results were caused by saturation of the metabolism of unchanged trametinib at high doses.

Male dogs received under fasted conditions a single oral dose of trametinib acetic acid 0.3 mg/kg or a single intravenous dose of trametinib free base 0.3 mg/kg, and plasma concentration of unchanged trametinib was determined (the table below). BA of trametinib after oral administration of trametinib acetic acid was 86%.

Male cynomolgus monkeys received a single oral or intravenous dose of unpulverized trametinib 0.3 mg/kg under fasted conditions and blood concentration of unchanged trametinib was determined (the table below). BA of trametinib after oral administration of unpulverized drug substance was 49%.

PK parameters of unchanged trametinib in each animal species (single intravenous or oral administration)

Animal species	Dose (route of administration)	Sex	C_{max}*1 (ng/mL)	t_{max}*3 (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	Vd_{ss} (L/kg)
Mice	0.3 mg/kg*4 (orally)	F	123 ± 14.8	1.0 (1.0, 1.0)	1046*2	5.3*2	-	-
	1 mg/kg*4 (orally)	F	615 ± 108	1.0 (1.0, 1.0)	4492*2	4.4*2	-	-
	3 mg/kg*4 (orally)	F	1662 ± 111	1.0 (1.0, 2.0)	14,462*2	3.8*2	-	-
	1 mg/kg*5 (intravenously)	F	1074 ± 56.6	-	4739*2	3.7*2	3.5*2	0.9*2
Rats	0.1 mg/kg*4 (orally)	M	1.85 ± 0.62	2.0 (2.0, 8.0)	49.2 ± 6.15	19.0 ± 2.6	-	-
	0.3 mg/kg*4 (orally)	M	9.23 ± 0.62	8.0 (4.0, 8.0)	172 ± 6.15	7.8 ± 0.6	-	-
	1 mg/kg*4 (orally)	M	59.7 ± 20.9	4.0 (4.0, 8.0)	868 ± 277	5.4 ± 0.5	-	-
	3 mg/kg*4 (orally)	M	249 ± 32.0	4.0 (4.0, 4.0)	3699 ± 732	6.8 ± 2.7	-	-
	3 mg/kg*6 (orally)	M	289 ± 86.2	4.0 (4.0, 4.0)	3754 ± 677	5.5 ± 0.7	-	-
	1 mg/kg*5 (intravenously)	M	382 ± 32	-	3016 ± 308	6.1 ± 0.9	5.7 ± 0.5	2.9 ± 0.4
Dogs	0.3 mg/kg*4 (orally)	M	80 ± 12.3	2.0 (2.0, 4.0)	1723 ± 431	13.3 ± 3.2	-	-
	0.3 mg/kg*5 (intravenously)	M	103 ± 16.6	-	2031 ± 61.5	14.5 ± 4.1	2.5 ± 0	3.0 ± 0.8
Monkeys	0.3 mg/kg*6 (orally)	M	34 ± 16	0.8 (0.2, 1.0)	276 ± 197	-	-	-
	0.3 mg/kg*6 (intravenously)	M	122 ± 38	-	350 ± 117	6.7 ± 4.3	14.5 ± 4.9	5.1 ± 1.4

n = 3; Mean ± SD; -, Not calculated; *1, C_{5min} in intravenous administration; *2, Mean; *3, Median (range); *4, Trametinib acetic acid administration; *5, Trametinib free base administration; *6, Trametinib administration

Male rats orally received a single dose of trametinib free base or unpulverized 3 mg/kg under fed conditions, and plasma concentration of unchanged trametinib was determined. Mean C_{max} of unchanged trametinib after administration of trametinib free base or unpulverized was 22.0 and 319 ng/mL, respectively, and mean $AUC_{0\text{-}24h}$ was 423 and 3334 ng·h/mL, respectively, showing higher exposure to unchanged trametinib after administration of the unpulverized drug substance than after administration of trametinib (free base). The applicant explained that, in the subsequent development, trametinib, which is the dimethyl sulfoxide adduct, was used on the basis of above results.

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

Female mice orally received trametinib 0.1, 0.3, or 1 mg/kg QD for 14 days under fed conditions, and plasma concentration of unchanged trametinib was determined (the table below). C_{max} and $AUC_{0\text{-}24h}$ of trametinib on Day 7 were higher than those on Day 1, while C_{max} and $AUC_{0\text{-}24h}$ of unchanged trametinib on Day 7 were similar to those on Day 14. Therefore, the applicant explained that the steady-state pharmacokinetics is reached within 7 days after the start of treatment.

PK parameters of unchanged trametinib (female mice, 14-day repeated oral administration)

Time points	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
1	0.1	18.9	0.5	122
	0.3	98.5	2.0	705
	1	310	2.0	1604
7	0.1	29.6	2.0	349
	0.3	165	4.0	1747
	1	786	4.0	6911
14	0.1	23.3	2.0	347
	0.3	155	4.0	1431
	1	944	2.0	6785

N = 3//time point (each PK parameter was calculated from mean plasma trametinib concentration at each time point)

Male and female rats orally received trametinib 0.016, 0.031, 0.0625, 0.125 mg/kg QD for 3 weeks under fed conditions, and plasma concentration of unchanged trametinib was obtained (the table below). C_{max} and $AUC_{0\text{-}24h}$ of unchanged trametinib in females were higher than those in males. Both in males and in females, C_{max} and $AUC_{0\text{-}24h}$ of unchanged trametinib increased almost dose-proportionally within the dose range tested.

PK parameters of unchanged trametinib
(male and female rats, 3-week repeated oral administration)

Time points (Day)	Dose (mg/kg)	C_{max} (ng/mL)		t_{max}*1 (h)		$AUC_{0\text{-}24h}$ (ng·h/mL)	
		Male	Female	Male	Female	Male	Female
1	0.016	-	0.53, 0.66*2	-	1.0, 8.0*2	-	-
	0.031	0.78 ± 0.08	1.19 ± 0.13	2.0 (2.0, 2.0)	2.0 (1.0, 2.0)	2.46, 4.84*2	18.1 ± 2.01
	0.0625	2.16 ± 0.31	3.53 ± 1.22	8.0 (2.0, 8.0)	2.0 (2.0, 2.0)	33.3 ± 1.11	52.2 ± 8.66
	0.125	5.48 ± 0.71	11.2 ± 1.24	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	64.2 ± 23.7	193 ± 29.8
21	0.016	1.78 ± 0.33	3.33 ± 0.65	4.0 (2.0, 4.0)	2.0 (0.5, 4.0)	35.0 ± 4.24	60.2 ± 15.0
	0.031	3.5 ± 0.63	6.28 ± 1.06	4.0 (4.0, 8.0)	4.0 (1.0, 8.0)	64.2 ± 12.4	126 ± 23.2
	0.0625	7.78 ± 1.68	13.0 ± 3.14	4.0 (4.0, 4.0)	1.0 (1.0, 4.0)	129 ± 29.1	211 ± 71.3
	0.125	13.3 ± 1.35	29.4 ± 1.72	4.0 (2.0, 4.0)	4.0 (2.0, 4.0)	218 ± 32.4	460 ± 16.3

n = 3, Mean ± SD (individual values if n = 2); -, Not calculated; *1, Median (range); *2, n = 2

Male and female dogs orally received trametinib 0.0075, 0.015, 0.03 mg/kg QD for 13 weeks under fed conditions, and plasma concentration of unchanged trametinib was measured (the table below). No clear sex difference was observed in C_{max} or $AUC_{0\text{-}24h}$ of unchanged trametinib. C_{max} and $AUC_{0\text{-}24h}$ of unchanged trametinib increased almost dose-proportionally within the dose range tested, at all time points. C_{max} and $AUC_{0\text{-}24h}$ of unchanged trametinib at Week 4 were higher compared to those on Day 1. C_{max} and $AUC_{0\text{-}24h}$ of unchanged trametinib at Week 4 and Week 13 were similar to each other. Therefore, the applicant explained that the steady-state pharmacokinetics is reached within 4 weeks after the start of treatment.

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

Time points	Dose (mg/kg)	n	C_{max} (ng/mL)		t_{max}*1 (h)		AUC_{0-24h} (ng·h/mL)	
			Male	Female	Male	Female	Male	Female
Day 1	0.0075	4	0.84 ± 0.05	0.87 ± 0.20	0.5 (0.5, 0.5)	0.5 (0.5, 1.0)	-	-
	0.015	6	1.57 ± 0.37	2.44 ± 0.47	0.5 (0.5, 1.0)	0.5 (0.5, 0.5)	2.96 ± 0.74	6.98 ± 5.44
	0.03*2	6	4.63 ± 0.95	5.42 ± 2.72	0.5 (0.5, 1.0)	0.5 (0.5, 2.0)	28.9 ± 2.19	33.3 ± 8.59
Week 4	0.0075	4	2.55 ± 0.51	3.56 ± 0.90	0.5 (0.5, 1.0)	0.5 (0.5, 0.5)	46.0 ± 11.7	60.7 ± 14.5
	0.015	6	5.45 ± 0.66	7.73 ± 1.22	2.0 (0.5, 2.0)	0.5 (0.5, 1.0)	94.5 ± 11.9	116 ± 25.2
	0.03*2	6	8.91 ± 1.04*3	12.0 ± 2.85	1.0 (0.5, 2.0)*3	1.0 (0.5, 2.0)	131 ± 16.9*3	177 ± 55.2
Week 13	0.0075	4	2.32 ± 0.61	2.71 ± 0.66	1.0 (0.5, 2.0)	0.75 (0.5, 1.0)	45.6 ± 10.9	51.8 ± 12.2
	0.015	6	5.15 ± 1.06	7.24 ± 0.78	1.0 (0.5, 4.0)	0.5 (0.5, 1.0)	95.5 ± 28.2	107 ± 15.8
	0.03*2	6	8.42 ± 1.26*3	9.78 ± 1.18	1.0 (0.5, 2.0)*3	0.5 (0.5, 1.0)	128 ± 9.28*3	150 ± 30.6

Mean ± SD; -, Not calculated; *1, Median (range); *2, Because of toxicity in the 0.03 mg/kg group, administration was discontinued from Day 11 or 12 in females and from Day 12 in males, and resumed at a reduced dose of 0.0225 mg/kg from Day 21 or 22 in females and from Day 22 in males; *3, n = 5

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

Permeability of trametinib through the membrane of the digestive tract was investigated in dog kidney-derived cell line MDCKII 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 trametinib (0.08-8 μg/mL) from the apical surface to the basal surface ($P_{appA\rightarrow B}$) at pH 5.5 and 7.4 was 18.6 × 10^{-6} to 61.1 × 10^{-6} and 16.2 × 10^{-6} to 59.5 × 10^{-6} cm/sec, respectively, which was higher than $P_{appA\rightarrow B}$ of the positive control labetalol 10 μmol/L (3.4 × 10^{-6} and 16.0 × 10^{-6} cm/sec, respectively). Thus the applicant explained that trametinib has a high passive membrane permeability.

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

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

Pigmented male rats orally received a single dose of ^{14}C-labeled trametinib 1 mg/kg, and tissue distribution of radioactivity was determined by quantitative whole-body autoradiography.

Radioactivity was distributed in a wide range of tissues after oral administration, and tissue radioactivity concentration reached the maximum level at 2 or 4 hours after administration in most tissues. Radioactivity concentration was particularly high, ≥1000 ng Eq./g, in the kidneys, liver, renal cortex, adrenal cortex, Harderian gland, pancreas, and salivary gland. Tissue radioactivity concentration decreased to below the lower limit of quantitation (11.0 ng Eq./g) in all tissues including melanin-containing tissues (choroid plexus, uvea, meninges, and pigmented skin) within 35 days after administration. Radioactivity (16.4-31.7 ng Eq./g) was detected in the brain at 2 to 8 hours after administration, thus the applicant explained that the data suggest trametinib and/or its metabolites (trametinib-related substances) are also distributed into the brain to a minor extent. Specific binding of trametinib-related substances to melanin-containing tissues was not observed.

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

Plasma samples of rats, dogs, and humans were incubated with ^{14}C-labeled trametinib (1-50 ng/mL), or human plasma samples with trametinib metabolite M5 (deacetylate; 5-50 ng/mL), for 8 hours at 37°C, and plasma protein binding of trametinib and M5 was investigated by equilibrium dialysis. The plasma protein binding of trametinib was 97.5% to 99.1%, 94.5% to 98.5%, and 96.3% to 98.6%, respectively, in rats, dogs, and humans, and the plasma protein binding of M5 was ≥97.8% in humans. The protein binding of trametinib and M5 did not depend on trametinib concentration in any species tested.

α1-acid glycoprotein (20 μmol/L) or human serum albumin (700 μmol/L) was incubated with ^{14}C-labeled trametinib (1-50 ng/mL) for 8 hours at 37°C. The binding rate of trametinib to α1-acid glycoprotein and human serum albumin was 13.2% to 19.8% and 96.1% to 98.0%, respectively, showing that the binding rates do not depend on trametinib concentration. The applicant explained that the above results suggest that trametinib and trametinib-related substances bind mainly to albumin in human plasma.

Blood samples of mice, rats, dogs, monkeys, and humans were incubated with trametinib (0.5, 5 μg/mL) for 30 minutes at 37°C, and distribution of trametinib in blood cells was investigated. The blood/plasma ratio of trametinib was 0.70 to 0.75, 0.88 to 0.89, 0.54 to 0.59, 0.63 to 0.72, and 0.50 to 0.56, respectively, in mice, rats, dogs, monkeys, and humans.

The rate of distribution of trametinib (0.001-0.05 μg/mL) in blood cells derived from healthy adult subjects and from cancer patients was 48% to 83% and 49% to 92%, respectively, and the blood/plasma ratio was 1.10 to 3.38 and 1.25 to 7.92, respectively, showing no clear difference between healthy adult subjects and cancer patients. In both populations, the rate of distribution in blood cells and the blood/plasma ratio tended to decrease with increasing trametinib concentration. The applicant explained that these results were possibly caused by saturation of trametinib binding to blood cells at high trametinib concentrations.

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

The applicant's explanation:

Although placental transfer of trametinib was not investigated, such a possibility cannot be excluded since trametinib 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

Liver microsomes or hepatocytes of mice, rats, dogs, monkeys, and humans were incubated with trametinib (0.5 μmol/L) for 30 minutes at 37°C, and intrinsic clearance (CL_{int}) of trametinib was investigated. CL_{int} was calculated from the clearance rate of trametinib in each species. CL_{int} of trametinib in liver microsomes was 0.8, <0.5, <0.5, ≥21, and 0.9 mL/min/g, and CL_{int} of trametinib in hepatocytes was 3.4, <0.5, 2.6, 13, and 0.5 mL/min/g in the respective species and humans.

Hepatocytes of mice, rats, rabbits, dogs, monkeys, and humans were incubated with ^{14}C-labeled trametinib (12.5 μmol/L) for 24 hours at 37°C, and the produced metabolites of trametinib were investigated. The major trametinib-related substance detected was unchanged trametinib in the hepatocytes of rats, dogs, and humans; M5 in the hepatocytes of mice and rabbits; and M6 (glucuronide conjugate of M5) in the hepatocytes of monkeys. In human hepatocytes, M5, M6, and M7 (oxidized form of M5) were detected as trametinib metabolites.

Human liver microsomes were incubated with ^{14}C-labeled trametinib (10 μmol/L) for 60 minutes at 37°C to investigate the formation of reactive metabolites. If the amount of covalently bound metabolites was <50 pmol/mg, reactive metabolites were to be considered unlikely to be produced. The results showed that the amount of covalent binding of trametinib to human liver microsomes and that of acetaminophen, the positive control, were 36 and 129 pmol/mg, respectively. On the basis of the results, the applicant explained that trametinib is unlikely to produce reactive metabolites in liver microsomes.

Enzymes involved in the metabolism of trametinib in humans were investigated as described below. The results suggested that in humans, carboxyesterase (CES) 1b, CES1c, and CES2 are involved in metabolizing trametinib to M5, and cytochrome P450 (CYP) 3A4 is involved in metabolizing trametinib to M7, M12 (oxidized form), M17 (oxidized form), and M22 (unidentified). The applicant explained that CES-mediated pharmacokinetic interaction is unlikely to affect the PK of trametinib because pharmacokinetic interaction through CES inhibition is considered unlikely (*Xenobiotica*. 2007;37:736-752).

- Human liver microsomes were incubated with ^{14}C-labeled trametinib (5 μmol/L) in the presence or absence of inhibitors of CYP isoforms (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) for 60 minutes at 37°C to identify CYP isoforms involved in the metabolism of trametinib. In the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH) and in the absence of CYP inhibitors, metabolites of trametinib (M5, M7, M10 [deiodinated form], M12, M13 [demethylated form], M17, M20 [unidentified], M21 [unidentified], and M22) were detected at approximately 1% of the total radioactivity added. M7, M12, M17, and M22 were not detected in the

presence of azamulin, a CYP3A inhibitor.

- ^{14}C-labeled trametinib (5 μmol/L) was incubated with membrane vesicles of insect ovary-derived cell line Sf9 expressing human CYP isoform (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4) for 60 minutes at 37°C, in order to identify CYP isoforms involved in the metabolism of trametinib. In CYP3A4 expression system, M5, M7, M10, M12, M13, M15, M16 (oxidized form), M17, M20, M21, and M22 were detected in the presence of NADPH, and M5, M10, M15, M20, and M21 were detected in the absence of NADPH. In other CYP isoform-expression systems, trametinib was hardly metabolized.

- Trametinib (0.5 μmol/L) was incubated with recombinant human CES (CES1b, CES1c, or CES2), acetylcholinesterase (AChE), or butyrylcholinesterase (BChE) in the presence or absence of esterase inhibitor for 120 minutes at 37°C to identify enzyme(s) involved in the metabolism of trametinib to M5. The results showed that M5 was formed by CES1b, CES1c, and CES2, and that M5 formation was inhibited by CES inhibitors (bis-*p*-nitrophenyl phosphate, telmisartan, and loperamide) and by eserine, an inhibitor of CES2, AChE, and BChE.

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

A single oral dose of ^{14}C-labeled trametinib 1, 0.5, and 1 mg/kg was administered to 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. On the basis of the study results, the applicant explained that unchanged trametinib was the major trametinib-related substance present in plasma and feces of rats and dogs.

- In male and female rats, unchanged trametinib was the major trametinib-related substance detected in plasma, and it accounted for 63.6% to 85.5% in males and 79.2% to 93.8% in females of the total radioactivity in plasma up to 24 hours after treatment. Trametinib metabolites detected in plasma of both males and females were M5, M7, M12, and M13. The major trametinib-related substance detected in feces from 72 to 144 hours after treatment was unchanged trametinib (46.2% and 52.1%, respectively of the total radioactivity administered in males and females), and the detected trametinib metabolites were M5, M7, M13, M17, M16, and M12.

- In male and female dogs, unchanged trametinib was the major trametinib-related substance detected in plasma, and the percentage of unchanged trametinib in the total radioactivity in plasma up to 24 hours after treatment was 57.6% to 76.7% in males and 68.1% to 79.2% in females. Trametinib metabolites detected in plasma of both males and females were M5, M7, M12, and M10. Trametinib-related substances detected in feces up to 120 hours after treatment were unchanged trametinib (9.25% and 11.7%, respectively, of the total radioactivity administered in males and females), M7, M12, and M13 (sum of the 3 metabolites; 14.1% and 6.54%, respectively), M23 (oxidized form of deiodinated trametinib; 8.95% and 13.4%, respectively), and M24 (oxidized form; 4.21% and 1.87%, respectively). Trametinib-related substances detected in urine from 24 to 48 hours after treatment were unchanged trametinib, M12, M23, M24, and 4 unidentified metabolites (each ≤1.2%).

- In biliary-cannulated male rats, trametinib-related substances detected in the bile up to 48 hours after treatment (up to 72 hours in 1 of 3 animals) were M4 (glucuronidation of oxidized trametinib), M6 and M18 (glucuronidation of oxidized trametinib) (sum of the 3 metabolites; 11.8% of the total radioactivity administered), M2 (glucuronidation of oxidized trametinib; 3.1%), M5 (2.0%), and unchanged trametinib (0.9%).

^{14}C-labeled trametinib (30 mg/kg) was perfused from portal vein into the liver of male rats, and metabolites in bile were determined. Approximately 1% to 5% of radioactivity was detected in bile, consisting of unchanged trametinib, M2, M4, M5, M1 (unidentified), and M3 (unidentified).

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

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

Male and female rats, male and female dogs, and biliary cannulated male rats orally received a single dose of ^{14}C-labeled trametinib 1, 0.5, and 1 mg/kg, respectively, and the urinary, fecal, and biliary excretion rates (the percentage of administered radioactivity excreted) were evaluated. On the basis of the results, the applicant explained that trametinib is mainly excreted in feces via bile.

- In rats, urinary and fecal excretion rates up to 168 hours after treatment were 0.63% and 97.6%, respectively, in males and 0.91% and 82.8%, respectively, in females, showing no clear sex difference.

- In dogs, urinary and fecal excretion rates up to 168 hours after treatment were 6.74% and 58.96%, respectively, in males and 5.52% and 66.20%, respectively, in females, showing no clear sex difference.

- In biliary cannulated male rats, biliary, urinary, and fecal excretion rates up to 96 hours after treatment were 40.6%, 0.67%, and 50.5%, respectively.

After a single oral administration of trametinib (acetic acid) to rats and dogs, plasma concentration of unchanged trametinib did not show a bimodal time-course (a pattern that suggests enterohepatic circulation). On the basis of this and other observations, the applicant explained that trametinib is unlikely to undergo enterohepatic circulation.

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

The applicant's explanation:
Although excretion of trametinib in milk was not investigated, such a possibility cannot be excluded since trametinib 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, or CYP3A)* were incubated with human liver microsomes in the presence of trametinib (0.01-10 μmol/L), and the effects of trametinib on the metabolism of each CYP isoform substrate were investigated.

*: The substrates of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A used were, respectively, phenacetin, coumarin, bupropion, rosiglitazone, diclofenac, S-mephenytoin, bufuralol and midazolam, and atorvastatin and nifedipine.

- Trametinib inhibited metabolism of the substrates of CYP2C8, CYP2C9, and CYP2C19 (IC_{50}: 0.34, 4.1, and 5.0 μmol/L, respectively).

- In human liver microsomes preincubated with trametinib, metabolism of each CYP isoform substrate was not affected by NADPH added in the preincubation, and trametinib did not have any clear inhibitory effects on metabolism of any CYP isoform substrates tested.

The applicant's explanation for the possibility of trametinib-induced pharmacokinetic interactions mediated by the inhibition of CYP isoforms:
When multiple oral doses of trametinib 2 mg QD were administered to patients with malignant melanoma with BRAF V600 mutations, C_{max} of trametinib under a steady state was 0.04 μmol/L [see 4.(ii).A.(2).3) Foreign phase I/II study"], which suggests that trametinib is unlikely to cause pharmacokinetic interactions mediated by CYP2C9 or CYP2C19 inhibition in clinical use.

3.(ii).A.(5).2) Enzyme induction

The enzyme-inducing activity of trametinib was evaluated as described below, and the results showed that trametinib induces CYP3A4 and CYP2B6. However, taking account that C_{max} of trametinib under a steady state was 0.04 μmol/L when multiple oral doses of trametinib 2 mg QD were administered to patients with malignant melanoma with BRAF V600 mutations [see 4.(ii).A.(2).3) Foreign phase I/II study"]. The applicant explained that trametinib is unlikely to cause pharmacokinetic interactions

mediated by CYP3A4 or CYP2B6 in clinical use, given the concentration of trametinib required to induce CYP3A4 and CYP2B6.

- Human hepatoma-derived cell line HepG2 cotransfected with human pregnane X receptor (PXR) and luciferase reporter gene containing PXR-responsive region of *CYP3A4* gene promoter was treated with trametinib (0.0002-10 μmol/L), and CYP3A4-inducing activity of trametinib was investigated. Trametinib (10 μmol/L) induced 33.6% to 50.4% as much CYP3A4 as the positive control, rifampicin (10 μmol/L), did.

- Human hepatocytes were treated with trametinib (0.01-10 μmol/L), and mRNA expression levels of CYP1A2, CYP2B6, and CYP3A4 were examined. Trametinib at 10 μmol/L increased the mRNA expression levels of CYP3A4 and CYP2B6 by 69% and 75%, respectively, of the increments achieved by the positive controls (rifampicin [10 μmol/L] for CYP3A4, phenytoin [50 μmol/L] for CYP2B6). Trametinib at the maximum concentration tested did not affect the mRNA expression level of CYP1A2.

3.(ii).A.(5).3) Transporters

The following study results demonstrated that trametinib is a substrate for P-gp and bile acid efflux pump (BSEP), and not a substrate for breast cancer resistance protein (BCRP), multidrug resistance-associated protein (MRP) 2, multidrug and toxin extrusion protein (MATE) 1, organic anion transporter polypeptide (OATP) 1B1, OATP1B3, or OATP2B1, or organic cation transporter (OCT) 1. However, the applicant explained that, since urinary excretion rate of radioactivity after a single oral administration of ^{14}C-labeled trametinib to rats and dogs was <1% and <7%, respectively [see "3.(ii).A.(4).1) Urinary, fecal, and biliary excretion"], inhibition of P-gp, a transporter involved in tubular secretion, is unlikely to affect the PK of trametinib, suggesting that concomitant use of trametinib with a substrate of P-gp is unlikely to cause pharmacokinetic interactions. The applicant explained also that, taking account of the fact that toxicology studies in mice, rats, and dogs did not show findings suggestive of trametinib-induced cholestasis, trametinib is unlikely to competitively inhibit the biliary excretion of bile acid (BSEP substrate), suggesting that trametinib is unlikely to cause pharmacokinetic interactions in clinical use.

- P-gp-mediated transport of trametinib (0.3-10.8 μmol/L) was investigated in P-gp-expressing MDCKII cell line. The quotient of the secretory permeability and the absorptive permeability (efflux ratio) was 0.6 to 0.8 in the presence of a P-gp inhibitor (GF120918, 2 μmol/L) and 2.2 to 38 in the absence of a P-gp inhibitor.

- BCRP-mediated transport of trametinib (0.05-10.8 μmol/L) was evaluated in MDCKII cell line engineered to express human BCRP (BCRP-expressing MDCKII cell line). The efflux ratio of trametinib in the presence and absence of BCRP inhibitor (GF120918, 2 μmol/L) was 0.6 to 0.7 and 0.8 to 1.7, respectively.

- BSEP-, MRP2-, and MATE1-mediated transport of ^{14}C-labeled trametinib (0.1, 1 μmol/L) were studied in vesicles prepared from recombinant baculovirus-infected insect cells engineered to express human BSEP (BSEP-expressing vesicles), or engineered to express MRP2 (MRP2-expressing vesicles), and human embryonic kidney-derived cell line HEK293 engineered to express MATE1 (MATE1-expressing HEK 293 cell line). ^{14}C-labeled trametinib was incorporated into BSEP-expressing vesicles to a greater extent than into BSEP-non-expressing vesicles. On the other hand, ^{14}C-labeled trametinib was incorporated into MRP2-expressing and -non-expressing vesicles to a similar extent and MATE1-expressing and -non-expressing HEK293 cell lines to a similar extent.

- Human OATP1B1-, OATP1B3-, OATP2B1-, and OCT1-mediated transport of ^{14}C-labeled trametinib (0.07-0.7 μmol/L) was examined in human hepatocytes. ^{14}C-labeled trametinib was incorporated into human hepatocytes, but the transport was not inhibited by concomitant use of the inhibitors of OATP1B1 and OATP1B3 (rifamycin and cyclosporine A), OATP2B1 (montelukast), and OCT1 (quinidine).

In addition, on the basis of the following study results, trametinib was shown to inhibit P-gp, BCRP, OATP1B1 and OATP1B3, organic anion transporter (OAT) 1 and OAT3, and MATE1. However, the applicant explained that, taking account that C_{max} of trametinib under a steady state was 0.04 μmol/L when multiple oral doses of trametinib 2 mg QD were administered to patients with malignant melanoma with BRAF V600 mutations [see 4.(ii).A.(2).3) Foreign phase I/II study"] and that plasma protein binding of trametinib is 96.3% to 98.6% [see "3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells"], trametinib is unlikely to cause in clinical use pharmacokinetic interactions mediated by inhibition of P-gp, BCRP, OATP1B1 and OATP1B3, OAT1 and OAT3, or MATE1.

- The inhibitory effect of trametinib (0.1-50 μmol/L) on P-gp-mediated transport of ^{3}H-labeled digoxin (30 nmol/L) was investigated in P-gp-expressing MDCKII cell line. Trametinib inhibited the transporting activity of P-gp (IC_{50}: 5.5 μmol/L).

- The inhibitory effect of trametinib (0.3-100 μmol/L) on BCRP-mediated transport of ^{3}H-labeled cimetidine (80 nmol/L) was investigated in BCRP-expressing MDCKII cell line. Trametinib inhibited the transporting activity of BCRP (IC_{50}: 1.1 μmol/L).

- The inhibitory effect of trametinib (0.1-30 μmol/L) on OATP1B1- or OATP1B3-mediated transport of ^{3}H-labeled estradiol-17β-D-glucuronide (0.02 μmol/L) was studied in Chinese hamster ovary-derived cell line (CHO cell line) engineered to express human OATP1B1 and HEK-MSRII cell line engineered to express human OATP1B3. Trametinib inhibited both OATP1B1 and OATP1B3 (IC_{50}: 1.3 and 0.94 μmol/L, respectively).

- The inhibitory effect of trametinib (0.03-30 μmol/L) on transport of each substrate* mediated by BSEP, MRP2, OAT1 and OAT3, OCT2, and MATE1 was investigated in human BSEP- or MRP2-expressing vesicles, murine proximal renal tubule-derived S_2 cell line engineered to express OAT1 or OAT3, HEK293 cell line engineered to express OCT2, and MATE1-expressing HEK293 cell line. Trametinib inhibited OAT1, OAT3, and MATE1 (IC_{50}: 1.34, 2.58, and 0.0609 μmol/L, respectively). Trametinib at 30 μmol/L inhibited OCT2, although IC_{50} value was not calculated. Trametinib did not inhibit BSEP or MRP2, even at the maximum concentration tested.
  *: Substrates used were ^{3}H-labeled taurocholic acid (2 μmol/L) for BSEP; ^{3}H-labeled estradiol-17β-D-glucuronide (10 μmol/L) for MRP2; ^{3}H-labeled *p*-aminohippuric acid (1 μmol/L) for OAT1; ^{3}H-labeled estrone sulfate (0.05 μmol/L) for OAT3; and ^{14}C-labeled metformin (10 μmol/L) for OCT2 and MATE1.

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

PMDA's view:
On the basis of the submitted data and the results of the following review, the applicant's discussion on the absorption, distribution, metabolism, excretion, and pharmacokinetic interactions of trametinib are acceptable.

Pharmacokinetic interactions
The applicant's explanation of the pharmacokinetic interactions of trametinib with the substrates of CYP2C8 in clinical use, on the basis of the results of *in vitro* studies suggesting that trametinib inhibits CYP2C8 [see "3.(ii).A.(5).1) Enzyme inhibition"]:

IC_{50} of CYP2C8 in an *in vitro* study [see "3.(ii).A.(5).1) Enzyme inhibition"] was higher than C_{max} under steady state following multiple oral administration of trametinib (2 mg QD) to patients with malignant melanoma with BRAF V600 mutations [see 4.(ii).A.(2).3) Foreign phase I/II study"]. These results suggest that trametinib in clinical use is unlikely to cause pharmacokinetic interactions mediated by CYP2C8. In patients treated concomitantly with trametinib and a CYP2C8 substrate in clinical studies, no adverse events caused by pharmacokinetic interaction were reported.

PMDA's discussion:
In clinical studies conducted so far, no clinically significant problems were caused by pharmacokinetic interactions between trametinib and CYP2C8 substrate. However, since information regarding pharmacokinetic interactions of trametinib mediated by drug-metabolizing enzymes and transporters is

important for the proper use of trametinib, such information should be collected continuously and new 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, pulverized trametinib was used unless otherwise specified. The vehicle used was a solution containing 1.5% HPMC, 5% mannitol, and 0.2% sodium lauryl sulfate.

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

3.(iii).A.(1).1) Micronucleus test in rats

No single-dose toxicity study was conducted in rats. Instead, acute toxicity and approximate lethal dose were determined based on the results of the micronucleus test in rats.

Rats (SD, n = 3/sex/group) orally received trametinib 0 (vehicle), 0.5, 1.5, 2.5 (male only), or 3 mg/kg/day for 2 days. Death occurred on Day 3 in 1 of 3 males in the 2.5 mg/kg/day group and in 1 of 3 in both males and females in the 3 mg/kg/day group. Loose stool/watery stool, piloerection, and decreased physical activity were observed in the ≥1.5 mg/kg/day groups, and decreased body weight was observed in females in the ≥0.5 mg/kg/day groups and in males in the ≥1.5 mg/kg/day groups.

According to the above results, rats (SD, n = 7 males/group) received trametinib 0 (vehicle), 1 or 2 mg/kg/day orally for 2 days. No deaths occurred. Piloerection, decreased physical activity, decreased body weight, etc., were observed in the ≥1 mg/kg/day groups.

Consequently, the approximate lethal dose in this study was estimated to be 3 mg/kg/day in females and 2.5 mg/kg/day in males.

3.(iii).A.(1).2) Acute toxicity in dogs (Reference data)

Dogs (beagle, n = 1/sex/group) received a single oral dose of non-pulverized trametinib 0.5 mg/kg, or non-pulverized trametinib 0.15 mg/kg/day on Day 1 and 3 mg/kg/day on Day 16.

In the 0.15 mg/kg/day and 3 mg/kg/day group, animals showed aggravation of clinical signs after treatment with trametinib at 3 mg/kg/day, and 1 animal each was sacrificed moribund 1 and 5 days after treatment with 3 mg/kg/day. Necropsy revealed gastric ulcer/erosion accompanied by hemorrhage and acute inflammation, necrosis of mucosa of small intestinal crypt, lymphoid tissue atrophy/necrosis in thymus and Peyer's patch, decreased bone marrow cellularity, etc.

Consequently, the approximate lethal dose in this study was 0.5 to 3 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 = 12/sex/group) orally received trametinib 0 (vehicle), 0.1, 0.3, or 1.0 mg/kg/day for a maximum of 26 weeks.

In the 1.0 mg/kg/day group, aggravation of clinical signs was observed. Administration was discontinued on Day 23 in males and all males in this group were sacrificed moribund on Day 42. Administration was interrupted on Day 22 in females, and was resumed at 0.6 mg/kg/day from Day 43, but was terminated on Day 78 because some females died or were sacrificed moribund. In the 0.3 mg/kg/day group, because some animals died or were sacrificed moribund, administration was terminated on Day 92 in females and on Day 93 in males. Animals dead or sacrificed moribund in the ≥0.3 mg/kg/day groups showed aggravation of clinical signs such as decreased physical activity, feeling cold, emaciation, hunchback position, collapse, hypotonia, partially closed eyes, pallor of skin, abdominal distension, abnormal respiration, ataxic gait, and tremor. Death and aggravation of clinical signs were attributed to erosion/ulcer/inflammation of colon and peritonitis caused by intestinal perforation.

Animals in the ≥0.1 mg/kg/day groups showed thickening/dark color/adhesion of cecum, colon, and rectum; enlargement/increased plasma cells in spleen, mandibular lymph nodes, and mesenteric lymph nodes; scab and ulcer of skin; extramedullary hemopoiesis in spleen; marrow hyperplasia; and extramedullary hemopoiesis/increased neutrophil count in hepatic sinusoids. Animals in the ≥0.3 mg/kg/day groups showed colonic perforation; smaller thymus; degeneration and necrosis of glandular stomach; increased lymphocyte count/lymphocyte necrosis in mandibular lymph nodes and mesenteric lymph nodes; thymic atrophy and atrophy of pancreatic acinar cells. Animals in the 1.0 mg/kg/day group showed degeneration/necrosis of bone marrow and single-cell necrosis in the liver. Animals in the 0.1 mg/kg/day group were subjected to ophthalmologic test, hematology, and organ weight measurement, and the results showed the following: increased total white blood cell count accompanied by increased neutrophil and monocyte counts; increased reticulocyte and platelet counts; decreased albumin and increased creatinine; and increased spleen weight.

Consequently, in this study, the no observed adverse effect level (NOAEL) was considered to be <0.1 mg/kg/day, and the maximum tolerated dose, 0.1 mg/kg/day. $AUC_{0\text{-}24h}$ in the 0.1 mg/kg/day group (453 ng·h/mL) was approximately 1.2 times the clinical exposure.*

*: In the Japanese phase I study (Study MEK114784), $AUC_{0\text{-}24h}$ was 375 ng·h/mL when multiple oral doses of trametinib 2 mg QD were administered to Japanese patients with advanced solid tumors.

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

Rats (SD, n = 10-16/sex/group) orally received trametinib 0 (vehicle), 0.016, 0.031, 0.0625, or 0.125 mg/kg/day for 3 weeks. Six males and females each in the 0, 0.0625, and 0.125 mg/kg/day groups were evaluated for reversibility after a 2-week recovery period.

In the 0.125 mg/kg/day group, 1 of 10 females showed aggravation of exudative skin lesions and decreased body weight, and was sacrificed moribund on Day 20. Necropsy showed acanthosis; skin ulcer accompanied by exudate and bacterial infection; mineral deposition in glandular stomach; hepatocellular necrosis accompanied by histiocyte infiltration; marrow hyperplasia; and increased lymphoplasmacyte cellularity in mandibular and cervical lymph nodes.

Males showed decreased reticulocyte and eosinophil counts, and vacuolated periportal hepatocytes in the ≥0.016 mg/kg/day groups; increased alanine aminotransferase (ALT), and mineral deposition in glandular stomach in the ≥0.031 mg/kg/day groups; increased phosphorus/calcium phosphate product/aspartate aminotransferase (AST), scab/acanthosis/ulcer of skin, and increased lymphoplasmacyte cellularity in mandibular and cervical lymph nodes in the ≥0.0625 mg/kg/day group; and increased neutrophil and monocyte counts, and decreased serum albumin in the 0.125 mg/kg/day group.

Females showed increased white blood cell/neutrophil/monocyte counts, increased ALT, mineral deposition in glandular stomach, and vacuolated periportal hepatocytes in the ≥0.016 mg/kg/day groups; increased phosphorus/calcium phosphate product/AST, decreased albumin, scab/acanthosis/ulcer of skin, and increased lymphoplasmacyte density in mandibular and cervical lymph nodes in the ≥0.0625 mg/kg/day groups; and decreased hemoglobin/hematocrit/red blood cell counts, increased reticulocyte count/red cell distribution width/eosinophil count/basophil count/large unstained cell count/platelet count, increased urine protein and urine protein/creatinine ratio, increased lymphoplasmacyte cellularity in axillary lymph nodes, and marrow hyperplasia in the 0.125 mg/kg/day group.

All findings were reversible or tended to be reversible after the recovery period.

Consequently, in this study, the NOAEL was considered to be <0.016 mg/kg/day in both males and females, and the maximum tolerated dose was 0.125 mg/kg/day in males and 0.0625 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 trametinib 0 (vehicle), 0.016 (females only), 0.031, 0.0625, or 0.125 (males only) mg/kg/day for a maximum of 13 weeks. Six males and females in each

group, except males in the 0.031 mg/kg/day group and females in the 0.016 mg/kg/day group, were evaluated for reversibility after a 4-week recovery period.

Three of 18 females in the 0.0625 mg/kg/day group, 2 of 18 males in the 0.0625 mg/kg/day group, and 3 of 18 males in the 0.125 mg/kg/day group were sacrificed moribund. Aggravated conditions resulting in moribund sacrifice were caused by gastric inflammation in 1 male in the 0.0625 mg/kg/day group and skin lesions in other animals. All surviving females in the 0.0625 mg/kg/day group and all surviving males in the 0.125 mg/kg/day group were sacrificed moribund on Day 50 and the study was terminated, precluding the reversibility test.

Males showed skin lesions (scab, dryness, reddening, etc.), increased neutrophil and monocyte counts, decreased lymphocyte count, enlarged lymph nodes, thickening/dark foci/retraction of gastric mucosa, erosion/inflammation/hyperplasia of gastric squamous epithelium, and acanthosis/erosion/ulcer/exudate/scab of skin in the ≥0.031 mg/kg/day groups; decreased red blood cell count/hemoglobin/hematocrit, increased ALT/AST/phosphorus, decreased total protein and albumin, acute or subacute skin inflammation, hyperplasia/degeneration/necrosis of bone marrow, vacuolated periportal hepatocytes, hepatocellular necrosis, hyperplasia of lymphoplasmacytes in lymph nodes, hypertrophy/hyperplasia of adrenal cortex, mineral deposition in glandular stomach, and glandular expansion in the ≥0.0625 mg/kg/day groups; and reduced body weight gain, decreased creatinine and potassium, thinning hair/depilation, splenic extramedullary hematopoiesis, and thickening of epiphyseal plate of the knee in the 0.125 mg/kg/day group.

Females showed skin lesions (scab, dryness, reddening, etc.), increased phosphorus, thinning hair/depilation, increased follicular cysts and decreased corpora lutea count, and decreased ovarian weight in the ≥0.016 mg/kg/day groups; increased neutrophil count, decreased lymphocyte count, decreased total protein and albumin, increased adrenal weight, enlarged lymph nodes, thickening/retraction of gastric mucosa, erosion/inflammation/hyperplasia of gastric squamous epithelium, acanthosis/erosion/ulcer/exudate/scab of skin, marrow hyperplasia, vacuolated periportal hepatocytes, hyperplasia of lymphoplasmacytes in lymph nodes, and splenic extramedullary hematopoiesis in the ≥0.031 mg/kg/day groups; and reduced body weight gain, decreased red blood cell count/hemoglobin/hematocrit, increased neutrophil count, increased ALT and AST, decreased serum creatinine and potassium, dark foci of gastric mucosa, acute or subacute skin inflammation, hypertrophy/hyperplasia of adrenal cortex, degeneration/necrosis of bone marrow, hepatocellular necrosis, mineral deposition in glandular stomach, and glandular expansion in the 0.0625 mg/kg/day group.

Findings observed during the treatment period were generally reversible or tended to be reversible, except those observed in females of the 0.0625 mg/kg/day group or in males of the 0.125 mg/kg/day group, which were not subjected to a reversibility test.

Consequently, in this study, the NOAEL was considered to be <0.031 mg/kg/day in males and <0.016 mg/kg/day in females, and the maximum tolerated dose was 0.031 mg/kg/day in both males and females. $AUC_{0\text{-}t}$ in females of the 0.016 mg/kg/day group and in females and males of the 0.031 mg/kg/day group (102, 158, and 95.4 ng·h/mL, respectively) was approximately 0.3 to 0.4 times the clinical exposure.*

*: In the Japanese phase I study (Study MEK114784), $AUC_{0\text{-}24h}$ was 375 ng·h/mL when multiple oral doses of trametinib 2 mg QD were administered to Japanese patients with advanced solid tumors.

3.(iii).A.(2).4) Three-week repeated oral dose toxicity study in dogs

Male dogs (beagle, n = 3-5/group) orally received trametinib 0 (vehicle), 0.025, 0.038, or 0.075 mg/kg/day, and female dogs (beagle, n = 3-5/group) orally received trametinib 0 (vehicle), 0.015, 0.020 or 0.025 mg/kg/day, for a maximum of 3 weeks. Except males in the 0.025 mg/kg/day group and females in the 0.015 mg/kg/day group, 2 males and females in each group were evaluated for reversibility after a 2-week recovery period following the treatment period.

One of 5 males in the 0.038 mg/kg/day group and 3 of 5 males in the 0.075 mg/kg/day group died or were sacrificed moribund. These animals showed anorexia, abnormal feces (loose stool, mucous feces, watery stool, and no-feces), unkempt fur, decreased body weight, etc., and the death and aggravated

conditions were considered to be caused by erosion of gastrointestinal tract accompanied by decreased lymphocyte count in lymph nodes attached to cecum and colon, and by neutrophil inflammation. Examinations of these animals showed changes secondary to inflammation, such as red pulp of the spleen, increased neutrophil count in the liver and cervical/mandibular lymph node sinusoids, marrow hyperplasia, and activation of hepatic Kupffer cells. No deaths occurred in females.

Two of 5 males in the 0.075 mg/kg/day group showed decreased physical activity, anorexia, abnormal feces, etc., and trametinib treatment was interrupted on Day 8 followed by transfusion and administration of antibiotics. All findings disappeared on or before the 10th day of interruption, and animals were necropsied on the 14th day of interruption. Findings in males were decreased reticulocyte count and serum albumin, decreased red blood cell count/hemoglobin/hematocrit, increased white blood cell/monocyte/neutrophil counts in the ≥0.025 mg/kg/day groups; increased ALP and cholesterol, marrow hyperplasia, and increased neutrophil count in splenic red pulp sinusoids in the 0.038 mg/kg/day group; and increased total bilirubin (Day 8 of study), increased triglycerides, and decreased thymic lymphocyte count in the 0.075 mg/kg/day group.

Examinations in females showed decreased reticulocyte count in the ≥0.015 mg/kg/day groups and increased monocyte count in the 0.025 mg/kg/day group, but no histopathological changes related to these observations were found, and thus these events were considered to be of little toxicological significance.

During the recovery period, investigations in males in the 0.075 mg/kg/day group showed further decreased reticulocyte count, increased ALT and glutamic acid dehydrogenase. Except for these findings, all other findings in the trametinib groups during the treatment period were reversible or tended to be reversible.

Consequently, in this study, the NOAEL was considered to be <0.025 mg/kg/day in males and 0.025 mg/kg/day in females, and the maximum tolerated dose, 0.025 mg/kg/day in both males and females.

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

Dogs (beagle, n = 4-6/sex/group) orally received trametinib 0 (vehicle), 0.0075, 0.015, or 0.03 mg/kg/day for 13 weeks at the maximum. Two males and females each in the vehicle group, the 0.015 mg/kg/day group, and the 0.03 mg/kg/day group were evaluated for reversibility after a 4-week recovery period.

Animals in the 0.03 mg/kg/day group first received the prescribed dose of 0.03 mg/kg/day, and showed severe skin lesions (e.g., scab accompanied by reddening of skin); decreased body weight; decreased food consumption and abnormal feces (loose stool, watery stool, and decreased feces). Treatment was interrupted on or after Day 11, and, after a 10 day interruption, was resumed at a reduced dose of 0.023 mg/kg/day and continued for 10 weeks. One of 6 males in the 0.03 mg/kg/day group was sacrificed moribund on Day 14 (2nd day of interruption) because of aggravation of clinical signs (collapse, dehydration, and increased rectal temperature, etc.), and the aggravation of conditions were attributed to erosion/ulcer of tongue, esophagus, and stomach accompanied by inflammation. Examination of this animal showed increased neutrophil and monocyte counts; marrow hyperplasia; atrophy of thymus and lymphatic tissues attached to ileum; and neutrophil infiltration/neutrophilic inflammation in the cecum, colon, mandibular/mesenteric lymph nodes, lymphatic tissues attached to ileum, and spleen.

Examinations of males showed decreased red blood cell count, hemoglobin, hematocrit, and albumin in the ≥0.0075 mg/kg/day groups; and decreased reticulocyte count in the ≥0.015 mg/kg/day groups.

Examinations of females showed decreased reticulocyte count and albumin in the ≥0.015 mg/kg/day groups; and decreased red blood cell count, hemoglobin, and hematocrit in the 0.03 mg/kg/day group.

Hematologic and clinical chemistry findings in surviving male and female animals were all mild, and not accompanied by related histopathological changes, and thus they were considered to be of little toxicological significance.

All findings observed during the treatment period were reversible after the recovery period.

Consequently, in this study, the NOAEL was considered to be 0.023 mg/kg/day in both males and females. $AUC_{0\text{-}t}$ in the 0.023 mg/kg/day group (139 ng·h/mL) was approximately 0.4 times the clinical exposure.*

*: In the Japanese phase I study (Study MEK114784), $AUC_{0\text{-}24h}$ was 375 ng·h/mL when multiple oral doses of trametinib 2 mg QD were administered for 15 days to Japanese patients with advanced solid tumors.

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

Genotoxicity studies consisted of a bacterial reverse mutation assay, a mouse lymphoma TK assay, and a rat micronucleus assay. Non-pulverized trametinib was used in these tests except in the micronucleus assay. No genotoxicity of trametinib was observed in any studies.

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

No carcinogenicity test was conducted since trametinib is intended for treating malignant melanoma.

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

The applicant conducted studies of embryo-fetal development in rats and rabbits as reproductive and developmental toxicity studies.

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation

No study of fertility and early embryonic development to implantation was conducted since trametinib is intended to be used for treating malignant melanoma.

No effects on male reproductive organs were observed in the repeat-dose toxicity studies in mice, rats, and dogs [see "3.(iii).A.(2) Repeat-dose toxicity"], and thus the applicant explained that trametinib is unlikely to affect male fertility.

Observed effects on female reproductive organs were increased follicular cysts and decreased corpora lutea count in the repeat-dose toxicity study in rats [see "3.(iii).A.(2).3) Thirteen-week repeated oral dose toxicity study in rats"]. In light of the following published reports, these findings are considered to be due to MEK inhibition by trametinib, suggesting that trametinib possibly has adverse effects on female fertility. The applicant therefore explained that caution statements would be included in the package insert etc., regarding the occurrence of these findings in rat toxicology studies.

- Inhibition of MEK-ERK pathway induces increased apoptosis and decreased survival of granulosa cells (*Zoolog Sci*. 2003;20:193-201).

- Inhibition of MEK-ERK pathway is suggested to decrease the activation of the transcription of genes inducing ovulation and follistatin, a protein that suppresses the release of follicle-stimulating hormone (*Endocr J*. 2006;53:225-235, *Mol Cell Endocrinol*. 2008;294:52-60).

- In theca cells collected from patients with polycystic ovarian syndrome, suppression of MEK-ERK pathway is observed (*Mol Endocrinol*. 2005;19:379-390).

- VEGF, a factor involved in the upstream of MEK-ERK pathway, plays an important role in folliculogenesis, luteinization, and luteal function (*Nat Med*. 1998;4:336-340).

3.(iii).A.(5).2) Embryo-fetal development

i) Rat embryo-fetal development study

Pregnant rats (SD, 21–22 animals/group) orally received trametinib 0 (vehicle), 0.062/0.016, 0.094/0.031, or 0.125/0.062 mg/kg/day (initial dose/second and subsequent doses) from Gestation Day 6 to Gestation Day 17. Because only minor toxicity was observed in maternal animals in the 0.125/0.062 mg/kg/day group, pregnant rats (SD, n = 4/group) orally received trametinib 0 (vehicle), or 0.375/0.125 mg/kg/day (initial dose/second and subsequent doses) from Gestation Day 6 to Gestation Day 17.

Maternal animals in the ≥0.125/0.062 mg/kg/day groups showed scabs. Animals showed decreased body weight gain from Gestation Day 6 to Gestation Day 9 in the ≥0.062/0.016 mg/kg/day groups, and from Gestation Day 12 to Gestation Day 15 in the 0.375/0.125 mg/kg/day group. However, body weight increase from Gestation Day 6 to Gestation Day 18 in any trametinib group did not show any clear difference from the control group, and thus the above findings were considered to be of little toxicological significance.

Decreased fetal body weight was observed in the ≥0.094/0.031 mg/kg/day groups and increased post-implantation mortality in the 0.375/0.125 mg/kg/day group in embryos and fetuses.

Consequently, in this study, the NOAEL was considered to be 0.094/0.031 mg/kg/day for maternal animals and 0.062/0.016 mg/kg/day for embryo-fetal development. $AUC_{0\text{-}t}$ in maternal animals and in embryos/fetuses at the NOAEL (110 and 52.3 ng·h/mL, respectively) was 0.3 and 0.14 times, respectively, the clinical exposure.*

*: In the Japanese phase I study (Study MEK114784), $AUC_{0\text{-}24h}$ was 375 ng·h/mL when multiple oral doses of trametinib 2 mg QD were administered to Japanese patients with advanced solid tumors.

ii) Rabbit embryo-fetal development study

Pregnant rabbits (Dutch Belted, n = 21-22/group) orally received trametinib 0 (vehicle), 0.077/0.0385, 0.154/0.077, or 0.308/0.154 mg/kg/day (initial dose/second and subsequent doses) from Gestation Day 7 to Gestation Day 19.

Maternal animals in the ≥0.077/0.0385 mg/kg/day groups showed a dose-dependent decreased body weight gain, and 1 maternal animal in the 0.308/0.154 mg/kg/day group had abortion on Gestation Day 18.

Embryos and fetuses showed decreased fetal body weight and incomplete ossification of metacarpal bone, parietal bone, hyoid bone, and sternebrae in the ≥0.077/0.0385 mg/kg/day groups; incomplete ossification of pedal phalanges and frontal bone and unossified talus and pubis in the ≥0.154/0.077 mg/kg/day groups; and incomplete ossification of caudal vertebral arch/body and interparietal bone, unossified pedal phalanges, abnormal morphology of nasal bone, curved scapula, and anterior fontanel dilatation in the 0.308/0.154 mg/kg/day group. The skeletal anomalies observed in the ≥0.077/0.0385 mg/kg/day groups showed correlation with decreased fetal body weight, thus they were considered to be changes related to delayed ossification associated with suppressed fetal growth. Cleft palate was observed in 3 of 137 fetuses in the 0.308/0.154 mg/kg/day group, but the findings were considered not caused by trametinib because all 3 of them were siblings and the incidence was within the range of the historical data at the study facility.

Consequently, in this study, the NOAEL was considered to be <0.077/0.0385 mg/kg/day for both maternal animals and embryo-fetal development. $AUC_{0\text{-}t}$ in maternal animals of the 0.077/0.0385 mg/kg/day group (31.9 ng·h/mL) was 0.09 times the clinical exposure.*

*: In the Japanese phase I study (Study MEK114784), $AUC_{0\text{-}24h}$ was 375 ng·h/mL when multiple oral doses of trametinib 2 mg QD were administered to Japanese patients with advanced solid tumors.

The above study results and the following published reports suggest the possible adverse effects of trametinib on embryo-fetal development. If trametinib is to be administered to women of childbearing potential they should be instructed to take appropriate contraceptive measures and explained about the risk to fetuses when they become pregnant. The applicant also explained that caution statements should be included in the package insert etc., so that trametinib should be used in pregnant women or in women who maybe pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.

- MEK-ERK pathway plays an important role in embryo-fetal development, and MEK1 and ERK2 deficiency causes malformation of placenta and extraembryonic tissue, respectively, with both leading to embryo-fetal death during the early to mid-gestation (*Development*. 2006;133:3429-3440, *Curr Biol*. 1999;9:369-372, *Genes Cells*. 2003;8:847-856, *EMBO Rep*. 2003;4:964-968).

- Skin-specific combined loss of *MEK1* and *MEK2* causes disruption of surface barrier function associated with skin hypoplasia, resulting in small-sized fetuses and their death (*Dev Cell*. 2007;12:615-629).

3.(iii).A.(5).3) Study on juvenile animals

Results from the studies in juvenile animals were not submitted in the present application.

PMDA asked the applicant to explain the results from studies in juvenile animals and possible risks of trametinib treatment in pediatric patients.

The applicant's response:

A study in which trametinib was administered to juvenile rats (7-45 days of age) was conducted. This study showed the effects on growth (decreased body weight gain and decreased femur length), delayed sexual maturation, effects on phosphorus homeostasis (e.g., increased phosphorus level), effects on bone (necrosis of primary spongy bone, accelerated bone resorption, and epiphyseal thickening/degeneration), eye (corneal mineralization/degeneration), skin, and liver, increased heart weight, the effects on mammary gland development, decreased corpora lutea count, and decreased ovarian weight. The NOAEL in this study was below the lowest dose tested, and AUC at the lowest dose (107.8 ng·h/mL) was below the clinical exposure.* Among the above findings, corneal mineralization/degeneration was not observed in mature rats. Thickening of epiphyseal plate was observed in the repeat-dose toxicity study in rats, etc. [see "3.(iii).A.(2).3) Thirteen-week repeated oral dose toxicity study in rats"], raising a concern about effects on bone in children before epiphyseal plate closure.

*: In the Japanese phase I study (Study MEK114784), $AUC_{0\text{-}24h}$ was 375 ng·h/mL when multiple oral doses of trametinib 2 mg QD were administered to Japanese patients with advanced solid tumors.

These results suggest the possibility that trametinib is more toxic in children than in adults. The applicant plans to raise caution in the package insert etc., that the efficacy and safety in children are not yet established. Also, whether or not trametinib is excreted in human milk is unknown, and thus nursing women should be instructed to discontinue breast feeding when trametinib is administered, given the possibility of children being exposed to trametinib via breast milk. Information regarding the results of the above study in juvenile animals will be provided to healthcare professionals in clinical settings through information materials etc.

3.(iii).A.(6) Other toxicities

3.(iii).A.(6).1) Cardiac toxicity

In order to investigate the mechanism of decreased ejection fraction of the left ventricle observed in clinical studies [see "4.(iii).B.(3).2) Cardiac disorder"], a study in primary cultured rat cardiac muscle cells and a study in mice were conducted, and the results were submitted as reference data.

The study in primary cultured rat cardiac muscle cells did not show any effect of trametinib on cell viability or on the function of mitochondria. In the study in which trametinib was administered orally to mice for 21 days at a maximum dose of 0.5 mg/kg/day, a dose-dependently reduced left ventricular function and decreased heart rate and heart weight were observed, but cardiac contractile reserve was not impaired. Necropsy and histopathological examination did not detect any change related to trametinib treatment.

The applicant's explanation:

On the basis of above results etc., the decreased ejection fraction of the left ventricle observed in clinical studies is not due to direct cytotoxicity to cardiac muscle cells or to mitochondrial dysfunction caused by trametinib.

3.(iii).A.(6).2) *In vitro* phototoxicity

Phototoxicity of trametinib was investigated at 0.1638 to 40 μg/mL in murine fibroblast-derived Balb/c 3T3 cell line. Photo irritation factor (IC_{50} in the UVA-non-irradiated group/IC_{50} in the UVA-irradiated group), calculated from IC_{50} of growth-inhibitory effects of trametinib under UVA irradiation and non-irradiation (2.92 μg/mL and 18.98 μg/mL, respectively), was 6.5, exceeding the positive reference criterion of 5, suggesting that trametinib is phototoxic.

Risks of phototoxicity-induced adverse events in trametinib treatment are described in "4.(iii).B.(3).7) Skin disorder," on the basis of clinical study results also.

3.(iii).A.(6).3) Four-week repeated oral dose toxicity study of concomitant use of trametinib with DAB in dogs

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

In the 0.0225/20 mg/kg/day group, 1 of 3 males was sacrificed moribund on Day 11 because of aggravation of clinical signs (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 0.0075/5 mg/kg/day group and all females in the 0.0225/20 mg/kg/day group showed obviously decreased body weight, and thus supplemental food was given on or after Day 12. By the end of the treatment period, the body weight of these females recovered and became comparable to those in the control group.

Animals in the ≥0.0075/5 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 0.0225/20 mg/kg/day group showed reddening of muzzle skin, scab of auricle, increased white blood cell, neutrophil, and monocyte counts, increased ALP, decreased albumin, decreased sperm count in epididymis, and degenerated sperm cells in lumen.

Treatment of trametinib/DAB enhanced systemic toxicity and neutrophilic inflammation in colon and rectum among findings that were also observed when either trametinib or DAB alone was administered. On the other hand, skin lesions, which occurred with a high incidence in repeat-dose toxicity studies of DAB, 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 trametinib/DAB, 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, trametinib is unlikely to pose safety problems related to this finding in the clinical use of trametinib, for the following reasons.
  - They are findings observed when reactions to foreign matters occur; they are routinely observed in the mesenteric lymph nodes.
  - The findings observed in this study were mild.
- The mechanism of occurrence of granulomatous inflammation in stomach is also unknown because (a) it is different histologically from histopathological change in gastrointestinal tract observed in repeat-dose toxicity studies of trametinib, 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, trametinib is unlikely to cause safety problems related to the finding in its clinical use for the following reasons.
  - The finding observed in this study was mild, suggesting that aggravation of general conditions is unlikely to occur.
  - In the clinical study (Study MEK115306) [see "4.(iv).(8) 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 trametinib/DAB compared with trametinib alone.

3.(iii).A.(6).4) Safety evaluation of impurities

Genotoxicity of impurities etc., formed during the manufacturing process of the drug substance was investigated by DEREK, an *in silico* analysis. The results suggested the genotoxicity risk of Compound A (the starting material) and Impurities A and B (related substances present in the starting material). The applicant explained these impurities as follows:

Compound A and Impurity A are reported to be positive in bacterial reverse mutation test (*Environ Mol Mutagen*. 1988;11 suppl.12:1-158). Impurity B was negative in bacterial reverse mutation test, but should be handled as a potential genotoxic substance because it is suggested to be converted to Compound A or Impurity A. However, when the maximum amount of the sum of Compound A and Impurities A and B was estimated (225 ppm) based on their contents in the drug substance, and their maximum intake in clinical use was calculated (0.45 μg/day), the level was below 1.5 μg/day, the Threshold of Toxicological Concern (ICH M7 Harmonized Tripartite Guideline [ICH, 2014]). Therefore, the applicant considered that genotoxicity caused by these impurities is unlikely to occur in clinical use of trametinib.

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

On the basis of submitted data and the results of the following review, PMDA concluded that non-clinical toxicity data do not pose any problems in the clinical use of trametinib.

Effects on bone

PMDA asked the applicant to explain the possible effects of trametinib on bone in clinical use considering the findings on bone (thickening of epiphyseal plate) in the repeat-dose toxicity study in rats [see "3.(iii).A.(2).3) Thirteen-week repeated oral dose toxicity study in rats"].

The applicant's response:

In the toxicity study in which trametinib was administered orally to rats for a maximum of 12 days, findings on bone or cartilage other than thickening of epiphyseal plate observed in the ≥1.0 mg/kg/day groups were subchondral bone infarction in the epiphysis.

Thickening of epiphyseal plate was also observed in rats administered with a MEK inhibitor other than trametinib (PD325901) or with an inhibitor of fibroblast growth factor receptor (FGFR) (PD176067) and in *FGFR-3* gene-deficient mice (e.g., *Toxicol Pathol*. 2005;33:449-455, *Cell*. 1996;84:911-921), suggesting the possibility that thickening of epiphyseal plate is caused by the blockage of FGFR pathway mediated by trametinib-induced MEK inhibition.

However, in light of the following findings, trametinib is unlikely to affect bones because epiphyseal line is closed in adults, and adults are the target patient population of trametinib in this application. Information regarding the findings on bone observed in the repeat-dose toxicity studies in rats will be provided to healthcare professionals in clinical settings appropriately through information materials etc.

- In rats that showed subchondral bone infarction in the epiphysis and thickening of epiphyseal plate after trametinib administration, epiphyseal closure was not observed even at 29 months after birth (*Contemp Top Lab Anim Sci*. 2002;41:21-26).
- In the repeat-dose toxicity study in 11 to 21 month-old dogs with closed epiphyses, trametinib had no effect on bones [see "3.(iii).A.(2).4) Three-week repeated oral dose toxicity study in dogs" and "3.(iii).A.(2).5) Thirteen-week repeated oral dose toxicity study in dogs"].

PMDA accepted the applicant's explanation.

4. Clinical data

The dose of trametinib dimethyl sulfoxide (hereinafter referred to as trametinib) is expressed as free-base equivalent.

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

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

There are 2 types of oral formulations of trametinib, formulations for clinical studies (0.125, 0.25, 0.5, 1, 2, and 5 mg tablets) and to-be-marketed formulations (0.5 and 2 mg tablets). Pharmacokinetics (PK) was investigated in both types of formulations (the table below). The colorant of the film-coating layer (0.5 mg tablets) and diameter, thickness, and surface area of the core tablet (2 mg tablets) of these 2 types of formulations are different from each other. The difference in formulation (a) between 0.5 mg tablets for clinical studies and 0.5 mg tablets to be marketed and (b) between 2 mg tablets for clinical studies and 2 mg tablets to be marketed corresponds to "Level B" according to the "Guideline for Bioequivalence Studies for Formulation Changes 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 for each pair.

Formulations used in each clinical study

Formulations	Studies
Formulations for clinical studies (0.125, 0.25, 0.5, 1, 2, 5 mg)	Japanese phase I study (Study MEK114784[*1]), foreign phase I studies (Studies MEK111054,[*2] MEK113709,[*3] MEK115064,[*3] and MEK112111[*4]), foreign phase I/II study (Study BRF113220[*5]), foreign phase II study (Study MEK113583[*4]), foreign phase III study (Study MEK114267[*5])
To-be-marketed formulations (0.5, 2 mg)	Japanese phase I/II study (Study MEK116885), Japanese phase II study (Study MEK117134), foreign phase III studies (Studies MEK115306 and MEK116513)

*1: 1 mg tablets were used. *2: 0.125, 0.25, 0.5, 1, and 2 mg tablets were used. *3: 2 mg tablets were used. *4: 0.25, 0.5, 1, and 2 mg tables were used. *5: 0.5, 1, and 2 mg tablets were used.

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

The table below shows the method employed in each clinical study for testing BRAF mutations, namely, mutations of codon 600 (for valine), in the protein encoded by v-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene (BRAF V600 mutations). A marketing application for "THxID BRAF Kit" of SYSMEX bioMérieux Co., Ltd. was submitted on March 19, 2015 as an *in vitro* diagnostic to support the evaluation of indication of trametinib and dabrafenib mesilate (DAB).

Testing method employed in each clinical study

Tests	Studies
Direct sequencing LSI Medience Corporation	Japanese phase I/II study (Study MEK116885 [phase I part])
Allele-specific PCR Response Genetics Inc.	Foreign phase III study (Study MEK114267)
Real time PCR (THxID BRAF Kit) 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/II study (Study BRF113220), foreign phase II study (Study MEK113583)

PCR: Polymerase chain reaction

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

Assay of trametinib in human plasma was performed by LC-MS/MS. The lower limit of quantitation was 0.25 ng/mL.

4.(i).A.(3) Japanese phase II study (5.3.1.2, Study MEK117134 [September 2013 – ongoing (data cut-off; July 4, 2014)])

An open-label, randomized study was conducted in 20 patients with locally advanced or metastatic biliary cancer (20 patients included in PK analysis) to investigate the PK of trametinib. Multiple oral doses of trametinib 2 mg QD in to-be-marketed formulations (0.5 and 2 mg tablets) were administered under fasted conditions (the table below).

No clear difference was observed in exposure to trametinib on Day 1 between patients receiving one 2-mg tablet and those receiving four 0.5 mg tablets.

PK parameters of trametinib in single-dose administration

Formulations used	C_{max} (ng/mL)	t_{max}* (h)	AUC_{0-24h} (ng·h/mL)
0.5-mg tablets	11.0 (82.8)	1.0 (1.0, 2.5)	73.5 (40.4)
2-mg tablet	14.1 (30.9)	1.2 (1.0, 2.0)	83.0 (27.5)

n = 10; Geometric mean (coefficient of variation [CV] %); *, Median (range)

4.(i).A.(4) Foreign phase I study (5.3.1.1, Study MEK115064 [June 2011 to December 2011])

An open-label study was conducted in 4 patients with solid tumors (4 patients included in PK analysis) to investigate the absolute bioavailability (BA) of trametinib. A single oral dose of trametinib 2 mg was administered under fasted conditions, and a single intravenous dose of ^{14}C-labeled trametinib 0.005 mg was 1.5 hours thereafter.

Absolute BA [90% confidence interval (CI)] (%), calculated from AUC_{0-t} of trametinib, was 72.3% [50.0, 104.6]. Blood clearance (CL) of trametinib following intravenous administration (approximately 1.0 L/h*) was lower than hepatic blood flow in human (approximately 87 L/h) (*Pharm Res*. 1993;10:1093-1095), and thus the applicant explained that hepatic extraction fraction and hepatic first-pass effects of trametinib are minor.

*: Calculated based on plasma CL of trametinib (3.2 L/h) and blood/plasma ratio of trametinib at around plasma trametinib concentration in clinical use (approximately 3) [see "4.(ii).A.(2).1) Foreign phase I study"].

4.(i).A.(5) Foreign phase I study (5.3.1.1, Study MEK113709 [May 2011 to September 2011])

A two-treatment, two-period, crossover study was conducted in 24 patients with solid tumors (22 patients included in PK analysis) to investigate food effect. A single dose of trametinib 2 mg in formulation for clinical studies (2 mg tablets) was administered orally under fasted conditions, or within 30 minutes from the start of a high fat/high calorie food intake (fat accounting for approximately 50% of the total calorie). There was a 7-day washout period between the first and second periods.

Median t_{max} of trametinib when administered after a high-fat/high-calorie food intake delayed compared with that when administered under fasted conditions. Mean geometric ratios [90% CI] of C_{max} and AUC_{inf} following administration after a high-fat/high-calorie food intake to those after administration under fasted conditions were 0.30 [0.24, 0.37] and 0.90 [0.80, 1.01], respectively. The applicant explained that the gastric emptying rate was delayed by food intake, resulting in a decreased absorption rate of trametinib, which in turn led to delayed t_{max} and gradually increasing plasma trametinib concentration, resulting in a marked decrease in C_{max}.

4.(i).A.(6) Effects of gastric pH on PK of trametinib

At 37°C, trametinib was only slightly soluble in Britton-Robinson buffer* over pH range from 2.0 to 8.0, with pH showing no clear effect on the solubility. The applicant therefore explained that changes in gastric pH due to antacid administration are unlikely to affect the PK of trametinib.

*: pH was adjusted by adding sodium hydroxide solution to mixed aqueous solution of boric acid, acetic acid, and phosphoric acid.

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

4.(i).B.(1) Bioequivalence between 0.5 mg and 2 mg tablets to be marketed

The applicant's explanation on the bioequivalence between 0.5 mg and 2 mg tablets to be marketed:
A dissolution test was conducted according to "Guideline on Bioequivalence Studies for Generic Pharmaceuticals" (PMSB/ELD Notification No. 64 dated February 14, 2000; partially revised by PFSB/ELD Notification No. 0229-(10) dated February 29, 2012). The results did not show the equivalence in dissolution behavior between 0.5 mg tablets and 2 mg tablets. In such a case, the above guideline requires conducting a bioequivalence test in humans. However, conducting a bioequivalence test seem to be infeasible for reasons described below. Moreover, the Japanese phase II study in patients with locally advanced or metastatic biliary cancer (Study MEK117134) showed no clear difference in the exposure to trametinib between administration of one 2-mg tablet and four 0.5-mg tablets [see "4.(i).A.(3) Japanese phase II study"].

- In foreign clinical studies of trametinib, serious adverse events including sudden death occurred, raising safety concerns about conducting a clinical study of trametinib in healthy adult subjects.
- Malignant melanoma with BRAF V600 mutations is a rare disease, and it would take a long time to enroll patients with the disease in a clinical study.

PMDA asked the applicant to explain the necessity of 0.5 mg tablets in clinical use and the interchangeability between 2 mg and 0.5 mg tablets.

The applicant's response:
In the Japanese phase I//II study (Study MEK116885) and in the foreign phase III studies (Studies MEK116513 and MEK115306), it was stipulated that, in case of reducing dosage of trametinib because of adverse events, 0.5 mg tablets should be used to administer reduced dose of trametinib 1.0 or 1.5 mg QD. As a result, ≥10% of patients in all of these clinical studies reduced the dose of trametinib because of adverse events. Given these results, it is likely that trametinib is used at reduced doses in clinical use as well in order to control adverse events. Thus, there is a high need for 0.5 mg tablets as a dosage form to be used in dose reduction.

Interchangeable use of 2 mg and 0.5 mg tablets is not recommended because bioequivalence of these formulations is not established. The following precautions will be provided appropriately through the package insert to healthcare professionals in clinical settings: only 2 mg tablet should be used when 2 mg of trametinib is to be administered.

PMDA accepted the applicant's explanation.

4.(i).B.(2) Food effect
The applicant's explanation on the timing of trametinib administration:
On the basis of the results of Study MEK113709 suggesting that food intake decreases exposure to trametinib [see "4.(i).A.(5) Foreign phase I study"], timing of trametinib administration was fixed at "1 hour before, or 2 hours after, meals" in the foreign phase III studies (Studies MEK115306 and MEK116513), and the efficacy and safety of trametinib were demonstrated under these conditions. Therefore, cautions will be provided appropriately to healthcare professionals in clinical settings through the package insert, to avoid administration of trametinib from 1 hour before meal to 2 hours after meal.

PMDA accepted the applicant's explanation.

4.(ii) Summary of clinical pharmacology studies

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

PK of trametinib when administered alone and in combination with gemcitabine hydrochloride (GEM) or DAB was investigated in cancer patients.

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

4.(ii).A.(1).1) Japanese phase I study (5.3.5.2, Study MEK114784 [January 2011 to July 2013])

An open-label, uncontrolled study was conducted to investigate the PK of trametinib in 13 patients with solid tumors (13 patients included in PK analysis). A single dose of trametinib 1, 2, or 3 mg was administered orally under fasted conditions and, after a 6-day washout period, trametinib 1, 2, or 3 mg QD was administered in multiple doses under fasted conditions to analyze plasma trametinib concentration (the table below).

$AUC_{0\text{-}24h}$ of trametinib on Day 15 increased in a dose-dependent manner within the dose range investigated. The ratio of $AUC_{0\text{-}24h}$ in multiple doses to that in single dose was 7.8-8.4. The applicant explained that steady state is reached within 15 days after starting multiple doses, on the basis of trough plasma trametinib concentration (C_{min}) on Days 8, 15, and 22.

PK parameters of trametinib

Time points	Dose (mg)	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{0-24h} (ng·h/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$*2 (h)
After single dose	1	4	3.9 (45.1)	1.5 (0.9, 2.0)	30.3 (21.8)	235 (30.0)	184 (26.7)
	2	6	7.2 (77.5)	2.0 (1.0, 3.0)	47.6 (37.2)	384 (17.7)	178 (42.3)
	3	3	7.4 (70.1)	2.0 (1.5, 4.0)	57.9 (58.1)	386 (44.9)	139 (8.64)
Day 15 of multiple doses	1	4	15.0 (33.9)	1.8 (1.5, 3.0)	236 (25.8)	-	121 (13.8)
	2	5	25.5 (36.3)	2.0 (1.0, 4.0)	375 (20.8)	-	129 (29.3)
	3	3	26.4 (42.4)	4.1 (3.0, 6.0)	487 (30.3)	-	131 (57.4)

Geometric mean (CV%); -, Not calculated; *1, Median (range); *2, Calculated based on accumulation ratio in multiple dose.

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 investigate the PK of trametinib etc. Single doses of trametinib (2 mg) and DAB (150 mg) were administered orally on Day 1, followed by multiple oral administration of trametinib (2 mg QD) and DAB (150 mg BID) on and after Day 2, and plasma concentrations of trametinib, DAB, and DAB metabolites M4 (carboxylate), M7 (hydroxylate), and M8 (desmethylate) were determined (the table below).

C_{min} (geometric mean) of trametinib and DAB was 13.8 to 13.72 ng/mL and 78.1 to 121.85 ng/mL, respectively, during Week 3 to Week 24, staying generally at constant levels which showed that steady state is reached at Week 3 for both trametinib and DAB.

PK parameters of trametinib

Time points	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{0-24h} (ng·h/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
Day 1	7.82 (112.1)	1.0 (0.9, 23.8)	82.5 (23.1)*2	376 (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

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

Time points	Analyte	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{0-12h} (ng·h/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
Day 1	DAB	2497 (69.7)	2.4 (1.4, 3.9)	11,415 (41.3)	13,486 (36.9)	4.9 (45.2)
	M4	3689 (75.5)	9.8 (7.9, 23.8)	18,964 (256)	125,749 (41.8)*2	15.7 (21.7)*2
	M7	1336 (70.1)	3.4 (2.9, 11.9)	7930 (64.3)	13,904 (67.9)	6.4 (145)
	M8	50.4 (150)	23.9 (11.7, 24.3)	116 (270)	4628*3	55.9*3
Day 21	DAB	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 if n = 1); -, Not calculated; *1, Median (range); *2, n = 5; *3, n = 1

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

4.(ii).A.(2).1) Foreign phase I study (5.3.3.2, Study MEK113708 [January 2011 to July 2011])

An open-label study was conducted in 2 patients with solid tumors to determine the mass balance of trametinib. A single dose of a solution containing ^{14}C-labeled trametinib 2 mg was administered orally under fasted conditions, and radioactivity concentrations in blood, plasma, urine, and feces, as well as plasma trametinib concentration were measured.

In the 2 patients receiving ^{14}C-labeled trametinib, the percentage of trametinib AUC_{0-t} (individual value) in the plasma radioactivity AUC_{0-t} was approximately 20% and 50%. Trametinib metabolites—M5 (deacetylated form), M6 (glucuronidation of M5), and M7 (oxygenation of M5)—were observed in plasma other than unchanged trametinib. The blood/plasma ratio of radioactivity at 3 to 240 hours after administration was generally constant, at approximately 3. Up to 10 days after administration, the urinary excretion rate of radioactivity (percentage of administered radioactivity excreted, individual value) was 9.0% and 2.1% (18.6% and 5.6%, of the total radioactivity recovered), and the fecal excretion

rate was 39.2% and 35.0% (81.3% and 94.3%, of the total radioactivity recovered) in the respective patients.

4.(ii).A.(2).2) Foreign phase I study (5.3.5.2, Study MEK111054 [July 2008 – ongoing (data cut-off; June 7, 2011)])

An open-label, uncontrolled study was conducted in 55 patients with solid tumors or lymphoma (54 patients included in PK analysis) to evaluate the PK of trametinib. Multiple oral doses of trametinib (0.125-10 mg QD) were administered under fasted conditions, and plasma trametinib concentration was measured (the table below).

After a single dose of trametinib, C_{max} increased generally dose-proportionally within the dose range investigated, whereas $AUC_{0\text{-}24h}$ increased more than dose proportionally. The applicant explained that the reason for the more than dose-proportional increase in $AUC_{0\text{-}24h}$ of trametinib is unclear. After multiple doses of trametinib, C_{max} and $AUC_{0\text{-}24h}$ increased generally dose-proportionally within the dose range investigated. In multiple administration of trametinib 2 mg QD, the ratio of the geometric mean of $AUC_{0\text{-}24h}$ (coefficient of variation [CV]%) on Day 15 to that on Day 1 was 5.97 (33%).

PK parameters of trametinib

Dose (mg)	Day of measurement	n	C_{max} (ng/mL)	t_{max} *1 (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	$t_{1/2}$ *2 (h)
0.125	Day 1	1*3	0.62	0.5	-	-
	Day 15	2	1.21, 1.58	1.0, 1.5	17.8, 14.6	-
0.25	Day 1	1	0.34	1.0	-	-
	Day 15	1	2.08	1.5	31.4	-
0.5	Day 1	2	0.85, 1.21	1.5, 1.5	9.7*4	-
	Day 15	2	3.91, 5.38	2.1, 1.0	60.2, 98.9	161*4
1	Day 1	2	1.71, 1.96	1.5, 1.5	13.4, 12.2	-
	Day 15	2	15.8, 7.96	0.8, 1.5	245, 95.1	296, 121
2	Day 1	3	6.68 (25)	1.5 (1.5, 2.0)	54.4 (31)	-
	Day 15	2*3	14.2, 28.4	1.5, 3.0	289, 493	97.4, 100
2.5	Day 1	9	9.32 (29)	1.5 (1.0, 2.0)	66.4 (26)*6	-
	Day 15	9	29.8 (39)	2.0 (1.0, 4.0)	470 (32)	121 (33)*6
3	Day 1	12	9.30 (81)	1.3 (0.5, 3.0)	64.9 (51)*5	-
	Day 15	11	33.0 (40)	2.1 (0.5, 10.0)	544 (35)	126 (50)*7
4	Day 1	3	25.8 (42)	1.0 (1.0, 1.0)	218 (25)	-
	Day 15	2*3	62.8, 43.8	1.0, 1.5	946, 546	48.8, 30.9
6	Day 1	10	20.1 (65)	1.5 (1.1, 8.1)	178 (51)	-
8	Day 1	7	11.9 (84)	3.0 (1.0, 24.0)	139 (63)	-
10	Day 1	4	78.2 (14)	1.5 (1.0, 2.0)	880 (12)	-

Geometric mean (CV%) (individual values if n = 1 or 2); -, Not calculated; *1, Median (range); *2, Calculated based on the accumulation ratio; *3, One patient was excluded from parameter calculation; *4, n = 1, *5, n = 11; *6, n = 7; *7, n = 10

4.(ii).A.(2).3) 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 trametinib, DAB, and its metabolites. Patients orally received trametinib 2 mg QD from Day 2 to Day 15 and a single dose of DAB 75 mg on Day 1 and Day 15.

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

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

The geometric mean ratios [90% CI] of C_{max} and AUC_{tau} of DAB (on Day 21) when trametinib 2 mg QD and DAB 150 mg BID coadministered to when DAB 150 mg BID administered alone were 1.16 [0.80, 1.68] and 1.23 [0.89, 1.69], respectively, showing that trametinib had no clear effect on the PK of DAB. The applicant also explained that the difference in the dose of DAB (75, 150 mg) did not have any significant impact on the PK of trametinib.

PK parameters of trametinib

Dosage regimens (trametinib/DAB)	Time points	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_{tau} (ng·h/mL)
2 mg QD/75 mg BID	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)
2 mg QD/150 mg BID	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)

PK parameters of DAB and its metabolites

Dosage regimen (trametinib/ DAB)	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	DAB	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)*4	-	-
	Day 21	DAB	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)	-	-
2 mg QD/ 75 mg BID	Day 1	DAB	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	DAB	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	DAB	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	DAB	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)	-	-
2 mg QD/ 150 mg BID	Day 1	DAB	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	DAB	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

4.(ii).A.(3) Interactions with GEM (5.3.3.4, Study MEK112111 [August 2009 to July 2011])

An open-label study was conducted in 31 patients with solid tumors (26 patients included in PK analysis) to evaluate the effects of GEM (gemcitabine) on the PK of trametinib. Patients received trametinib 1-2.5 mg QD orally and GEM (1000 mg/m^2) intravenously on Days 1, 8, and 15, and the PK of trametinib was evaluated.

The geometric mean (CV%) of $AUC_{0\text{-}6h}$ of trametinib when trametinib 2 mg was administered for 15 days was 69.7 ng·h/mL (121%), which was not significantly different from $AUC_{0\text{-}6h}$ of trametinib in Study MEK111054 (97 ng·h/mL [33%]).

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

The applicant explained that trametinib is unlikely to induce QT interval prolongation, taking account of the following study results:

- In the foreign phase I study (Study MEK111054), the relationship between exposure to trametinib and QT adjusted by the estimate of population-specific exponent (QTcP) [0.429] or QT interval adjusted by the Fridericia method (QTcF) was investigated. The results did not show any clear relationship between plasma trametinib concentration and QTcP or QTcF. Multiple oral doses of trametinib 2 mg QD were administered, and at C_{max} (22.2 ng/mL) under a steady state [see "4.(ii).A.(2).2) Foreign phase I study"], the estimated median change in QTcP [90% CI] was 2.2 [0.2, 4.0] msec.
- In the Japanese phase I study (Study MEK114784), the relationship between exposure to trametinib and QT interval adjusted by the Bazett method (QTcB) was investigated. The results did not show any clear relationship between plasma trametinib concentration and QTcB.

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

A non-linear mixed effect model (software NONMEM version 7.2) -based PPK analysis (PPK analysis of trametinib monotherapy) was performed on PK data of trametinib (3120 time points in 493 patients) obtained from foreign clinical studies (Studies MEK111054, MEK113583, and MEK114267), where the PK of trametinib was described by a 2-compartment model with a biphasic first order absorption process.

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

Covariates investigated

PK parameters	Covariates
CL/F	Body weight, sex, age, hepatic impairment,*1 renal impairment,*2
Vc/F	Body weight, sex, age
Q/F	Body weight, sex

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

Body weight and sex were identified as significant covariates for CL/F, and body weight was for Q/F. No significant covariates were identified for Vc/F.

The applicant's explanation on these results:

- C_{max} and $AUC_{0\text{-}24h}$ of trametinib estimated by PPK analysis in a male patient with the lowest body weight (52 kg) were 5% and 7% higher, respectively, and in a male patient with the highest body weight (152 kg) were 28% and 13% lower, respectively, than in male patients with median body weight (79 kg). The respective estimated PK parameters in a female patient with the lowest body weight (41.2 kg) were 4% and 7% higher, and in a female patient with the highest body weight (131 kg) were 23% and 10% lower than female patients with median body weight (79 kg). Considering that the inter-individual variability (CV%) of CL/F in the final model was 24%, body weight-induced variations in C_{max} and $AUC_{0\text{-}24h}$ are generally within the range of inter-individual variability, suggesting that body weight has a minimal impact on the PK of trametinib. The results of the subpopulation analysis of the foreign phase III study (Study MEK114267) did not show any clear difference in efficacy or safety of trametinib among groups classified by body weight.
- The estimated CL/F of trametinib in male patients with median body weight was 26% higher than in female patients with median body weight. However, given the inter-individual variability (CV%) in CL/F of 24% in the final model, sex is considered to have a minimal impact on the PK of trametinib. The results of the subpopulation analysis of the foreign phase III study (Study MEK114267) did not show any clear difference in efficacy or safety of trametinib between men and women.

A non-linear mixed effect model (software NONMEM version 7.2.0) -based PPK analysis (PPK analysis in trametinib/DAB combination therapy) was performed on PK data of DAB (2405 time points in 349 patients) and trametinib (1513 time points in 295 patients) obtained from the foreign clinical study (Study BRF113220) pooled with PK data used in PPK analysis of DAB or trametinib when administered alone. In this PPK analysis, the model developed for PPK analysis of trametinib or DAB monotherapy (see "Review Report (1) Tafinlar Capsules 50 mg, Tafinlar Capsules 75 mg dated November 13, 2015" [in Japanese only]) was used.

In this analysis, the effects of the following factors on the PK of DAB and trametinib were investigated: body weight, sex, renal impairment, hepatic impairment, concomitant use of cytochrome P450 (CYP) 3A inhibitor, concomitant use of CYP3A inducer, and type of capsule used.

Body weight and sex were identified as significant covariates for CL/F of trametinib. These covariates were identical to those identified in the PPK analysis of trametinib monotherapy mentioned above, and therefore the applicant explained that the covariates identified had a minimal impact on the PK of trametinib.

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

The applicant explained that renal impairment is unlikely to affect the PK of trametinib, taking account of the following:

- The results of Study MEK113708 showed that the urinary excretion rate of trametinib and its metabolites combined was <19% of the total radioactivity recovered [see "4.(ii).A.(2).1) Foreign phase I study"], suggesting that the contribution of renal excretion in the elimination of trametinib is minimal.
- The absolute BA of trametinib was 72.3% [see "4.(i).A.(4) Foreign phase I study"].
- PPK analysis of trametinib monotherapy included 223 patients with mild renal impairment and 35 patients with moderate renal impairment (45.2% and 7.1%, respectively, of the entire PPK population), and difference in CL/F of trametinib between patients with normal renal function and those with mild or moderate renal impairment was <6%, while inter-individual variability of CL/F estimated in the PPK analysis was 24%, which suggests that renal impairment has a minimal impact on CL/F of trametinib.

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

On the basis of the data obtained from the foreign phase II study (Study MEK113583) and the foreign phase III study (Study MEK114267), the relationship between C_{min} of trametinib under steady state (measured value) or average plasma trametinib concentration (C_{avg}, predicted value) and efficacy (progression-free survival [PFS], response rate, and speed of tumor growth) or safety was investigated. C_{min} of trametinib and the predicted C_{avg} value used in this analysis were estimated based on PPK analysis of trametinib monotherapy [see "4.(ii).A.(5) Population pharmacokinetic (PPK) analysis].

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

Data of Studies MEK113583 and MEK114267 were stratified by median C_{avg} of trametinib, and the stratified hazard ratio of PFS was determined by the Cox proportional hazards model. PFS tended to increase in the strata with higher-than-median exposure compared to the strata with lower-than median-exposure.

Patients were classified into 4 groups by quartiles of C_{avg} of trametinib according to the results of Study MEK114267, and the relationship between exposure and response rate was investigated. No clear relationship was noted between exposure to trametinib and response rate.

On the basis of the results of Studies MEK113583 and MEK114267, the relationship between C_{min} (measured value) of trametinib and the speed of tumor growth* after tumor shrinkage was evaluated. The results showed a correlation between exposure and speed of tumor growth after tumor shrinkage.

*: Calculated from the extent of tumor growth and parameters of the mixed effect model.

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

Relationships have been suggested between inhibitors of mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK) and cardiac disorder, diarrhoea, visual disturbance, hypertension, skin disorder, hepatic dysfunction, and pneumonia (*Biochim Biophys Acta*. 2007;1773:1248-1255), possibly affecting survival or the quality of life seriously. Thus, the relationships between C_{avg} of trametinib and the incidences of the above adverse events were investigated on the basis of the results of Studies MEK113583 and MEK114267. The results did not show any clear relationship between C_{avg} and any of the above adverse events.

4.(ii).A.(8) Relationship between exposure and efficacy or safety in trametinib/DAB combination therapy

On the basis of the data obtained from the foreign phase III study (Study MEK115306), the relationships were evaluated between C_{min} of trametinib, DAB, and DAB metabolites (M7 and M8) or C_{avg} of DAB and efficacy or safety during concomitant use of trametinib with DAB. Individual C_{avg} and C_{min} values used in this evaluation were estimated by PPK analysis in trametinib/DAB 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_{min} of trametinib and C_{avg} of DAB, and the relationship between exposure and PFS was investigated. No clear relationship was observed between exposure to trametinib and PFS, whereas PFS tended to be lower in the group with the highest exposure to DAB 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_{min} of trametinib, DAB, and DAB metabolites (M7 and M8) and C_{avg} of DAB, and the relationship between exposure and the incidence of pyrexia was investigated. The results suggested that the incidence of pyrexia increased with increasing exposure to trametinib, DAB, and M7.

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

The applicant explained that there is no distinct difference in the PK of trametinib alone or in combination with DAB between Japanese and non-Japanese patients, given the following findings:

- In the Japanese phase I study (Study MEK114784) and the foreign phase I study (Study MEK111054) of trametinib monotherapy, in which a single or multiple oral doses of trametinib 1, 2, or 3 mg QD were administered, the PK of trametinib showed no distinct difference between Japanese and non-Japanese patients [see "4.(ii).A.(1).1) Japanese phase I study" and "4.(ii).A.(2).2) Foreign phase I study"].
- In the foreign phase I/II study (Study BRF113220) and the Japanese phase I/II study (Study MEK116885), in which trametinib 2 mg was administered concomitantly with DAB 150 mg, the PK of trametinib, DAB, or DAB metabolites (M4, M7, and M8) showed no distinct difference between Japanese and non-Japanese patients [see "4.(ii).A.(1).2) Japanese phase I/II study" and "4.(ii).A.(2).3) Foreign phase I/II study"].

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

4.(ii).B.(1) Administration of trametinib in patients with hepatic dysfunction

The applicant's explanation of trametinib administration in patients with hepatic dysfunction:

Although no clinical study data are available on the PK of trametinib in patients with hepatic dysfunction, the previous sections have shown that CES1, CES2, etc., are involved in the metabolism of trametinib [see 3.(ii).A.(3).1) *In vitro* metabolism"]. Since CES1 is expressed mainly in the liver and CES2 mainly in the liver and small intestine (*Drug Metab Pharmacokinet*. 2015;30:30-51), patients with hepatic dysfunction may have decreased CES1 and CES2 activities, resulting in a reduced trametinib-metabolizing activity in the liver. Also, since trametinib is excreted mainly in feces [see "4.(ii).A.(2).1) Foreign phase I study"], the biliary excretion rate of trametinib and its metabolites may be decreased by hepatic dysfunction, resulting in a delay in the elimination of trametinib from the body. The following observations seem to raise no particular safety concerns in administering trametinib to patients with mild hepatic dysfunction. However, administering trametinib to patients with moderate or severe hepatic

dysfunction needs caution because none of these patients have been treated with trametinib. A clinical study of trametinib (Study MEC116354) in patients with hepatic dysfunction is currently ongoing, and the results will be obtained in [redacted] 20[redacted].

- No clear difference between patients with mild hepatic dysfunction and those with normal hepatic function was noted in the incidence of adverse events.
- PPK analysis of trametinib monotherapy included 64 patients with mild hepatic dysfunction (13.0% of the entire population), and the difference in CL/F of trametinib between patients with normal hepatic function and those with mild hepatic dysfunction was 2%. Compared with the inter-individual variability of CL/F (24%) estimated in this analysis, the effects of hepatic dysfunction on CL/F of trametinib is minor.

PMDA's view:
PMDA accepted the applicant's explanation. The results of ongoing Study MEC116354 should be provided to healthcare professionals in clinical settings appropriately as soon as they become available.

4.(ii).B.(2) Pharmacokinetic interaction between trametinib and DAB

The applicant's explanation of low likelihood of the pharmacokinetic interaction between trametinib and DAB:

- In the foreign phase I/II study (Study BRF113220), trametinib/DAB combination therapy did not affect the PK of DAB [see "4.(ii).A.(2).3) Foreign phase I/II study"].
- No clear difference in PK parameters of trametinib was observed between the trametinib 2 mg QD/DAB 150 mg BID group in the foreign phase I/II study (Study BRF113220) or the Japanese phase I/II study (Study MEK116885) and the trametinib 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).1) Japanese phase I study," "4.(ii).A.(1).2) Japanese phase I/II study," "4.(ii).A.(2).2) Foreign phase I study," and "4.(ii).A.(2).3) 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 9 studies: 1 Japanese phase I study; 1 Japanese phase I/II study; 3 foreign phase I studies; 1 foreign phase I/II study; and 3 foreign phase III studies. The applicant also submitted the results from a total of 5 studies as reference data: 1 Japanese phase I study; 2 foreign phase I studies; 1 foreign phase I/II study; and 1 foreign phase II study.

List of clinical studies on efficacy and safety

Data category	Region	Study	Phase	Study population	No. of enrollment	Dosage regimen	Main endpoints
Evaluation	Japan	MEK114784	I	Patients with solid tumors	18 (a) 13 (b) 5	(a) Oral dose of trametinib 1, 2, or 3 mg QD (b) Oral dose of trametinib 2 mg QD, and intravenous dose of GEM 1000 mg/m^2 on Days 1, 8, and 15 in each cycle of 28 days	Safety PK
	Japan	MEK116885	I/II	Patients with solid tumors, or unresectable malignant melanoma, with BRAF V600 mutations	12 6 in phase I 6 in phase II	Oral dose of trametinib 2 mg QD and DAB 150 mg BID	Efficacy Safety PK
	Overseas	MEK113709	I	Patients with solid tumors	24	Single oral dose of trametinib 2 mg under fasted conditions or after intake of high-fat/high-calorie diet	PK
	Overseas	MEK113708	I	Patients with solid tumors	2	Single oral dose of ^{14}C-labeled trametinib (oral solution) 2 mg	PK
	Overseas	MEK112111	I	Patients with solid tumors	31	Oral dose of trametinib 1, 2, or 2.5 mg QD and intravenous dose of GEM 1000 mg/m^2 on Days 1, 8, and 15 in each cycle of 28 days	PK Safety
	Overseas	BRF113220 (phase II part)	I/II	Patients with unresectable malignant melanoma with BRAF V600 mutations	162	Oral dose of trametinib 1 or 2 mg QD with DAB 150 mg BID, or DAB 150 mg BID monotherapy	Efficacy Safety PK
	Overseas	MEK114267 (METRIC)	III	Patients with unresectable malignant melanoma with BRAF V600 mutations	322 (a) 214 (b) 108	(a) Oral dose of trametinib 2 mg QD (b) Intravenous dose of dacarbazine 1000 mg/m^2 or paclitaxel 175 mg/m^2 at 3-week intervals	Efficacy Safety
	Overseas	MEK115306 (COMBI-D)	III	Patients with unresectable malignant melanoma with BRAF V600 mutations	423 (a) 211 (b) 212	(a) Oral dose of trametinib 2 mg QD with DAB 150 mg BID or (b) oral dose of placebo with DAB 150 mg BID	Efficacy Safety
	Overseas	MEK116513 (COMBI-V)	III	Patients with unresectable malignant melanoma with BRAF V600 mutations	704 (a) 352 (b) 352	(a) Oral dose of trametinib 2 mg QD with DAB 150 mg BID (b) Oral dose of vemurafenib 960 mg BID	Efficacy Safety
Reference	Japan	MEK117134	II	Patients with biliary cancer	20	Oral dose of trametinib 2 mg QD	PK
	Overseas	MEK115064	I	Patients with solid tumors	4	Single oral dose of trametinib 2 mg followed by a single intravenous dose of ^{14}C-labeled trametinib 5 μg	PK Safety
	Overseas	MEK111054	I	Patients with solid tumors	206 (a) 55 (b) 112 (c) 39	(a) Oral dose of trametinib 0.125-2 mg QD for 21 days, followed by washout period of 7 days in each cycle of 28 days (b) Oral dose of trametinib 6, 8, or 10 mg QD for 1 or 2 days, followed by oral dose of trametinib 2, 2.5, or 3 mg QD (c) Oral dose of trametinib 2.5, 3, or 4 mg QD (d) Oral dose of trametinib 0.5, 1, 2, or 2.5 mg QD for 15 days, followed by oral dose of trametinib 2 or 2.5 mg QD	Efficacy Safety PK
	Overseas	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 trametinib 2 mg QD from Day 2 to Day 14 and oral dose of DAB 75 mg on Days 1 and 15 (b) Oral dose of trametinib 1, 1.5, or 2 mg QD with DAB 75 or 150 mg BID (c) Oral dose of DAB 75 or 150 mg BID monotherapy, or trametinib 2 mg QD with DAB 75 or 150 mg BID	Efficacy Safety PK
	Overseas	MEK113583	II	Patients with malignant melanoma with BRAF V600 mutations	97	Oral dose of trametinib 2 mg QD	Efficacy Safety PK

The outline of each clinical study is 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 3 clinical pharmacology studies in patients with 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 during study periods.

1) Foreign phase I study (5.3.1.1, Study MEK113709 [May to September 2011])
2) Foreign phase I study (5.3.3.2, Study MEK113708 [January to July 2011])
3) Foreign phase I study (5.3.3.4, Study MEK112111 [August 2009 to July 2011])

(2) Japanese clinical studies

1) Japanese phase I study (5.3.5.2, Study MEK114784 [January 2011 to July 2013])

An open-label, uncontrolled study in patients with solid tumors (target sample size: a maximum of 24 patients in part 1; a maximum of 12 patients in part 2) was conducted at 2 Japanese medical institutions to investigate the safety and the PK of trametinib.

In part 1, patients orally received a single dose of trametinib 1, 2, or 3 mg, and after a 6-day washout period, received trametinib 1, 2, or 3 mg QD. In part 2, patients orally received trametinib 2 mg QD, and GEM (1000 mg/m^2) intravenously on Days 1, 8, and 15 in each cycle of 28 days. In both parts, treatment was continued until disease progression or any other criteria for discontinuation (occurrence of an adverse event, consent withdrawal, etc.).

All 18 patients enrolled in the study (13 in part 1; 5 in part 2) received the study drug and were included in the safety analysis.

In part 1, dose-limiting toxicity (DLT) was observed in 1 of 6 patients in the trametinib 2 mg group (pneumonia) but not observed in any of 3 patients in the trametinib 3 mg group, thus the maximum tolerated dose (MTD) was not reached in this study. On the basis of the results in part 1 and other results, the recommended trametinib dose in part 2 was considered to be 2 mg QD.

In part 2, no DLT was observed, but serious interstitial lung disease was observed in 3 of 5 patients.

Death during the treatment period or within 28 days after the last dose occurred in 1 patient in part 2, and was considered as a safety issue. The death was caused by interstitial lung disease, and its causal relationship to the study drug could not be 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; target sample size, 6 patients) and (b) patients with unresectable malignant melanoma with BRAF V600 mutations*[1] (phase II; target sample size, 6 patients) was conducted at 2 Japanese medical institutions to investigate the efficacy, safety, and PK of trametinib/DAB*[2].

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

Patients orally received a single dose of trametinib 2 mg and DAB 150 mg on Day 1 and continued to receive trametinib 2 mg QD and DAB 150 mg BID from Day 2 onward until disease progression, death, or an unacceptable adverse event.

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

In phase I part, none of the 5 patients* to be evaluated for DLT developed it.

*: One of 6 patients enrolled in phase I part was excluded from DLT evaluation due to aggravation of systemic symptoms associated with the progression of the primary disease.

The response rate* assessed by the investigator based on RECIST ver.1.1, the primary endpoint for the efficacy in phase II part, is shown in the following table.

*: 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 occurred that led to death 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) [20 - ongoing (data cut-off; , 20)])

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, 150 patients) to compare the safety, efficacy, and PK between the trametinib/DAB group and the DAB group.

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

Patients orally received trametinib 1, 2 mg QD and DAB 150 mg BID in combination, or DAB (150 mg) BID alone, until disease progression or any other discontinuation criteria (e.g., occurrence of an adverse event, consent withdrawal) occurred.

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

*: One patient assigned to the DAB alone group received trametinib 2 mg concomitantly by mistake and was therefore included in the trametinib 2 mg + DAB group.

Adverse events leading to death during the treatment period or within 14 days after the last dose*[1] occurred in 1 of 54 patients (1.9%) in the trametinib 1 mg + DAB group; 4 of 55 patients (7.3%) in the trametinib 2 mg + DAB group; and 5 of 53 patients (9.4%) in the DAB alone group. The deaths were caused by sepsis in 1 patient in the trametinib 1 mg + DAB 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 trametinib 2 mg + DAB group. Causal relationship to the study drug was ruled out for all of them. Death due to disease progression occurred in 28 patients in the trametinib 1 mg + DAB group; 28 patients in the trametinib 2 mg + DAB group; and 5 patients in the DAB alone 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 trametinib 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 trametinib treatment (trametinib therapy ended on Day 944) and died of cerebrovascular accident on Day 961.
*4: A man aged 74 years. The patient experienced pulmonary embolism (Grade 3) on Day 335 of trametinib treatment, received heparin and other drugs, and recovered on Day 340. On Day 375 (trametinib therapy 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 trametinib treatment (trametinib therapy 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 MEK114267 [METRIC] [November 2010 – ongoing (data cut-off; October 26, 2011)])

An open-label, randomized, comparative study was conducted in patients with unresectable malignant melanoma with BRAF V600 mutations* (target sample size, 297 patients) to compare the efficacy and safety between trametinib monotherapy and investigator-selected treatment (DTIC or paclitaxel [PTX]) (chemotherapy) at 86 medical institutions overseas.

*: Determined by PCR

Patients in the trametinib group orally received trametinib 2 mg QD and patients in the chemotherapy group received DTIC 1000 mg/m^2 or PTX 175 mg/m^2 intravenously once every 3 weeks until disease progression, death, or study termination.

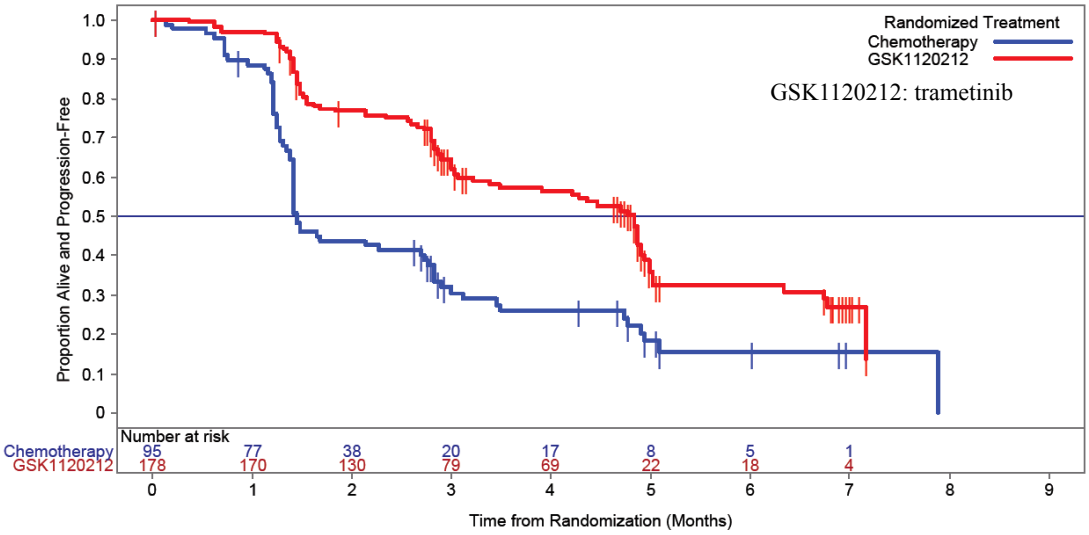
All 322 patients enrolled and randomized in the study (214 in the trametinib group, 108 in the chemotherapy group) were included in the ITT population. Of those in the ITT population, 273 patients without a history of brain metastasis (178 in the trametinib group, 95 in the chemotherapy group) were included in the primary efficacy population and subjected to efficacy analysis. Of those in the ITT population, 310 patients who received ≥1 dose of the study drug (211 in the trametinib group, 99 in the chemotherapy group) were included in safety analysis.

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

Analysis of PFS (primary efficacy population; assessed by investigator; data cut-off, October 26, 2011)

	Trametinib	Chemotherapy
Number of patients	178	95
Number of death or aggravation (%)	96 (53.9)	68 (71.6)
Median [95% CI] (months)	4.8 [3.5, 4.9]	1.4 [1.4, 2.7]
Hazard ratio [95% CI]*1	0.44 [0.31, 0.64]	
P value (two-sided)*2	<0.0001	

*1, Pike's estimate; *2, Stratified log-rank test (stratified by lactic dehydrogenase (LDH) level and by history of chemotherapy); significance level (one-sided) 0.025



Kaplan-Meier curves of PFS (primary efficacy population; assessed by investigator; data cut-off, October 26, 2011)

Adverse events leading to death occurred during the treatment period or within 30 days after the last dose in 4 of 211 patients (1.9%) in the trametinib group and 2 of 99 patients (2.0%) in the chemotherapy group. Causes of death were myocardial infarction,*1 renal failure, duodenal perforation, hepatic failure/renal failure*2 in 1 patient each in the trametinib group and pneumonia and cholecystitis in 1 patient each in the chemotherapy group. Of these, a causal relationship to the study drug could not be ruled out for renal failure in the trametinib group. Death due to disease progression occurred in 29 patients in the trametinib group and in 12 patients in the chemotherapy group.

*1: A man aged 77 years with a history of atrial fibrillation and anemia. He was hospitalized for syncope on Day 11 of trametinib treatment. On Day 15, he had chest pain, and myocardial infarction (Grade 3) was diagnosed upon examination such as electrocardiography, cardiac catheterization, and he was implanted with a coronary stent. On Day 63 (the last day of trametinib therapy), he had dyspnoea and hypoxaemia immediately after blood transfusion for anaemia. Upon detailed examination, myocardial infarction was diagnosed and he was hospitalized. Supportive measures including oxygen supplementation were given, but he died of myocardial infarction on Day 65.

*2: A man aged 23 years with normal renal and hepatic function before trametinib therapy. On Day 104 of trametinib therapy (trametinib was discontinued on Day 105), he was hospitalized for vomiting (Grade 2). Detailed examination revealed renal and hepatic disorder. Carboplatin and paclitaxel treatment were started on Day 111. Oedema and bleeding tendency were observed on Day 114 and renal and hepatic failure were noted on Day 115. He died of renal and hepatic failure on Day 119.

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 at 163 medical institutions overseas in patients with unresectable malignant melanoma with BRAF V600 mutations* (target sample size, 694 patients) to compare the efficacy and safety between the trametinib/DAB group and the vemurafenib (Vem) group.

*: Determined by THxID BRAF kit

Patients in the trametinib/DAB group orally received trametinib 2 mg QD and DAB 150 mg BID, and patients in the Vem group orally received Vem 960 mg BID, 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 trametinib/DAB group, 352 in the Vem group) were included in the ITT population and subjected to efficacy analysis. Of those, 699 patients who received ≥1 dose of the study drug (350 in the trametinib/DAB group, 349 in the Vem group) were included in the safety analysis.

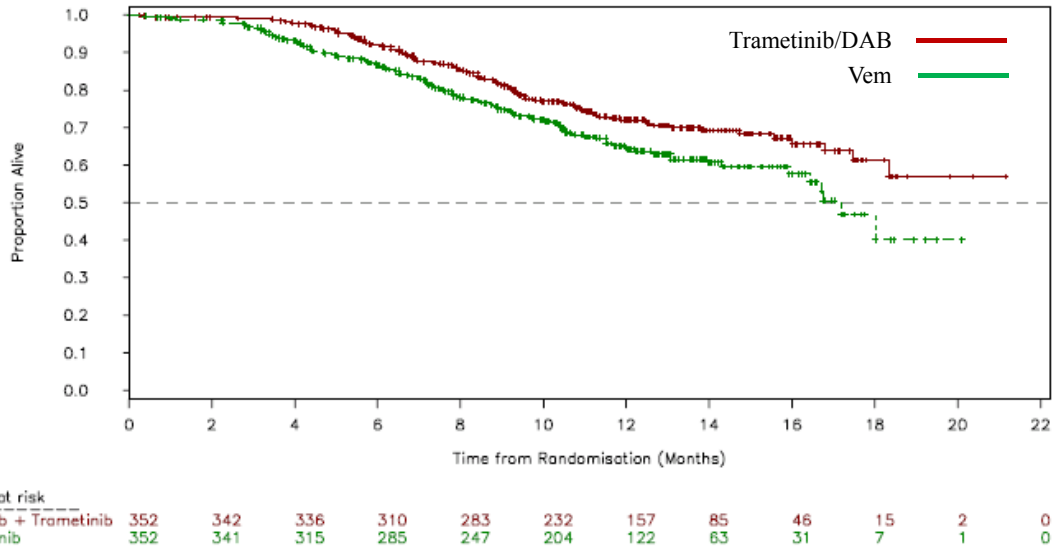
The primary endpoint of the study was overall survival (OS). An interim analysis for efficacy and futility was conducted at the time point when 202 OS events (70% of the target number of events) occurred. Type 1 error probability associated with the interim analysis of OS was adjusted for by O'Brien-Fleming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

Results of the interim analysis of OS and Kaplan-Meier curves are 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)

	Trametinib/DAB	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	

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



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 3 of 350 patients (0.9%) in the trametinib/DAB group and in 3 of 349 patients (0.9%) 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 trametinib/DAB 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 trametinib/DAB group and in 115 patients in the Vem group.

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

*2: A man aged 66 years. He was hospitalized for decreased platelet count and pulmonary embolism (Grade 3) on Day 320 of trametinib therapy. Acute myeloid leukaemia was diagnosed, and chemotherapy was started. On Day 334 (the last day of trametinib therapy was Day 321), he fell 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 for paralysis on her right side, vomiting, etc., on Day 236 of trametinib treatment (the last day 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., was administered, but she died of brain stem haemorrhage on the same day. Autopsy did not show findings such as brain metastatic lesion 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 trametinib/DAB group and the placebo/DAB group (concomitant use of DAB with placebo).

*: Determined by THxID BRAF kit.

Patients orally received trametinib 2 mg QD or placebo + DAB 150 mg BID until disease progression, death, an unacceptable adverse event, or consent withdrawal.

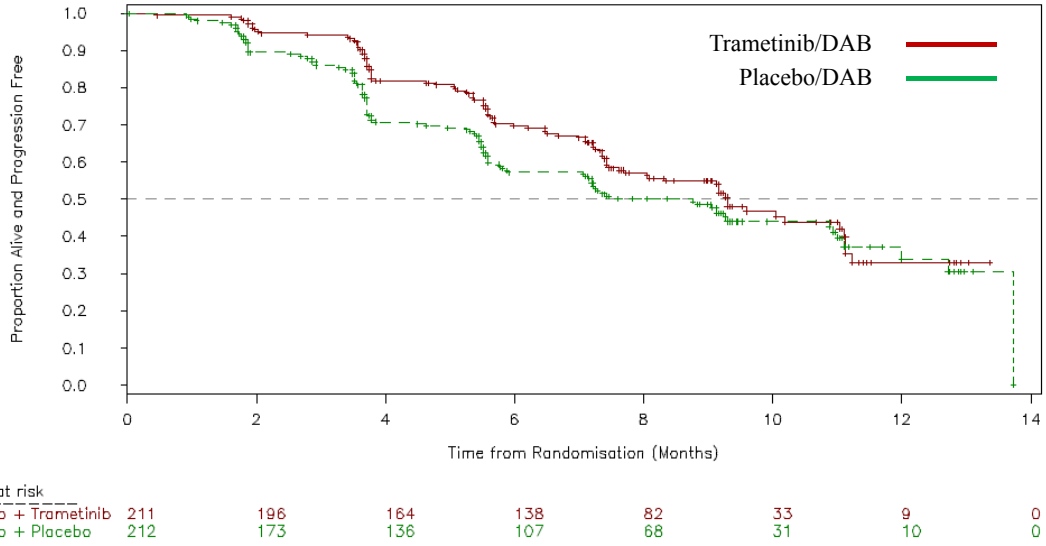
All 423 patients enrolled and randomized in the study (211 in the trametinib/DAB group, 212 in the placebo/DAB group) were included in the ITT population and subjected to efficacy analysis. Of those, 420 patients (209 in the trametinib/DAB group, 211 in the placebo/DAB group) receiving ≥1 dose of the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

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

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

	Trametinib/DAB	Placebo/DAB
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 5 of 209 patients (2.4%) in the trametinib/DAB group and in 1 of 211 patients (0.5%) in the placebo/DAB 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 trametinib/DAB group and bile duct adenocarcinoma*6 in 1 patient in the placebo/DAB group. A causal relationship to the study drug could not be ruled out for bile duct adenocarcinoma in the placebo/DAB group. Death due to disease progression occurred in 90 patients in the trametinib/DAB group and in 119 patients in the placebo/DAB 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 trametinib treatment (the last day was Day 121), she was hospitalized for vomiting. Detailed examination detected not brain metastasis but cerebral

haemorrhage, and the patient died of cerebral haemorrhage on Day 126.

*3: A man aged 75 years with a history of hypertension. Hyperglycemia was noted on Day 85 of trametinib treatment, and an oral hypoglycemic drug administration was started on Day 92. On Day 144 (trametinib 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 valve stenosis who was being treated with anticoagulants, etc. On Day 126 of trametinib treatment (the last day was Day 127), she was hospitalized with suspected cerebrovascular accident. Prolonged activated partial thromboplastin time and increased prothrombin time were observed, 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 trametinib treatment, decreased ejection fraction was noted, whereupon trametinib 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) Clinical pharmacology

The applicant submitted data from the following 3 clinical pharmacology studies in patients with biliary cancer, solid tumors, and lymphoma [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. Adverse events leading to death during these clinical studies occurred in 1.9% (4 of 206) of patients. The causes of death were pulmonary embolism, sudden death, renal failure, and haemorrhage from brain metastatic lesion in 1 patient each. Of these, a causal relationship to trametinib could not be ruled out for sudden death.* Death due to disease progression occurred in 32 patients.

*: A woman aged 67 years with a history of chronic obstructive pulmonary disease. She did not have a history of cardiac disease or pulmonary embolism, and showed normal electrocardiogram on the screening test. She did not have any noteworthy problems until Day 138 of trametinib therapy, but was found dead in her house on Day 139. There were no medical findings suggestive of the cause of death, and no autopsy was performed.

1) Japanese phase II study (5.3.1.2, Study MEK117134 [September 2013 – ongoing (data cut-off; July 4, 2014)])
2) Foreign phase I study (5.3.1.1, Study MEK115064 [June to December 2011])
3) Foreign phase I study (5.3.5.2, Study MEK111054 [July 2008 – ongoing (data cut-off; June 7, 2011)])

(2) Foreign clinical studies

1) 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, approximately 146 patients) to investigate the safety of trametinib, DAB, and trametinib/DAB.

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

Adverse events leading to death occurred during the treatment period or within 14 days after the last dose in 5 of 253 patients (2.0%). The causes of death were convulsion,*1 ventricular arrhythmia,*2 hyponatraemia, completed suicide, and pulmonary embolism*3 in 1 patient each. Of these, 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 thrombus was being treated with anticoagulants. On Day 89 of trametinib therapy, rectal haemorrhage was noted, whereupon trametinib was discontinued on Day 91. On Day 92, a pacemaker was implanted for atrioventricular block. During the implantation procedure, Grade 2 convulsions occurred, followed by consciousness disturbed. Head CT on Day 94 revealed cerebral haemorrhage. On Day 100, convulsions occurred again and he died of convulsions on Day 102.

*2: A man aged 69 years with a history of hypothyroidism, deep vein thrombosis, and hypertension. Since he was aware of decreased appetite, fatigue, dizziness, and chills, he was advised by the attending physician on Day 327 to temporarily withdraw from the study, but continued to receive the study drug by 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 trametinib 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 lesion but decreased cardiac output was noted. The patient did not respond to treatments given

in the intensive-care units 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 hemorrhage. She was hospitalized for acute pancreatitis on Day 310 of trametinib 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, the patient did not recover and died of pulmonary embolism on the same day.

2) Foreign phase II study (5.3.5.2, Study MEK113583 [November 2009 to January 2013])

An open-label, uncontrolled study was conducted in patients with unresectable malignant melanoma with BRAF V600 mutations (target sample size, 110 patients) to investigate the safety, efficacy, and PK of trametinib at 10 medical institutions overseas.

All 97 patients who were registered in the study and received ≥1 dose of the study drug were included in the safety analysis.

There was no adverse event leading to death during the treatment period or within 28 days after the last dose. Death due to disease progression occurred in 68 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 trametinib were 3 foreign phase III studies (Study MEK114267 [METRIC], Study MEK116513 [COMBI-V], and Study MEK115306 [COMBI-D]) in patients with unresectable malignant melanoma with BRAF V600 mutations, and decided to focus on evaluating the submitted data of these studies.

The efficacy and safety of trametinib in Japanese patients were to be evaluated mainly on the basis of data from 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 efficacy of trametinib 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 rational for selecting the control group in the METRIC, COMBI-V, and COMBI-D studies:

At the time when the METRIC study was started (November 2010), the standard therapy for patients with unresectable malignant melanoma with BRAF V600 mutations was DTIC in the EU and DTIC or PTX in the US (European Society for Medical Oncology clinical recommendations for diagnosis, treatment, and follow up, 2009, National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology Melanoma [NCCN Guidelines], 2009). Therefore, the DTIC or PTX group was selected by the investigator as the control group in the METRIC 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 Guidelines [v.3.2012]). Accordingly, a Vem group was selected as the control group in the COMBI-V study.

In the COMBI-D study, a study to demonstrate an add-on effects of trametinib/DAB over DAB alone, placebo/DAB was selected as the control because (i) foreign phase III study (Study BRF113683 [BREAK-3 study]) in patients with unresectable malignant melanoma with BRAF V600 mutations was ongoing to compare the efficacy and safety between DAB monotherapy and DTIC, and (ii) DAB monotherapy was likely to be demonstrated to be effective for this patient population.

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 METRIC and COMBI-D studies:

In patients with unresectable malignant melanoma with BRAF V600 mutations, the target patient population in the METRIC and COMBI-D studies, prolonged PFS means an increase in time to occurrence of tumor aggravation, which in turn results in an improvement in QOL of patients and is of clinical significance. It is therefore appropriate to have selected PFS as the primary endpoint in these studies.

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 METRIC and COMBI-D studies to evaluate the efficacy of trametinib in these patients. On the other hand, PFS may have a certain clinical significance depending on the intensity of its effects. In the METRIC and COMBI-D studies, 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 that OS was selected as the primary endpoint.

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

(a) METRIC study

The superiority of the trametinib group over the chemotherapy group 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 (primary efficacy population; independent assessment; data cut-off, October 26, 2011)

	Trametinib	Chemotherapy
Number of patients	178	95
Number of deaths or aggravations (%)	82 (46.1)	67 (70.5)
Median [95% CI] (months)	4.9 [4.5, 5.1]	1.6 [1.4, 2.8]
Hazard ratio [95% CI]*1	0.41 [0.29, 0.60]	
P value (two-sided)*2	<0.0001	

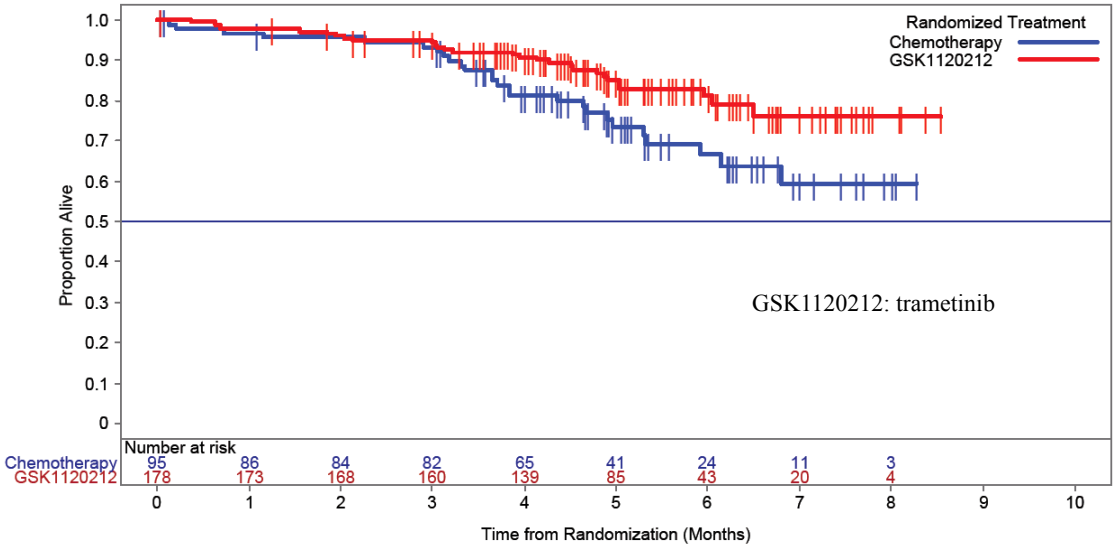
*1, Pike's estimate; *2, Stratified log-rank test (stratified by LDH level and by history of chemotherapy)

Results of OS, a secondary endpoint, and Kaplan-Meier curves are shown in the following table and figure, respectively. At the time of OS analysis, trametinib was being administered to 51 of 108 patients (47.2%) in the chemotherapy group in a crossover manner.

Results of OS analysis (primary efficacy population; data cut off, October 26, 2011)

	Trametinib	Chemotherapy
Number of patients	178	95
Number of deaths (%)	28 (15.7)	26 (27.4)
Median [95% CI] (months)	NE	NE
Hazard ratio [95% CI]*1	0.53 [0.30, 0.94]	
P value (two-sided)*2	0.0181	

NE, Not estimable; *1, Pike's estimate; *2, Stratified log-rank test (stratified by LDH level and by history of chemotherapy)



Kaplan-Meier curves of OS (primary efficacy population; data cut-off, October 26, 2011)

(b) COMBI-V study

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

(c) COMBI-D study

The superiority of the trametinib/DAB group over the placebo/DAB group has been demonstrated in investigator-assessed PFS, the primary endpoint [see "4.(iii).A *Evaluation data* (3).4) 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, August 26, 2013)

	Trametinib/DAB	Placebo/DAB
Number of patients	211	212
PD or number of deaths (%)	93 (44.1)	94 (44.3)
Median [95% CI] (months)	10.1 [8.3, 11.8]	9.5 [7.3, 12.7]
Hazard ratio [95% CI]*1	0.78 [0.59, 1.04]	
P value (two-sided)*2	0.084	

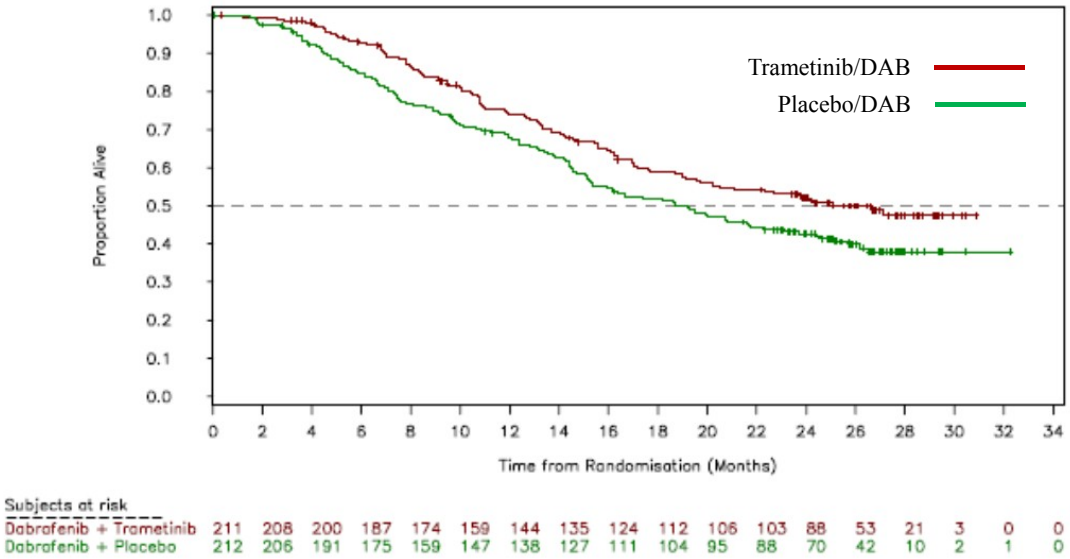
*1, Pike's estimate; *2, Stratified log-rank test (stratified by LDH level and by *BRAF* mutation type)

Final analysis results of OS, assessed as a secondary endpoint, and Kaplan-Meier curves are shown in the following table and figure, respectively. An interim analysis and the final analysis of OS were to be carried out when a statistically significant difference was observed in PFS. Type 1 error probability associated with the interim analysis of OS was to be adjusted for by O'Brien-Fleming type α-spending function based on the Lan-DeMets method.

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

	Trametinib/DAB	Placebo/DAB
Number of patients	211	212
PD or 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)

Since DAB, concomitantly administered with trametinib in the COMBI-V and COMBI-D studies, 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 DAB in patients with malignant melanoma.

The applicant's response:
The efficacy of DAB in patients with unresectable malignant melanoma with BRAF V600 mutations can be considered demonstrated by the following clinical study results.

- BREAK-3 study compared the efficacy and safety between DAB monotherapy and DTIC in patients with unresectable malignant melanoma with BRAF V600 mutations. The superiority of DAB over DTIC in investigator-assessed PFS, the primary endpoint, has been demonstrated (*Lancet*. 2012;380:358-365).

PMDA's view:
PMDA has concluded that the efficacy of trametinib monotherapy has been demonstrated in patients with unresectable malignant melanoma with BRAF V600 mutations: in the METRIC study, for the following reasons: (a) trametinib was superior to chemotherapy 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 trametinib group did not tend to decrease compared with OS in the chemotherapy group.

PMDA has concluded that the efficacy of trametinib/DAB 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 trametinib monotherapy and DAB monotherapy, respectively, in addition to the above COMBI-V and COMBI-D studies.

4.(iii).B.(2).4) Efficacy in Japanese patients
In 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%) [see "4.(iii).A *Evaluation data* (2).2) Japanese phase I/II study"]. No clinical data of trametinib monotherapy in Japanese patients with malignant melanoma with BRAF V600 mutations are presently available.

PMDA's view:
On the basis of the above results, PMDA has concluded that efficacy of trametinib/DAB can be expected in these patients [see "4.(iii).B.(4) Clinical positioning" for clinical usefulness of trametinib monotherapy in Japanese patients with malignant melanoma with BRAF V600 mutations], although the

efficacy of trametinib in Japanese patients can only be evaluated to a limited extent since the number of Japanese patients in Study MEK116885 was extremely 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 the adverse events that need particular cautions in treatment with trametinib are the following: cardiac disorders, hepatic dysfunction, pyrexia, eye disorders, and rhabdomyolysis.

In addition to these adverse events, in treatment with trametinib, attention should also be paid to the occurrence of hypertension, skin disorders, bone marrow depression, interstitial lung disease, deep vein thrombosis, pulmonary embolism, cerebrovascular disorder, and renal impairment. With these premises, PMDA has concluded that trametinib 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 the physician with sufficient knowledge and experience of cancer chemotherapy. Because of the extremely limited experience of treatment with trametinib in Japanese patients, information should be continuously collected after market launch, and new safety information, should be provided appropriately to healthcare professionals in clinical settings.

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

(a) Safety profile of trametinib monotherapy

The applicant's explanation on the safety profile of trametinib monotherapy:
The following table summarizes the safety in the METRIC study.

Summary of safety (METRIC study)

	Number of patients (%)	
	Trametinib (n = 211)	Chemotherapy (n = 99)
All adverse events	209 (99.1)	91 (91.9)
Grade ≥3 adverse events	100 (47.4)	34 (34.3)
Adverse events leading to death	4 (1.9)	2 (2.0)
Serious adverse events	38 (18.0)	20 (20.2)
Adverse events leading to treatment discontinuation	20 (9.5)	9 (9.1)
Adverse events leading to treatment interruption	74 (35.1)	22 (22.2)
Adverse events leading to dose reduction	58 (27.5)	10 (10.1)

Adverse events with an incidence ≥10% higher in the trametinib group than in the chemotherapy group were rash (57.3% in the trametinib group, 10.1% in the chemotherapy group), dermatitis acneiform (19.0%, 1.0%), dry skin (11.4%, 0%), diarrhoea (43.1%, 16.2%), and oedema peripheral (25.6%, 3.0%). Grade ≥3 adverse events with an incidence ≥2% higher were rash (7.6%, 0%) and hypertension (12.3%, 3.0%). There were no serious adverse events, or adverse events leading to treatment discontinuation with an incidence ≥2% higher in the trametinib group than in the chemotherapy group. Adverse events leading to treatment interruption with an incidence ≥2% higher were rash (9.0%, 0%), ejection fraction decreased (3.8%, 0%), and diarrhoea (2.8%, 0%). Adverse events leading to dose reduction with an incidence ≥2% higher were rash (9.0%, 2.0%) and ejection fraction decreased (2.8%, 0%).

The applicant's explanation on the difference in the safety of trametinib monotherapy between Japanese and non-Japanese patients:
The following table summarizes the safety in the trametinib group in Study MEK114784 in Japanese patients and in the METRIC study in non-Japanese patients.

Summary of safety in Japanese and non-Japanese patients (Study MEK114784 and METRIC study)

	Number of patients (%)	
	Japanese patients (Study MEK114784)	Non-Japanese patients (METRIC study)
	Trametinib (n = 13)	Trametinib (n = 211)
All adverse events	13 (100)	209 (99.1)
Grade ≥3 adverse events	4 (30.8)	100 (47.4)
Adverse events leading to death	0	4 (1.9)
Serious adverse events	3 (23.1)	38 (18.0)
Adverse events leading to treatment discontinuation	1 (7.7)	20 (9.5)
Adverse events leading to treatment interruption	8 (61.5)	74 (35.1)
Adverse events leading to dose reduction	3 (23.1)	58 (27.5)

Adverse events with an incidence≥20% higher in Japanese patients than in non-Japanese patients were rash (84.6% in Japanese patients, 57.3% in non-Japanese patients), palmar-plantar erythrodysaesthesia syndrome (38.5%, 4.3%), aspartate aminotransferase (AST) increased (76.9%, 8.5%), alanine aminotransferase (ALT) increased (53.8%, 6.6%), blood alkaline phosphatase (ALP) increased (38.5%, 5.7%), blood LDH increased (30.8%, 3.8%), stomatitis (38.5%, 6.2%), malaise (23.1%, 0.5%), decreased appetite (30.8%, 7.1%), and somnolence (23.1%, 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 (urticaria/tonsillitis/photopsia/vitreous floaters, feeling abnormal/dyskinesia, herpes zoster/cataract/leukocyturia/cholelithiasis/ligament sprain, hypogeusia/hiccups, vocal cord paralysis/pharyngeal oedema/musculoskeletal discomfort, delirium, pharyngeal inflammation) were Grade 1 or 2.

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

(b) Safety profile of trametinib/DAB combination therapy

The applicant's explanation on the safety profile of trametinib/DAB combination therapy:
The following table summarizes 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	
	Trametinib/DAB (n = 350)	Vem (n = 349)	Trametinib/DAB (n = 209)	Placebo/DAB (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)	1 (0.5)
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 trametinib/DAB group than in the Vem group were pyrexia (52.6% in the trametinib/DAB 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 trametinib/DAB 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 trametinib/DAB 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 trametinib/DAB 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 trametinib/DAB group than in the placebo/DAB group were pyrexia (56.9% in the trametinib/DAB group, 32.7% in the placebo/DAB 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 trametinib/DAB group than in the placebo/DAB 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 trametinib/DAB group than in the placebo/DAB 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 trametinib/DAB combination therapy between Japanese and non-Japanese patients:
The following table summarizes the safety results from Study MEK116885 in Japanese patients and from the pooled data of the trametinib/DAB 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-V study, and COMBI-D study)

	Number of patients (%)	
	Japanese patients (Study MEK116885)	Non-Japanese patients (COMBI-V and COMBI-D studies)
	Trametinib/DAB (n = 12)	Trametinib/DAB (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 in Japanese patients than in non-Japanese patients after trametinib/DAB combination therapy. However, they were mild in severity, suggesting that trametinib/DAB is well tolerated also in Japanese patients.

PMDA's view:
The above results (a) from the METRIC study showed that the trametinib group did not show any clear tendency of higher incidence than the chemotherapy group in all adverse events, Grade ≥3 adverse

events, adverse events leading to death, or serious adverse events. Also, the above results (b) from the COMBI-V and COMBI-D studies showed that the trametinib/DAB group did not show any clear tendency of higher incidence than the control group in any of these adverse events. On the above basis, PMDA considers that trametinib and trametinib/DAB are well tolerated if appropriate measures such as treatment interruption, dose reduction, and treatment discontinuation are taken when necessary.

Information on adverse events (rash, dermatitis acneiform, dry skin, diarrhoea, oedema peripheral) that occurred with a higher incidence in the trametinib group than in the chemotherapy group in the METRIC 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, and diarrhoea) observed at a higher incidence in the trametinib/DAB group than in the control group in the COMBI-V and COMBI-D 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 trametinib 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: pyrexia, palmar-plantar erythrodysaesthesia syndrome, AST increased, ALT increased, blood ALP increased, blood LDH increased, stomatitis, malaise, decreased appetite, somnolence, oedema peripheral, and nasopharyngitis. 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 trametinib group or the trametinib/DAB group than in the control group, as well as on those with a higher incidence in Japanese patients than in non-Japanese patients, on the basis of the safety results mainly from Study MEK116885, the METRIC study, the COMBI-V study, and the COMBI-D study.

4.(iii).B.(3).2) Cardiac disorders

The applicant's explanation on cardiac disorders associated with trametinib:
The following table shows the incidence of cardiac disorders* associated with trametinib monotherapy in Study MEK114784 and the METRIC study.

*: In Study MEK114784, events corresponding to left ventricular dysfunction, a preferred term in MedDRA 16.0/J16.0; in the METRIC study, events corresponding to ejection fraction decreased, left ventricular dysfunction, and cardiac failure, preferred terms in MedDRA 14.1/J14.1.

Incidence of cardiac disorder (Study MEK114784 and METRIC study)

Preferred terms	Number of patients (%)					
	Study MEK114784 (MedDRA ver16.0/J16.0)		METRIC study (MedDRA ver14.1/J14.1)			
	Trametinib (n = 13)		Trametinib (n = 211)		Chemotherapy (n = 99)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac disorders	2 (15.4)	0	14 (6.6)	2 (1.0)	0	0
Ejection fraction decreased	0	0	11 (5.2)	1 (0.5)	0	0
Left ventricular dysfunction	2 (15.4)	0	3 (1.4)	1 (0.5)	0	0
Cardiac failure	0	0	1 (0.5)	1 (0.5)	0	0

In the trametinib group of the METRIC study, no fatal cardiac disorders occurred. Serious cardiac disorders occurred in 3 of 211 patients (1.4%). Cardiac disorders resulted in treatment discontinuation in 4 of 211 patients (1.9%), in treatment interruption in 10 of 211 patients (4.7%), and in dose reduction in 7 of 211 patients (3.3%). In Study MEK114784, no patients developed cardiac disorders that were fatal, serious, or resulted in treatment discontinuation or dose reduction, while 1 of 13 patients (7.7%) developed cardiac disorders that resulted in treatment interruption.

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

*: Events corresponding to left ventricular dysfunction, cardiac failure, or ejection fraction decreased, preferred terms in 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	
	Trametinib/DAB (n = 12)	Trametinib/DAB (n = 350)	Vem (n = 349)	Trametinib/DAB (n = 209)	Placebo/DAB (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 patients for whom trametinib is indicated, in clinical studies:

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

(b) Cardiac function was monitored periodically 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 a history of heart-related disease (controllable hypertension, dyslipidemia, arrhythmia, diabetes mellitus, chronic and obstructive pulmonary disease, etc.) were enrolled. In the COMBI-V study, 21 of 29 patients (72.4%) who showed decreased ejection fraction had a history of heart related disease.

PMDA's view:

When trametinib or trametinib/DAB is administered, attention should be paid to occurrence of cardiac disorder since (a) in the METRIC study, cardiac disorders occurred at a higher frequency in the trametinib group than in the chemotherapy group, (b) in the COMBI-V study, cardiac disorders occurred at a higher frequency in the trametinib/DAB group than in the Vem group, and most of them were serious events requiring dose adjustment, and (c) some patients died of myocardial infarction, myocardial ischaemia, and ventricular arrhythmia, respectively, in the METRIC study, the COMBI-D study, and Study BRF113220 [see "4.(iii).A *Evaluation data* (3).2) Foreign phase III study," "4.(iii).A *Evaluation data* (3).4) Foreign phase III study," and "4.(iii).A *Reference data* (2).1) Foreign phase I/II study"]. Information on the occurrences of cardiac disorders in clinical studies should be provided appropriately to healthcare professionals in clinical settings through package insert etc. In addition, cautions should be provided appropriately to healthcare professionals in clinical settings through package insert etc., so that patients eligible to be treated with trametinib are carefully selected; cardiac ultrasonography is performed periodically; and appropriate actions are taken if cardiac disease occurs.

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

The applicant's explanation on hepatic dysfunction associated with trametinib therapy:

The following table shows the incidence of hepatic dysfunction* associated with trametinib monotherapy in Study MEK114784 and the METRIC study.

*: In Study MEK114784, events corresponding to ALT increased or AST increased, preferred term in MedDRA16.0/J16.0; in the METRIC study, events corresponding to ALT increased, AST increased, or blood bilirubin increased, preferred terms in MedDRA 14.1/J14.1.

Incidence of hepatic dysfunction (Study MEK114784 and METRIC study)

Preferred terms	Number of patients (%)					
	Study MEK114784 (MedDRA ver16.0/J16.0)		METRIC study (MedDRA ver14.1/J14.1)			
	Trametinib (n = 13)		Trametinib (n = 211)		Chemotherapy (n = 99)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic dysfunction	10 (76.9)	0	20 (9.5)	5 (2.4)	4 (4.0)	2 (2.0)
AST increased	10 (76.9)	0	18 (8.5)	2 (1.0)	1 (1.0)	0
ALT increased	7 (53.8)	0	14 (6.6)	4 (1.9)	2 (2.0)	0
Blood bilirubin increased	0	0	2 (1.0)	1 (0.5)	1 (1.0)	1 (1.0)

In the trametinib group of the METRIC study, no fatal hepatic dysfunction occurred. Serious hepatic dysfunction occurred in 1 of 211 patients (0.5%), hepatic dysfunction resulted in treatment discontinuation in 1 of 211 patients (0.5%), in treatment interruption in 5 of 211 patients (2.4%), and in dose reduction in 2 of 211 patients (0.9%). In Study MEK114784, no patients developed hepatic dysfunction that were fatal, serious, or resulted in either treatment discontinuation or dose reduction, while 1 of 13 patients (7.7%) developed hepatic dysfunction that resulted in treatment interruption.

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

*: Events corresponding to ALT increased, liver function test abnormal, ascites, hepatic encephalopathy, AST increased, hepatic enzyme increased, hepatic function abnormal, bilirubin conjugated increased, blood ALP increased, blood bilirubin increased, cholestasis, hepatocellular injury, hepatotoxicity, transaminases increased, gamma-glutamyltransferase increased, and hypertransaminasaemia, preferred terms in 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	
	Trametinib/DAB (n = 12)	Trametinib/DAB (n = 350)	Vem (n = 349)	Trametinib/DAB (n = 209)	Placebo/DAB (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 trametinib/DAB group of the COMBI-V and COMBI-D studies, the median time to the first-time onset (range) of hepatic dysfunction was 57 days (8-681 days), showing no specific tendency in the time to onset.

In Study MEK114784, Study MEK116885, the METRIC study, the COMBI-D study, or the 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) occurred.

PMDA's view:

When trametinib or trametinib/DAB is administered, attention should be paid to occurrence of hepatic dysfunction since (a) the incidence was higher in Japanese patients than in non-Japanese patients; (b) in the COMBI-D study, hepatic dysfunction occurred at a higher frequency in the trametinib/DAB group than in the trametinib/placebo group, and serious hepatic dysfunction was observed; and (c) in the METRIC study, serious or fatal trametinib-associated hepatic dysfunction occurred. Information on the incidence of hepatic dysfunction in clinical studies should be appropriately provided to healthcare professionals in clinical settings through package insert, etc. In addition, cautions should be appropriately provided to healthcare professionals in clinical settings through package insert, etc., so

that a hepatic function should be tested periodically during treatment with trametinib and, if hepatic dysfunction occurs, appropriate measures should be taken.

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

The applicant's explanation on pyrexia-related events associated with trametinib therapy:

The following table shows the incidence of pyrexia-related events* associated with trametinib monotherapy in Study MEK114784 and the METRIC study.

*: In Study MEK114784, events corresponding to influenza like illness or pyrexia, preferred terms in MedDRA 16.0/J16.0; in the METRIC study, events corresponding to influenza like illness or pyrexia, preferred terms in MedDRA 14.1/J14.1.

Incidence of pyrexia-related events (Study MEK114784 and METRIC study)

Preferred terms	Number of patients (%)					
	Study MEK114784 (MedDRA ver16.0/J16.0)		METRIC study (MedDRA ver14.1/J14.1)			
	Trametinib (n = 13)		Trametinib (n = 211)		Chemotherapy (n = 99)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Pyrexia-related events	2 (15.4)	0	17 (8.1)	1 (0.5)	12 (12.1)	1 (1.0)
Pyrexia	1 (7.7)	0	12 (5.7)	1 (0.5)	10 (10.1)	1 (1.0)
Influenza like illness	1 (7.7)	0	6 (2.8)	0	2 (2.0)	0

In the trametinib group of the METRIC study, a serious pyrexia-related event occurred in 1 of 211 patients (0.5%). Pyrexia-related events resulted in treatment discontinuation in 1 of 211 patients (0.5%), treatment interruption in 4 of 211 patients (1.9%), and dose reduction in 1 of 211 patients (0.5%). In Study MEK114784, no patients developed pyrexia-related events that were serious or resulted in either treatment discontinuation or dose reduction, while 1 of 13 patients (7.7%) developed pyrexia-related events that resulted in treatment interruption.

The following table shows the incidence of pyrexia-related events* associated with trametinib/DAB combination therapy in Study MEK116885, the COMBI-V study, and the COMBI-D study.

*: Events corresponding to body temperature increased, hyperthermia, sweating fever, influenza like illness, or pyrexia, preferred terms in 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	
	Trametinib/DAB (n = 12)	Trametinib/DAB (n = 350)	Vem (n = 349)	Trametinib/DAB (n = 209)	Placebo/DAB (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 trametinib/DAB group of the COMBI-V and COMBI-D studies, the median time to the first-time onset (range) of pyrexia-related events was 31 days (1-774 days), showing no specific tendency in the time to onset.

PMDA's view:

When trametinib or trametinib/DAB is administered, attention should be paid to occurrence of pyrexia since (a) the incidence of pyrexia was higher in Japanese patients than in non-Japanese patients, and (b) the incidence of all-Grade pyrexia and serious pyrexia were higher in the trametinib/DAB 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 package insert, etc. In addition, cautions should be appropriately provided to healthcare professionals in clinical settings through package insert, etc., so that patient conditions are monitored periodically during treatment with trametinib and, if pyrexia occurs, appropriate actions are taken.

4.(iii).B.(3).5) Eye disorders

The applicant's explanation on trametinib-associated eye disorders:

The following table shows the incidence of eye disorders* associated with trametinib monotherapy in Study MEK114784 and the METRIC study.

*: In Study MEK114784, events corresponding to visual impairment, photopsia, vision blurred, or vitreous floaters, preferred terms in MedDRA 16.0/J16.0; in the METRIC study, events corresponding to vision blurred, chorioretinopathy, papilloedema, dry eye, photophobia, visual acuity reduced, or visual impairment, preferred terms in MedDRA 14.1/J14.1.

Incidence of eye disorders (Study MEK114784 and METRIC study)

Preferred terms	Number of patients (%)					
	Study MEK114784 (MedDRA ver16.0/J16.0)		METRIC study (MedDRA ver14.1/J14.1)			
	Trametinib (n = 13)		Trametinib (n = 211)		Chemotherapy (n = 99)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Eye disorders	3 (23.1)	0	18 (8.5)	1 (0.5)	3 (3.0)	0
Vision blurred	3 (23.1)	0	8 (3.8)	1 (0.5)	1 (1.0)	0
Photopsia	1 (8.7)	0	0	0	0	0
Dry eye	0	0	6 (2.8)	0	0	0
Chorioretinopathy	0	0	1 (0.5)	1 (0.5)	0	0
Papilloedema	0	0	1 (0.5)	0	0	0
Photophobia	0	0	1 (0.5)	0	0	0
Visual acuity reduced	0	0	1 (0.5)	0	0	0
Visual impairment	2 (15.4)	0	1 (0.5)	0	0	0
Vitreous floaters	1 (8.7)	0	0	0	1 (1.0)	0

In the trametinib group of the METRIC study, no patients developed eye disorders that were serious or resulted in dose reduction and 1 of 211 patients (0.5%) each developed those that resulted in treatment discontinuation or interruption. In Study MEK114784, no patients developed eye disorders that were serious or resulted in treatment discontinuation, interruption, or dose reduction.

The following table shows the incidence of eye disorders* associated with trametinib/DAB combination therapy in Study MEK116885, the COMBI-V study, and the COMBI-D study.

*: 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, visual field defect, visual impairment, vitreous detachment, dry eye, or vitreous floaters, preferred terms in MedDRA 17.0/J17.0.

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

	Number of patients (%)				
	Study MEK116885	COMBI-V study		COMBI-D study	
	Trametinib/DAB (n = 12)	Trametinib/DAB (n = 350)	Vem (n = 349)	Trametinib/DAB (n = 209)	Placebo/DAB (n = 211)
All adverse events	3 (25.0)	39 (11.1)	47 (13.5)	27 (12.9)	23 (10.9)
Grade ≥3 adverse events	1 (8.3)	2 (0.6)	4 (1.1)	3 (1.4)	0
Adverse events leading to death	0	0	0	0	0
Serious adverse events	0	3 (0.9)	3 (0.9)	3 (1.4)	3 (1.4)
Adverse events leading to treatment discontinuation	1 (8.3)	1 (0.3)	1 (0.3)	2 (0.9)	1 (0.5)
Adverse events leading to treatment interruption	0	4 (1.1)	6 (1.7)	9 (4.3)	6 (2.8)
Adverse events leading to dose reduction	0	2 (0.6)	1 (0.3)	2 (0.9)	1 (0.5)

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

PMDA's view:
When trametinib or trametinib/DAB is administered, attention should be paid to occurrence of eye disorders since (a) in the METRIC study, the incidence of eye disorders tended to be higher in the trametinib group than in the chemotherapy group, and (b) in the COMBI-V and COMBI-D studies, serious eye disorders occurred with trametinib/DAB combination therapy. Information on the incidence of eye disorders in clinical studies should be provided appropriately to healthcare professionals in clinical settings through package insert etc. In addition, cautions should be provided appropriately to healthcare professionals in clinical settings through package insert etc., so that patients are periodically monitored for eye disorders during trametinib treatment and, if eye disorders occur, appropriate actions are taken.

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

The applicant's explanation on hypertension associated with trametinib therapy:
The following table shows the incidence of hypertension* associated with trametinib monotherapy in Study MEK114784 and the METRIC study.

*: In Study MEK114784, events corresponding to hypertension, a preferred term in MedDRA 16.0/J16.0; in the METRIC study, events corresponding to blood pressure increased or hypertension, preferred terms in MedDRA 14.1/J14.1.

Incidence of hypertension (Study MEK114784 and METRIC study)

Preferred terms	Number of patients (%)					
	Study MEK114784 (MedDRA ver16.0/J16.0)		METRIC study (MedDRA ver14.1/J14.1)			
	Trametinib (n = 13)		Trametinib (n = 211)		Chemotherapy (n = 99)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypertension	1 (7.7)	0	33 (15.6)	26 (12.3)	7 (7.1)	3 (3.0)
Hypertension	1 (7.7)	0	32 (15.2)	26 (12.3)	7 (7.1)	3 (3.0)
Blood pressure increased	0	0	1 (0.5)	0	0	0

In the trametinib group of the METRIC study, no patients developed hypertension that was serious or resulted in treatment discontinuation, while hypertension resulted in treatment interruption in 3 of 211 patients (1%) and in dose reduction in 2 of 211 patients (1%). In Study MEK114784, no patients developed hypertension that was serious or resulted in treatment discontinuation, interruption, or dose reduction.

In clinical studies including the METRIC study, patients with poorly controlled hypertension were excluded and those with controllable hypertension were enrolled; however, 26 of 33 patients (78.8%) with hypertention had hypertension complications in the METRIC study.

The following table shows the incidence of hypertension* associated with trametinib/DAB combination therapy in Study MEK116885, the COMBI-V study, and the COMBI-D study.

*: Events corresponding to blood pressure diastolic increased, blood pressure increased, hypertension, blood pressure systolic increased, or diastolic hypertension, preferred terms in 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	
	Trametinib/DAB (n = 12)	Trametinib/DAB (n = 350)	Vem (n = 349)	Trametinib/DAB (n = 209)	Placebo/DAB (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 occurred only in limited number of patients after administration of trametinib. However, the incidence of Grade ≥3 hypertension was higher in the trametinib group in the METRIC study and in the trametinib/DAB group in the COMBI-V study, than in the respective control groups, suggesting that the onset of hypertension should be monitored closely in treatment with trametinib or trametinib/DAB. Information regarding the occurrence of hypertension in clinical studies should be provided appropriately to healthcare professionals in clinical settings through package insert etc. In addition, information regarding the occurrence of trametinib-associated hypertension should be continuously collected after market launch and the necessity of providing caution statements should be considered on the basis of these results.

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

The applicant's explanation on skin disorders associated with trametinib therapy:

The following table shows the incidence of skin disorders* associated with trametinib monotherapy in Study MEK114784 and the METRIC study.

*: In Study MEK114784, events corresponding to rash, seborrhoeic dermatitis, dermatitis acneiform, palmar-plantar erythrodysaesthesia syndrome, acne, pruritus, dermatitis contact, dry skin, skin fissures, toxic skin eruption, or urticaria, preferred terms in MedDRA 16.0/J16.0; in the METRIC study, events corresponding to rash, seborrhoeic dermatitis, dermatitis acneiform, rash pustular, palmar-plantar erythrodysaesthesia syndrome, erythema, rash maculo-papular, photosensitivity reaction, acne, dermatitis, rash macular, rash generalised, rash pruritic, or skin exfoliation, preferred terms in MedDRA 14.1/J14.1.

Incidence of skin disorders (Study MEK114784 and METRIC study)

Preferred terms	Number of patients (%)					
	Study MEK114784 (MedDRA ver16.0/J16.0)		METRIC study (MedDRA ver14.1/J14.1)			
	Trametinib (n = 13)		Trametinib (n = 211)		Chemotherapy (n = 99)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin disorders	13 (100)	0	184 (87.3)	25 (11.8)	13 (13.1)	0
Rash	11 (84.6)	0	121 (57.3)	16 (7.6)	10 (10.1)	0
Seborrhoeic dermatitis	1 (7.7)	0	3 (1.4)	0	0	0
Dermatitis acneiform	1 (7.7)	0	40 (21.7)	2 (1.0)	1 (1.0)	0
Rash pustular	0	0	10 (4.7)	2 (1.0)	0	0
PPES	5 (38.4)	0	9 (4.3)	0	0	0
Erythema	0	0	8 (3.8)	1 (0.5)	0	0
Rash maculo-papular	0	0	5 (2.4)	1 (0.5)	0	0
Photosensitivity reaction	0	0	3 (1.4)	1 (0.5)	2 (2.0)	0
Acne	1 (7.7)	0	4 (1.9)	1 (0.5)	0	0
Dermatitis	0	0	4 (1.9)	1 (0.5)	0	0
Rash macular	0	0	4 (1.9)	0	0	0
Rash generalised	0	0	1 (0.5)	1 (0.5)	0	0
Rash pruritic	0	0	1 (0.5)	0	0	0
Skin exfoliation	0	0	1 (0.5)	0	0	0
Pruritus	2 (15.4)	0	0	0	0	0
Dermatitis contact	1 (7.7)	0	0	0	0	0
Dry skin	1 (7.7)	0	0	0	0	0
Skin fissures	1 (7.7)	0	0	0	0	0
Toxic skin eruption	1 (7.7)	0	0	0	0	0
Urticaria	1 (7.7)	0	0	0	0	0

PPES: Palmar-plantar erythrodysaesthesia syndrome

In the trametinib group of the METRIC study, serious skin disorders occurred in 3 of 211 patients (1.4%), and skin disorders resulted in treatment discontinuation in 2 of 211 patients (0.9%), in treatment interruption in 25 of 211 patients (11.8%), and in dose reduction in 25 of 211 patients (11.8%). In Study MEK114784, no serious skin disorders occurred, while skin disorders resulted in treatment discontinuation in 1 of 13 patients (7.7%), in treatment interruption in 3 of 13 patients (23.1%), and in dose reduction in 1 of 13 patients (7.7%).

The following table shows the incidence of skin disorders* associated with trametinib/DAB combination therapy in Study MEK116885, the COMBI-V study, and the 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 in 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	
	Trametinib/DAB (n = 12)	Trametinib/DAB (n = 350)	Vem (n = 349)	Trametinib/DAB (n = 209)	Placebo/DAB (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 trametinib was phototoxic [see "3.(iii).A.(6).2) *In vitro* phototoxicity"]. Therefore, clinical study protocols of trametinib required that trametinib should not be exposed to sunlight unnecessarily and trametinib was well tolerated when in compliance with this requirement.

PMDA's view:
In clinical studies, serious skin disorders occurred only in limited numbers of patients after administration of trametinib. However, in the METRIC study, the incidence was higher in the trametinib group than in the chemotherapy group, and higher in Japanese patients than in non-Japanese patients, suggesting that the occurrence of skin disorders should be monitored closely in treatment with trametinib or trametinib/DAB. Information concerning the occurrence of skin disorders in clinical studies should be provided appropriately to healthcare professionals in clinical settings through package insert etc. In addition, information concerning the occurrence of trametinib-associated skin disorders should be continuously collected after market launch and the necessity of providing caution statements should be considered on the basis of these results.

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

The applicant's explanation on trametinib-associated bone marrow depression:
The following table shows the incidence of bone marrow depression* associated with trametinib monotherapy in Study MEK114784 and the METRIC study.

*: In Study MEK114784, events corresponding to white blood cell count decreased, haemoglobin decreased, platelet count decreased, anaemia, or thrombocytopenia, preferred terms in MedDRA 16.0/J16.0; in the METRIC study, events corresponding to neutropenia, white blood cell count decreased, neutrophil count decreased, pancytopenia, haemoglobin decreased, platelet count decreased, anaemia, or thrombocytopenia, preferred terms in MedDRA 14.1/J14.1.

Incidence of bone marrow depression (Study MEK114784 and METRIC study)

Preferred terms	Number of patients (%)					
	Study MEK114784 (MedDRA ver16.0/J16.0)		METRIC study (MedDRA ver14.1/J14.1)			
	Trametinib (n = 13)		Trametinib (n = 211)		Chemotherapy (n = 99)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Bone marrow depression	5 (38.4)	0	20 (9.5)	6 (2.8)	26 (26.3)	8 (8.1)
Neutropenia	0	0	3 (1.4)	0	6 (6.1)	3 (3.0)
White blood cell count decreased	1 (7.7)	0	1 (0.5)	0	1 (1.0)	1 (1.0)
Neutrophil count decreased	0	0	1 (0.5)	0	5 (5.1)	4 (4.0)
Pancytopenia	0	0	1 (0.5)	0	2 (2.0)	1 (1.0)
Haemoglobin decreased	1 (7.7)	0	2 (1.0)	1 (0.5)	1 (1.0)	0
Platelet count decreased	1 (7.7)	0	1 (0.5)	0	5 (5.1)	0
Anaemia	1 (7.7)	0	12 (5.7)	4 (1.9)	11 (11.1)	0
Thrombocytopenia	1 (7.7)	0	2 (1.0)	0	5 (5.1)	1 (1.0)

In the trametinib group of the METRIC study, no patients developed fatal bone marrow depression, and serious bone marrow depression occurred in 4 of 211 patients (1.9%). Bone marrow depression resulted in treatment discontinuation in 1 of 211 patients (0.5%), in treatment interruption in 4 of 211 patients (1.9%), and in dose reduction in 1 of 211 patients (0.5%). In Study MEK114784, bone marrow depression resulted in treatment interruption in 1 of 13 patients (7.7%), while no patients developed bone marrow depression that resulted in treatment discontinuation or dose reduction.

The following table shows the incidence of bone marrow depression* associated with trametinib/DAB combination therapy in Study MEK116885, the COMBI-V study, and the 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 in 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	
	Trametinib/DAB (n = 12)	Trametinib/DAB (n = 350)	Vem (n = 349)	Trametinib/DAB (n = 209)	Trametinib/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 occurred only in limited number of patients after administration of trametinib. However, since the incidence was higher in the trametinib/DAB group than in the control group, and higher in Japanese patients than in non-Japanese patients in both COMBI-V and COMBI-D studies, occurrence of bone marrow depression should be monitored carefully in treatment with trametinib or trametinib/DAB. Information regarding the occurrence of bone marrow depression in clinical studies should be provided appropriately to healthcare professionals in clinical settings through package insert etc. In addition, information regarding the occurrence of trametinib-associated bone marrow depression should be continuously collected after market launch and the necessity of providing caution statements should be considered on the basis of these results.

4.(iii).B.(3).9) Oedema

The applicant's explanation on oedema associated with trametinib therapy:

The following table shows the incidence of oedema associated with trametinib monotherapy in Study MEK114784 and the METRIC study.

*: In Study MEK114784, events corresponding to oedema peripheral, a preferred term in MedDRA 16.0/J16.0: in the METRIC study, events corresponding to oedema peripheral, localised oedema, lymphoedema, or oedema, preferred terms in MedDRA 14.1/J14.1.

Incidence of oedema (Study MEK114784 and METRIC study)

Preferred terms	Number of patients (%)					
	Study MEK114784 (MedDRA ver16.0/J16.0)		METRIC study (MedDRA ver14.1/J14.1)			
	Trametinib (n = 13)		Trametinib (n = 211)		Chemotherapy (n = 99)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Oedema	3 (23.1)	0	68 (32.2)	3 (1.4)	4 (4.0)	0
Oedema peripheral	3 (23.1)	0	54 (25.6)	2 (1.0)	3 (3.0)	0
Localised oedema	0	0	1 (0.5)	0	1 (1.0)	0
Oedema	0	0	6 (2.8)	0	1 (1.0)	0
Lymphoedema	0	0	12 (5.7)	1 (0.5)	0	0

In the trametinib group of the METRIC study, no patients developed oedema that resulted in dose reduction, while serious oedema occurred in 1 of 211 patients (0.5%), and oedema resulted in treatment discontinuation in 1 of 211 patients (0.5%) and in treatment interruption in 5 of 211 patients (2.4%). In Study MEK116885, no patients developed oedema that was serious or resulted in treatment discontinuation, interruption, or dose reduction.

The following table shows the incidence of trametinib/DAB-associated oedema* in Study MEK116885, the COMBI-V study, and the COMBI-D study.

*: Events corresponding to generalised oedema, lymphoedema, oedema peripheral, localised oedema, or oedema, preferred terms in MedDRA 17.0/J17.0.

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

	Number of patients (%)				
	Study MEK116885	COMBI-V study		COMBI-D study	
	Trametinib/DAB (n = 12)	Trametinib/DAB (n = 350)	Vem (n = 349)	Trametinib/DAB (n =209)	Placebo/DAB (n = 211)
All adverse events	7 (58.3)	63 (18.0)	44 (12.6)	53 (25.4)	23 (10.9)
Grade ≥3 adverse events	0	1 (0.3)	3 (0.9)	3 (1.4)	1 (0.5)
Adverse events leading to death	0	0	0	0	0
Serious adverse events	0	0	0	0	0
Adverse events leading to treatment discontinuation	0	1 (0.3)	1 (0.3)	1 (0.5)	0
Adverse events leading to treatment interruption	0	5 (1.4)	3 (0.9)	5 (2.4)	2 (0.9)
Adverse events leading to dose reduction	0	1 (0.3)	1 (0.3)	1 (0.5)	0

PMDA's view:

In clinical studies, there were only limited cases of serious oedema associated with trametinib. However, the incidence of oedema in the trametinib/DAB group in the METRIC study and COMBI-D study was higher than in the respective control groups. Also, the incidence was higher in Japanese patients than in non-Japanese patients. Information on the incidence of trametinib-associated oedema should be continuously collected after market launch and the necessity of providing caution statements should be considered on the basis of the results.

4.(iii).B.(3).10) Secondary malignant tumor

The applicant's explanation on trametinib-associated secondary malignant tumor:

No secondary malignant tumor associated with trametinib monotherapy was observed in Study MEK114784 or the METRIC study.

By contrast, the following table shows the incidence of trametinib/DAB-associated secondary malignant tumor* in the COMBI-V and COMBI-D studies. In Study MEK116885, there was no secondary malignant tumor associated with trametinib/DAB combination therapy.

*: Events corresponding to squamous cell carcinoma, squamous cell carcinoma of skin, keratoacanthoma, Bowen's disease, malignant melanoma, superficial spreading melanoma stage III, acute myeloid leukaemia, ovarian neoplasm, papillary thyroid cancer, phaeochromocytoma malignant, prostate cancer, or lung adenocarcinoma, preferred terms in MedDRA 17.0/J17.0.

Occurrence of secondary malignant tumor (COMBI-V and COMBI-D studies)

Preferred term (MedDRA ver17.0/J17.0)	Number of patients (%)			
	COMBI-V study		COMBI-D study	
	Trametinib/DAB (n = 350)		Trametinib/DAB (n = 209)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Squamous cell carcinoma	3 (0.9)	3 (0.9)	3 (1.4)	3 (1.4)
Squamous cell carcinoma of skin	1 (0.3)	1 (0.3)	2 (1.0)	2 (1.0)
Keratoacanthoma	1 (0.3)	1 (0.3)	1 (0.5)	1 (0.5)
Bowen's disease	0	0	3 (1.4)	0
Malignant melanoma	1 (0.3)	1 (0.3)	1 (0.5)	1 (0.5)
Superficial spreading melanoma stage III	1 (0.3)	1 (0.3)	0	0
Acute myeloid leukaemia	1 (0.3)	1 (0.3)	0	0
Lung adenocarcinoma	1 (0.3)	1 (0.3)	0	0
Ovarian neoplasm	1 (0.3)	1 (0.3)	0	0
Papillary thyroid cancer	0	0	1 (0.5)	0
Phaeochromocytoma malignant	0	0	1 (0.5)	1 (0.5)
Prostate cancer	0	0	1 (0.5)	1 (0.5)

In the COMBI-V and COMBI-D studies, trametinib therapy could be continued in all patients who experienced cuSCC, and in 6 of 9 patients who experienced non-cuSCC secondary malignant tumor after the tumor was surgically resected.

PMDA's view:
Although there were no patients who experienced secondary malignant tumor associated with trametinib monotherapy in the METRIC study, there were patients who experienced secondary malignant tumor associated with trametinib/DAB combination therapy in the COMBI-V and COMBI-D studies. Information on trametinib-associated secondary malignant tumor should be continuously collected after market launch and the necessity of providing caution should be considered on the basis of the results.

4.(iii).B.(3).11) Others
The applicant's explanation on adverse events that resulted in death in multiple patients in clinical studies and those with caution statements included in foreign package inserts, from (a) to (f).

(a) Interstitial lung disease*
*: Events corresponding to interstitial lung disease or pneumonitis, preferred terms in MedDRA 16.0/J16.0 in Study MEK114784, MedDRA 14.1/J14.1 in the METRIC study, and MedDRA 17.0/J17.0 in other clinical studies.

In the METRIC study, interstitial lung disease was observed in 2 of 211 patients (0.9%) treated with trametinib monotherapy, and the event was serious, resulting in discontinuation of trametinib treatment.

In Study MEK116885, the COMBI-V study, and the COMBI-D study, interstitial lung disease was observed after trametinib/DAB combination therapy in 1 of 12 patients (8.3%), 4 of 350 patients (1.1%), and 2 of 209 patients (1.0%), respectively. The event was Grade ≥3 in 1 of 350 patients (0.3%) in the COMBI-V study, and was serious in 1 of 12 patients (8.3%) in Study MEK116885, 2 of 350 patients (0.6%) in the COMBI-V study, and 1 of 209 patients (0.5%) in the COMBI-D study.

In Study MEK114784, serious interstitial lung disease occurred in 3 of 5 patients following concomitant use of trametinib with GEM, and one of them died [see "4.(iii).A *Evaluation data* (2).1) Japanese phase I study"].

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

In the METRIC study, deep vein thrombosis or pulmonary embolism associated with trametinib monotherapy occurred in 4 of 211 patients (1.9%). The event was serious in all of them and the severity was Grade ≥3 in 2 patients.

In the COMBI-V and COMBI-D studies, deep vein thrombosis or pulmonary embolism was observed after trametinib/DAB combination therapy in 8 of 350 patients (2.3%) and 6 of 209 patients (2.9%),

respectively. The event was Grade ≥3 in 7 of 350 patients (2.0%) in the COMBI-V study and in 4 of 209 patients (1.9%) in the COMBI-D study, and was serious in 4 of 350 patients (1.1%) and 4 of 209 patients (1.9%), respectively.
In the clinical pharmacology study and in the foreign clinical studies, 1 patient each died of pulmonary embolism [see "4.(iii).A *Reference data* (1) Clinical pharmacology" and "4.(iii).A *Reference data* (2).1) Foreign phase I/II study"].

(c) Cerebrovascular disorders*

*: In the METRIC study, events corresponding to ischaemic stroke, a preferred term in MedDRA 14.1/J14.1; in other clinical studies, events corresponding to cerebral haemorrhage, brain stem haemorrhage, cerebrovascular accident, subdural haematoma, or transient ischaemic attack, preferred terms in MedDRA 17.0/J17.0.

In the METRIC study, serious cerebrovascular disorders associated with trametinib monotherapy occurred in 1 of 211 patients (0.5%), but trametinib treatment was continued.

In the COMBI-V and COMBI-D studies, cerebrovascular disorder occurred after trametinib/DAB combination therapy in 5 of 350 patients (1.4%) and 4 of 209 patients (1.9%), respectively, and 3 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 disorder [see "4.(iii).A *Evaluation data* (3).3) Foreign phase III study" and "4.(iii).A *Evaluation data* (3).4) Foreign phase III study"].

(d) Renal impairment*

*: In Study MEK114784, events corresponding to proteinuria, a preferred term in MedDRA 16.0/J16.0; in the METRIC study, events corresponding to proteinuria, renal failure, blood urea increased, or blood creatinine increased, preferred terms in MedDRA 14.1/J14.1; in other clinical studies, events corresponding to blood creatinine increased, blood urea increased, renal failure, renal failure acute, creatinine renal clearance decreased, glomerular filtration rate decreased, hyperazoturia, nephritis, or nephropathy toxic, preferred terms in MedDRA17.0/J17.0.

In Study MEK114784 and the METRIC study, renal impairment occurred after trametinib monotherapy in 2 of 13 patients (15.4%) and 6 of 211 patients (2.8%), respectively. The event was Grade ≥3 in 2 of 211 patients (1.0%) in the METRIC study and was serious in 2 of 211 patients (1.0%). In the COMBI-V and COMBI-D studies, renal impairment was observed after trametinib/DAB combination therapy in 24 of 350 patients (6.9%) and 8 of 209 patients (3.8%), respectively. The event was Grade ≥3 in 5 of 350 patients (1.4%) in the COMBI-V study and in 2 of 209 patients (1.0%) in the COMBI-D study, and was serious in 9 of 350 patients (2.9%) in the COMBI-V study and in 2 of 209 patients (1.0%) in the COMBI-D study.

Two patient in the METRIC study and 1 patient in the clinical pharmacology study died of renal failure [see "4.(iii).A *Reference data* (1) Clinical pharmacology"].

(e) Rhabdomyolysis*

*: In Study MEK114784, events corresponding to blood creatine phosphokinase increased, a preferred term in MedDRA 16.0/J16.0; in the METRIC study, events corresponding to myopathy, rhabdomyolysis, or blood creatine phosphokinase increased, preferred terms in MedDRA 14.1/J14.1; in other clinical studies, events corresponding to rhabdomyolysis or blood creatine phosphokinase increased, preferred terms in MedDRA 17.0/J17.0.

In Study MEK114784 and the METRIC study, rhabdomyolysis occurred after trametinib monotherapy in 3 of 13 patients (23.1%) and 11 of 211 patients (5.2%), respectively. The event was Grade ≥3 in 1 of 13 patients (7.7%) in Study MEK114784 and in 5 of 211 patients (2.4%) in the METRIC study, and was serious in 3 of 211 patients (1.4%) in the METRIC study.

In the COMBI-V and COMBI-D studies, rhabdomyolysis occurred after trametinib/DAB combination therapy in 8 of 350 patients (2.3%) and 6 of 209 patients (2.9%), respectively. The event was Grade ≥3 in 6 of 350 patients (1.7%) in the COMBI-V study, and was serious in 4 of 350 patients (1.1%) in the COMBI-V study.

(f) Haemorrhage*

*: In Study MEK114784, events corresponding to haematochezia, epistaxis, or haemoglobin decreased, preferred terms in MedDRA 16.0/J16.0; in the METRIC study, events corresponding to petechiae, post procedural haemorrhage, gingival bleeding, haematochezia, haemoglobin decreased, haematuria, rectal haemorrhage, purpura, haemorrhoidal haemorrhage, bloody discharge, intra-abdominal haematoma, melaena, conjunctival haemorrhage, contusion, epistaxis, vaginal hemorrhage, gastric haemorrhage, or periorbital haematoma, preferred terms in MedDRA 14.1/J14.1; in other clinical studies, events corresponding to activated partial thromboplastin time prolonged, gingival bleeding, anal haemorrhage, haematochezia, haematocrit decreased, 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 hemorrhage, fibrin D dimer increased, vascular rupture, vessel puncture site haematoma, gastritis haemorrhagic, wound haemorrhage, haematuria, brain stem haemorrhage, haemarthrosis, laryngeal haemorrhage, or post procedural haematoma, preferred terms in MedDRA 17.0/J17.0.

In Study MEK114784 and the METRIC study, haemorrhage occurred after trametinib monotherapy in 3 of 13 patients (23.1%) and 36 of 211 patients (17.1%), respectively. Haemorrhage was Grade ≥3 in 4 of 211 patients (1.9%) in the METRIC study and was serious in 2 of 211 patients (0.9%) in the METRIC study.

In the COMBI-V and COMBI-D studies, haemorrhage occurred after trametinib/DAB combination therapy in 62 of 350 patients (17.7%) and 40 of 209 patients (19.1%), respectively. Haemorrhage was Grade ≥3 in 10 of 350 patients (2.9%) in the COMBI-V study and in 6 of 209 patients (2.9%) in the COMBI-D study, and was serious in 11of 350 patients (3.1%) in the COMBI-V study and in 6 of 209 patients (2.9%) in the COMBI-D study.

PMDA's view:
Information on the incidence of the above adverse events (a) to (e) in clinical studies should be appropriately provided to healthcare professionals in clinical settings through the package insert, for the reasons listed below. Although adverse events (f) occurred only infrequently in clinical studies, some of them were serious haemorrhage. Information on the incidence of haemorrhage associated with trametinib therapy should be continuously collected after market launch and the necessity of providing caution statements should be considered on the basis of the results.

(a) In Study MEK114784, 1 patient died of interstitial lung disease. Therefore, attention should be paid to occurrence of interstitial lung disease in treatment with trametinib or trametinib/DAB.

(b) In foreign clinical pharmacology studies and Study BRF113220, patients died of pulmonary embolism. Therefore, attention should be paid to occurrence of deep vein thrombosis and pulmonary embolism in treatment with trametinib or trametinib/DAB.

(c) In the COMBI-V study, the COMBI-D study, and Study BRF113220, there were multiple events of fatal cerebrovascular disorders. Thus, occurrence of cerebrovascular disorder should be carefully monitored in treatment with trametinib or trametinib/DAB.

(d) In the METRIC study and the clinical pharmacology study, patients died of renal failure. Thus, occurrence of renal impairment should be carefully monitored in treatment with trametinib or trametinib/DAB.

(e) In the METRIC study, the incidence of rhabdomyolysis tended to be higher in the trametinib group than in the chemotherapy group. Thus, occurrence of rhabdomyolysis should be carefully monitored in treatment with trametinib or trametinib/DAB.

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

In clinical practice guidelines and leading clinical oncology textbooks in and out of Japan, trametinib treatment of unresectable malignant melanoma with BRAF V600 mutations is described as shown below.

[Clinical practice guidelines]

- NCCN Guidelines (v.3.2015): Trametinib/DAB is recommended for patients with unresectable malignant melanoma with BRAF V600 mutations (category 1*[1]). Trametinib is a treatment option for patients intolerant to BRAF inhibitors (category 2A*[2]).

*1: Based on high-level evidence with uniform NCCN consensus that the intervention is appropriate.
*2: Based on relatively low-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): Trametinib and trametinib/DAB 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 trametinib and chemotherapy (DTIC or PTX), and the results showed improved life expectancy in the trametinib group.

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

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

The applicant's explanation on the clinical positioning of trametinib monotherapy and trametinib/DAB combination therapy:
Although the results of the METRIC study showed a statistically significant increase in PFS, the primary endpoint, in the trametinib monotherapy group compared with the chemotherapy (DTIC or PTX) group, the PFS-prolonging effect was limited. In the foreign phase II study (Study MEK113583) in patients with unresectable malignant melanoma with BRAF V600 mutations who had been treated with a BRAF inhibitor, trametinib was ineffective in patients who showed disease progression during treatment with BRAF inhibitor (NCCN Guideline [v.3.2015]). However, trametinib monotherapy can be positioned as a treatment option for patients for whom trametinib/DAB is not recommended, for example in patients with low tolerance to DAB, for the following reasons.

- The METRIC study showed the superiority of trametinib over chemotherapy in investigator-assessed PFS, the primary endpoint [see "4.(iii).A *Evaluation data* (3).2) Foreign phase III study"].
- In Study MEK113583, trametinib was effective in 2 of 3 patients who had discontinued BRAF inhibitor because of adverse events.
- Although study results of trametinib monotherapy in Japanese patients with unresectable malignant melanoma with BRAF V600 mutations are not available, trametinib monotherapy was well tolerated in Japanese patients in Study MEK114784.

The results of COMBI-V and COMBI-D studies have demonstrated the clinical usefulness of trametinib/DAB in patients with unresectable malignant melanoma with BRAF V600 mutations. Therefore, trametinib/DAB can be positioned as a treatment option for this patient population.

PMDA's view:
The applicant's explanation on the treatment with trametinib/DAB was accepted. On the other hand, trametinib monotherapy should not be recommended in Japanese patients with unresectable malignant melanoma with BRAF V600 mutations because no clinical results are available in this patient population [see "4.(iii).B.(2).4) Efficacy in Japanese patients"].

4.(iii).B.(5) Indication
The proposed indication of trametinib was "Malignant melanoma with BRAF V600 mutations." The Precautions for Indications section included the following description.

- Trametinib 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.

- The physician should be thoroughly versed in the content of the "Clinical Studies" section and fully understand the efficacy and safety of trametinib before selecting patients eligible to be treated.

- The efficacy and safety of trametinib as an adjuvant chemotherapy have not been established.

Upon evaluating "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 trametinib should be "unresectable malignant melanoma with *BRAF* mutations." PMDA also concluded that information on BRAF testing kits used in Study MEK116885, COMBI-V study, and COMBI-D study, and on *BRAF* mutation types in patients enrolled in these studies should be provided in the Clinical Studies section of the package insert, and that the proposed Precautions for Indication should be modified as shown below.

- Trametinib should be administered to patients with known *BRAF* mutations through tests performed by a thoroughly experienced pathologist or testing laboratories. 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 trametinib before selecting the patients eligible to be treated.

- The efficacy and safety of trametinib in the adjuvant chemotherapy have not been established.

4.(iii).B.(5).1) The target patient population and indication of trametinib

PMDA asked the applicant's opinion about trametinib treatment in patient population not included in COMBI-D, COMBI-V, or other studies, namely patients with resectable malignant melanoma and patients with wild-type BRAF malignant melanoma.

The applicant's response:

Since surgical removal is recommended for patients with resectable malignant melanoma, trametinib treatment in these patients is not recommended.

Similarly, trametinib 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 trametinib in this patient population, and (b) trametinib has a lower inhibitory effect on BRAF wild-type melanoma than BRAF mutated melanoma [see "3.(i).A.(1).5) Studies on cell growth-inhibitory effects of trametinib and on related factors"].

On the above basis, the patients to be treated with trametinib 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 *BRAF* mutation types in patients enrolled in Study MEK116885, the COMBI-V study, and the COMBI-D study and the Precautions for Indication section included caution stating that trametinib should be administered to patients known to have *BRAF* mutations.

PMDA's view:

The applicant's opinion is basically acceptable, but the indication should be "unresectable malignant melanoma with *BRAF* mutations" for the following reasons.

- Patients enrolled in Study MEK116885, the COMBI-V study, or the COMBI-D study were those with unresectable malignant melanoma with *BRAF* mutations.
- In Study MEK116885, the COMBI-V study, and the COMBI-D study, patients were selected by THxID BRAF Kit, and the efficacy and safety of trametinib in these patients were confirmed. It is therefore recommended to use this kit as the companion diagnostic for selecting patients eligible to be treated with trametinib in clinical settings.

4.(iii).B.(5).2) Efficacy and safety of trametinib as an adjuvant chemotherapy

The applicant's explanation:

Since there are no clinical data on the efficacy and safety of trametinib as an adjuvant chemotherapy, caution would be provided to those effects 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 2 mg of trametinib administered orally once daily." The Precautions for Dosage and Administration section included the following.

- See the "Clinical Studies" section and the package insert of DAB before trametinib treatment.
- Postprandial administration of trametinib was reported to decrease C_{max} and AUC. In order to avoid food effect, trametinib should be administered either ≥1 hour before meal or ≥2 hours after meal.
- Criteria for trametinib dose adjustment
- A 2-mg tablet should be used when 2 mg is to be administered.
- Patients should be instructed to receive trametinib only if the next scheduled dose is ≥12 hours away in case of a missed dose.

The result of evaluating "4.(i).B.(1) Bioequivalence between 0.5-mg and 2-mg tablets to be marketed," "4.(i).B.(2) Food effect," and "4.(iii).B.(4) Clinical positioning" as well as the following section, PMDA concluded that the dosage and administration of trametinib should be "The usual adult dosage is 2 mg of trametinib administered orally once daily under fasted conditions in combination with dabrafenib," and that the following should be included in the Precautions for Dosage and Administration section.

- Postprandial administration of trametinib was reported to decrease C_{max} and AUC. It is desirable to refrain from receiving trametinib from 1 hour before meal to 2 hours after meal to avoid food effect.
- If adverse drug reaction occurs after the use of trametinib, trametinib treatment 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, trametinib may be continued without interruption or dose reduction after appropriate actions such as surgical resection. The 0.5-mg tablets should be used only in administration at reduced doses.

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 1-level lower dose.
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	2 mg/dose (once daily)
1-level dose reduction	1.5 mg/dose (once daily)
2-level dose reduction	1 mg/dose (once daily)
3-level dose reduction	Discontinue

4.(iii).B.(6).1) Trametinib monotherapy and concomitant use with antineoplastic agents other than DAB

PMDA asked the applicant to explain the efficacy and safety of trametinib monotherapy and of concomitant use with antineoplastic agents other than DAB.

The applicant's response:
On the basis of the results of the METRIC study etc., trametinib monotherapy is considered 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 trametinib with antineoplastic agents other than DAB in patients with unresectable malignant melanoma with BRAF V600 mutations. Thus, concomitant administration of trametinib with antineoplastic agents other than DAB is not recommended.

PMDA's view:
Taking account of the following, the dosage and administration should clearly indicate that trametinib is to be concomitantly administered with DAB.

- Trametinib monotherapy is not recommended in Japanese patients with unresectable malignant melanoma with BRAF V600 mutations [see "4.(iii).B.(4) Clinical positioning"].
- There are no clinical study data confirming the efficacy and safety of concomitant use of trametinib with antineoplastic agents other than DAB in patients with unresectable malignant melanoma with BRAF V600 mutations.

4.(iii).B.(6).2) Dosage and administration of trametinib

The applicant explained the rationale for the proposed dosage and administration of trametinib in trametinib/DAB combination therapy:
In the foreign phase I study (Study MEK111054) in patients with advanced solid tumors, DLT was observed in 1 of 3 patients (chorioretinopathy) in the trametinib 4 mg QD group, and MTD in trametinib monotherapy was considered to be 3 mg QD. Also, the results of this study suggested the efficacy of trametinib at 2 mg QD, a lower dose than MTD, thus the recommended dosage and administration of trametinib was considered to be 2 mg QD. Also, from the results of phase I part of the foreign phase I/II study (Study BRF113220), the recommended doses in trametinib monotherapy and DAB monotherapy (trametinib 2 mg QD and DAB 150 mg BID) were shown to be well-tolerated. In addition, the results in phase II part showed that PFS tended to increase in the trametinib 2 mg + DAB group compared with the trametinib 1 mg + DAB group. On the basis of the results, the dosage regimen of "trametinib 2 mg QD and DAB 150 mg BID" was employed in the COMBI-D study, the COMBI-V study, and Study MEK116885, and the results showed the clinical significance of trametinib/DAB combination therapy in patients with unresectable malignant melanoma with BRAF V600 mutations. Accordingly, the proposed dosage and administration was determined based on the dosage regimen used in these studies.

PMDA accepted the applicant's explanation.

4.(iii).B.(6).3) Dose adjustment etc.

The applicant's explanation on the dose adjustment of trametinib:
In Study MEK116885, the COMBI-V study, and the COMBI-D study, the criteria for dose adjustment of trametinib were specified according to the severity etc., of adverse events observed, and trametinib was tolerated when administered in compliance with the criteria. Therefore, the dose adjustment criteria were set in the Precautions for Dosage and Administration section by referring to these criteria. Since pyrexia of ≥38.5°C and uveitis are adverse events specific to DAB, the dose adjustment of trametinib is unnecessary even if these events are observed. On the other hand, left ventricular ejection fraction decreased, retinal vein occlusion, detachment of retinal pigment epithelium, and interstitial pneumonia/pneumonitis are adverse events specific to trametinib, and no dose adjustment of DAB is needed in case of these events. Adverse drug reactions that require dose adjustment of either trametinib or DAB 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 trametinib or DAB only

Interruption, dose reduction, or discontinuation of trametinib only	Left ventricular ejection fraction decreased, retinal vein occlusion, detachment of retinal pigment epithelium, interstitial pneumonia, pneumonitis
Interruption, dose reduction, or discontinuation of DAB only	Pyrexia of ≥38°C, uveitis

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 trametinib only or DAB only, when the following results are taken into account. Therefore the above setting is concluded to be not appropriate.

- In the METRIC study, some patients experienced pyrexia after administration of trametinib alone, resulting in dose adjustment.
- In the COMBI-V and COMBI-D studies, some patients experienced pyrexia or uveitis after administration of trametinib/DAB, resulting in dose adjustment for both trametinib and DAB. In the COMBI-V and COMBI-D studies, some patients experienced ventricular ejection fraction decreased, detachment of retinal pigment epithelium, interstitial pneumonia/pneumonitis, pyrexia, or uveitis after receiving trametinib/DAB, resulting in dose adjustment for both trametinib and DAB.

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 trametinib in routine clinical use after market launch, a post-marketing surveillance in all patients treated with trametinib (the surveillance) will be conducted.

Since trametinib/DAB 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 based on the incidence of adverse drug reactions in Japanese and foreign clinical studies in which trametinib/DAB 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 sample size was set to 200 patients receiving trametinib/DAB, on the basis of the incidence of the planned priority survey items 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 trametinib administered to Japanese patients with unresectable malignant melanoma with *BRAF* mutations. Therefore, a post-marketing surveillance should be conducted in all patients treated with trametinib in order 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 Japanese and foreign clinical studies, the following adverse events are considered to require particular caution in trametinib/DAB combination therapy, and should be included in the priority items in the surveillance: Cardiac disorder, hepatic dysfunction, pyrexia, eye disorder, rhabdomyolysis, spinocellular carcinoma, and secondary malignant tumor other than spinocellular carcinoma.

The number of patients to be surveyed and the follow-up period should be re-examined in the light of the nature of the priority survey items.

Since trametinib and DAB 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 trametinib with DAB should be designed.

4.(iv) Adverse events etc., observed in clinical studies

Deaths reported in clinical data submitted for safety evaluation were described in "4.(iii) Summary of clinical efficacy and safety." Major adverse events other than death were as shown below.

4.(iv).(1) Japanese phase I study (Study MEK114784)

4.(iv).(1).1) Part 1

Adverse events and those for which a causal relationship to the study drug could not be ruled out occurred in all patients treated with trametinib: 4 patients in the 1 mg group; 6 patients in the 2 mg group; and 3 patients in the 3 mg group. Adverse events with an incidence of ≥40% in any group are shown in the following table.

Adverse events with an incidence of ≥40% in any group

System organ classes Preferred terms (MedDRA/J ver16.0)	Number of patients (%)					
	1 mg (n = 4)		2 mg (n = 6)		3 mg (n = 3)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	4 (100)	1 (25)	6 (100)	1 (17)	3 (100)	2 (67)
Skin and subcutaneous tissue disorders						
Rash	4 (100)	0	5 (83)	0	2 (67)	0
Palmar-plantar erythrodysaesthesia syndrome	1 (25)	0	2 (33)	0	2 (67)	0
Investigations						
AST increased	3 (75)	0	5 (83)	0	2 (67)	0
ALT increased	2 (50)	0	3 (50)	0	2 (67)	0
Blood ALP increased	1 (25)	0	2 (33)	0	2 (67)	0
Blood LDH increased	3 (75)	0	1 (17)	0	0	0
Gastrointestinal disorders						
Diarrhoea	3 (75)	0	2 (33)	0	1 (33)	0
Stomatitis	1 (25)	0	2 (33)	0	2 (67)	0
Nausea	0	0	2 (33)	0	2 (67)	0
General disorders and administration site conditions						
Malaise	0	0	1 (17)	0	2 (67)	0
Oedema peripheral	0	0	1 (17)	0	2 (67)	0
Metabolism and nutrition disorders						
Decreased appetite	0	0	1 (17)	0	3 (100)	0
Eye disorders						
Visual impairment	0	0	0	0	2 (67)	0

AST, Aspartate aminotransferase; ALT, Alanine aminotransferase, ALP, Alkaline phosphatase; LDH, Lactic dehydrogenase

Serious adverse events occurred in 1 of 4 patients (25%) in the 1 mg group, 1 of 6 patients (17%) in the 2 mg group, and 1 of 3 patients (33%) in the 3 mg group: laryngeal oedema and dyspnoea in 1 patient (25%) each, pneumonia in 1 patient (17%), and cellulitis in 1 patient (33%) in the respective groups. Of these, a causal relationship to the study drug could not be ruled out for laryngeal oedema in 1 patient in the 1 mg group, pneumonia in 1 patient in the 2 mg group, and cellulitis in 1 patient in the 3 mg group.

An adverse event leading to study drug discontinuation occurred in 1 of 6 patients (17%) in the 2 mg group, which was rash and its causal relationship to the study drug could not be ruled out.

4.(iv).(1).2) Part 2

Adverse events occurred in all 5 patients, and adverse events for which a causal relationship to the study drug could not be ruled out also occurred in all patients. Adverse events with an incidence of ≥50% are shown in the following table.

Adverse events with an incidence of ≥50%

System organ classes Preferred terms (MedDRA/J ver16.0)	Number of patients (%) Trametinib/GEM (n = 5)	
	All Grades	Grade ≥3
All adverse events	5 (100)	5 (100)
Gastrointestinal disorders		
Stomatitis	5 (100)	0
Nausea	4 (80)	0
Investigations		
ALT increased	4 (80)	0
AST increased	4 (80)	0
Blood creatine phosphokinase increased	3 (60)	0
Platelet count decreased	3 (60)	1 (20)
Respiratory, thoracic and mediastinal disorders		
Interstitial lung disease	3 (60)	2 (40)
Skin and subcutaneous tissue disorders		
Rash	5 (100)	0
General disorders and administration site conditions		
Fatigue	4 (80)	0
Metabolism and nutrition disorders		
Decreased appetite	3 (60)	0

AST, Aspartate aminotransferase; ALT, Alanine aminotransferase

Serious adverse events occurred in 4 of 5 patients (80%): interstitial lung disease in 3 patients (60%); pulmonary alveolar haemorrhage, peritonitis, pneumonia, amylase increased and altered state of consciousness in 1 patient (20%) each. Of these, a causal relationship to the study drug could not be ruled out for interstitial lung disease in 3 patients, pulmonary alveolar haemorrhage, pneumonia, and amylase increased in 1 patient.

Adverse events leading to study drug discontinuation occurred in 4 of 5 patients (80%), which events were interstitial pneumonia in 3 patients (60%) and pneumonia in 2 patients (40%), and a causal relationship to the study drug could not be ruled out for all of them.

4.(iv).(2) Japanese phase I/II study (Study MEK116885)

4.(iv).(2).1) Phase I part

Adverse events were observed in all 6 patients, and adverse events for which a causal relationship to the study drug could not be ruled out also occurred in all patients. Adverse events with an incidence of ≥40% are shown in the following table.

Adverse events with an incidence of ≥40%

System organ classes Preferred terms (MedDRA/J ver17.0)	Number of patients (%) Trametinib (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 occurred in 1 of 6 patients (17%). The event was pneumonitis and its causal relationship to the study drug could not be ruled out.

An adverse event leading to study drug discontinuation was blood ALP increased, which occurred in 1 of 6 patients (17%) and 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, and adverse events for which a causal relationship to the study drug could not be ruled out were also noted in all patients.

Adverse events with an incidence of ≥40% were pyrexia and oedema peripheral in 4 patients (67%) each and AST increased and stomatitis in 3 patients (50%) each. None of them were Grade ≥3.

No serious adverse events occurred.

An adverse event leading to study drug discontinuation was uveitis, which occurred in 1 of 6 patients (17%), and its causal relationship to the study drug could not be ruled out.

4.(iv).(3) Foreign phase I study (Study MEK113709)

Adverse events occurred in 9 of 10 patients (90%) receiving a single dose of trametinib (2 mg) under fasted conditions followed by a single dose of trametinib (2 mg) after meals (AB group) and in 9 of 14 patients (64%) receiving a single dose of trametinib (2 mg) after meals followed by a single dose of trametinib (2 mg) under fasted conditions (BA group). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 1 of 10 patients (10%) in the AB group and in 2 of 14 patients (14%) in the BA group.

Adverse events with an incidence of ≥20% in any group were vomiting and arthralgia in 2 patients (20%) each in the AB group. Of these, vomiting in 1 patient was Grade ≥3.

Serious adverse events were vomiting and metabolic encephalopathy, respectively, that occurred in 1 of 10 patients (10%) in the AB group and in 1 of 14 patients (7%) in the BA group. A causal relationship to the study drug was ruled out for both of them.

An adverse event leading to study drug discontinuation was vomiting, which occurred in 1 of 14 patients (7%) in the BA group and its causal relationship to the study drug was ruled out.

4.(iv).(4) Foreign phase I study (Study MEK113708)

No adverse events occurred.

4.(iv).(5) Foreign phase I study (Study MEK112111)

Adverse events occurred in all patients, i.e., 6 patients in the trametinib 1 mg QD/GEM group, 21 patients in the trametinib 2 mg QD/GEM group, and 4 patients in the trametinib 2.5 mg QD/GEM group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 6 of 6 patients (100%), 20 of 21 patients (95%), and 4 of 4 patients (100%) in the respective groups. Adverse events with an incidence of ≥30% in any group are shown in the following table.

Adverse events with an incidence of ≥30% in any group

System organ classes Preferred terms MedDRA 14.0/J14.0	Number of patients (%)					
	Trametinib 1 mg QD/GEM (n = 6)		Trametinib 2 mg QD/GEM (n = 21)		Trametinib 2.5 mg QD/GEM (n = 4)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	6 (100)	6 (100)	21 (100)	17 (81)	4 (100)	4 (100)
Gastrointestinal disorders						
Nausea	5 (83)	0	12 (57)	0	2 (50)	0
Vomiting	2 (33)	0	12 (57)	1 (5)	2 (50)	0
Diarrhoea	1 (17)	0	11 (52)	0	3 (75)	0
Constipation	2 (33)	0	9 (43)	0	1 (25)	0
Abdominal pain	2 (33)	0	7 (33)	0	0	0
Stomatitis	1 (17)	0	7 (33)	0	1 (25)	0
Flatulence	2 (33)	0	1 (5)	0	0	0
General disorders and administration site conditions						
Fatigue	3 (50)	0	16 (76)	1 (5)	2 (50)	0
Pyrexia	2 (33)	0	9 (43)	0	2 (50)	0
Oedema peripheral	2 (33)	0	8 (38)	0	0	0
Blood and lymphatic system disorders						
Thrombocytopenia	4 (67)	3 (50)	14 (67)	4 (19)	1 (25)	1 (25)
Neutropenia	4 (67)	4 (67)	9 (43)	6 (29)	1 (25)	1 (25)
Anaemia	4 (67)	2 (33)	7 (33)	2 (10)	1 (25)	1 (25)
Skin and subcutaneous tissue disorders						
Dry skin	2 (33)	0	7 (33)	0	2 (50)	0
Rash	3 (50)	0	5 (24)	0	2 (50)	0
Dermatitis acneiform	1 (17)	0	7 (33)	2 (10)	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	3 (50)	0	4 (19)	0	1 (25)	0
Dyspnoea	1 (17)	0	1 (5)	0	2 (50)	1 (25)
Metabolism and nutrition disorders						
Decreased appetite	2 (33)	0	12 (57)	0	1 (25)	0
Nervous system disorders						
Dysgeusia	3 (50)	0	3 (14)	0	0	0
Headache	2 (33)	0	2 (10)	0	0	0

Serious adverse events occurred in 3 of 6 patients (50%) in the trametinib 1 mg QD/GEM group, 8 of 21 patients (38%) in the trametinib 2 mg QD/GEM group, and 3 of 4 patients (75%) in the trametinib 2.5 mg QD/GEM group. The observed serious adverse events were febrile neutropenia, deep vein thrombosis, and mental status changes and ureteric obstruction in 1 patient (17%) each in the trametinib 1 mg QD/GEM group; febrile neutropenia, pneumonitis, anaemia, bacteraemia, cellulitis, cholangitis, depression, ileus, mesenteric vein thrombosis, pneumonia, and pyrexia in 1 patient (5%) each in the trametinib 2 mg QD/GEM group; and febrile neutropenia, pneumonitis, and dyspnoea in 1 patient (25%) each in the trametinib 2.5 mg QD/GEM group. Of these, a causal relationship to the study drug could not be ruled out for febrile neutropenia in 1 patient in the trametinib 1 mg QD/GEM group, febrile neutropenia and pneumonitis in 1 patient each in the trametinib 2 mg QD/GEM group, and febrile neutropenia, pneumonitis, and dyspnoea in 1 patient each in the trametinib 2.5 mg QD/GEM group.

Adverse events leading to study drug discontinuation occurred in 1 of 6 patients (17%) in the trametinib 1 mg QD/GEM group, 5 of 21 patients (24%) in the trametinib 2 mg QD/GEM group, and 2 of 4 patients (50%) in the trametinib 2.5 mg QD/GEM group. They were pneumonitis in 1 patient (17%) in the trametinib 1 mg QD/GEM group; ALT increased, depression, ejection fraction decreased, fatigue, papilloedema, and vision blurred in 1 patient (5%) each in the trametinib 2 mg QD/GEM group; and pneumonitis, dyspnoea, and retinopathy in 1 patient (25%) each in the trametinib 2.5 mg QD/GEM group. Of these, a causal relationship to the study drug could not be ruled out for pneumonitis in 1 patient in the trametinib 1 mg QD/GEM group, ALT increased, ejection fraction decreased, fatigue, papilloedema, and vision blurred in 1 patient each in the trametinib 2 mg QD/GEM group, and pneumonitis, dyspnoea, and retinopathy in 1 patient each in the trametinib 2.5 mg QD/GEM group.

4.(iv).(6) Foreign phase I/II study (Study BRF113220) (phase II part)

Adverse events occurred in 53 of 53 patients (100%) in the DAB monotherapy group, 53 of 54 patients (98%) in the trametinib 1 mg + DAB group, and 55 of 55 patients (100%) in the trametinib 2 mg + DAB group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 51 of 53 patients (96%), 52 of 54 patients (96%), and 55 of 55 patients (100%) in the respective groups. Adverse events with an incidence of ≥30% in any group are shown in the following table.

Adverse events with an incidence of ≥30% in any group

System organ classes Preferred terms (MedDRA/J ver16.1)	Number of patients (%)					
	DAB monotherapy (n = 53)		Trametinib 1 mg + DAB (n = 54)		Trametinib 2 mg + DAB (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 14 of 53 patients (26%) in the DAB monotherapy group, 23 of 54 patients (43%) in the trametinib 1 mg + DAB group, and 38 of 55 patients (69%) in the trametinib 2 mg + DAB group. Serious adverse events reported in ≥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 DAB monotherapy 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 trametinib 1 mg + DAB 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 trametinib 2 mg + DAB 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 DAB monotherapy 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 trametinib 1 mg + DAB 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 trametinib 2 mg + DAB group.

Adverse events leading to study drug discontinuation occurred in 1 of 53 patients (2%) in the DAB monotherapy group, 3 of 54 patients (6%) in the trametinib 1 mg + DAB group, and 8 of 55 patients (15%) in the trametinib 2 mg + DAB group. The noted adverse events leading to study drug discontinuation were blood creatinine increased in 1 patient (2%) in the DAB monotherapy group; pyrexia, chills, colitis, pain in extremity, and sepsis in 1 patient (2%) each in the trametinib 1 mg + DAB group; 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 trametinib 2 mg + DAB group. Of these, a causal relationship to the study drug could not be ruled out for blood creatinine increased in 1 patient in the DAB monotherapy group; pyrexia, chills, and pain in extremity in 1 patient each in the trametinib 1 mg + DAB group; and pyrexia in 2 patients, fatigue, nausea, and renal failure in 1 patient each in the trametinib 2 mg + DAB group.

4.(iv).(7) Foreign phase III study (Study MEK114267)

Adverse events occurred in 209 of 211 patients (>99%) in the trametinib group and in 91 of 99 patients (92%) in the chemotherapy group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 205 of 211 patients (97%) and in 77 of 99 patients (78%) in the respective groups. Adverse events with an incidence of ≥10% in either group are shown in the following table.

Adverse events with an incidence of ≥10% in either group

System organ classes Preferred terms (MedDRA/J ver14.1)	Number of patients (%)			
	Trametinib (n = 211)		Chemotherapy (n = 99)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	209 (>99)	100 (47)	91 (92)	34 (34)
Skin and subcutaneous tissue disorders				
Rash	121 (57)	16 (8)	10 (10)	0
Dermatitis acneiform	40 (19)	2 (<1)	1 (1)	0
Alopecia	36 (17)	1 (<1)	19 (19)	0
Dry skin	24 (11)	0	0	0
Pruritus	21 (10)	4 (2)	1 (1)	0
Gastrointestinal disorders				
Diarrhoea	91 (43)	0	16 (16)	2 (2)
Nausea	38 (18)	2 (<1)	37 (37)	1 (1)
Constipation	30 (14)	0	23 (23)	1 (1)
Vomiting	27 (13)	2 (<1)	19 (19)	2 (2)
General disorders and administration site conditions				
Fatigue	54 (26)	8 (4)	27 (27)	3 (3)
Oedema peripheral	54 (26)	2 (<1)	3 (3)	0
Asthenia	12 (6)	1 (<1)	10 (10)	1 (1)
Pyrexia	12 (6)	1 (<1)	10 (10)	1 (1)
Infections and infestations				
Paronychia	21 (10)	0	1 (1)	0
Nervous system disorders				
Headache	26 (12)	2 (<1)	13 (13)	0
Vascular disorders				
Hypertension	32 (15)	26 (12)	7 (7)	3 (3)
Metabolism and nutrition disorders				
Decreased appetite	15 (7)	2 (<1)	10 (10)	0
Blood and lymphatic system disorders				
Anaemia	12 (6)	4 (2)	10 (10)	0

Serious adverse events occurred in 38 of 211 patients (18%) in the trametinib group and in 20 of 99 patients (20%) in the chemotherapy group. They were cellulitis in 4 patients (2%) and anaemia and pulmonary embolism in 3 patients (1%) each in the trametinib group; and pyrexia in 4 patients (4%), anaemia and cholecystitis in 2 patients (2%) each, bronchitis, pneumonia, axillary pain, pain, blood bilirubin increased, haemoglobin decreased, blood albumin decreased, hepatic enzyme increased, vomiting, nausea, constipation, diarrhoea, leukopenia, pancytopenia, acute coronary syndrome, cholangitis, anaphylactic reaction, dehydration, infusion related reaction, and testicular pain in 1 patient (1%) each in the chemotherapy group. Of these, a causal relationship to the study drug could not be ruled out for anaemia in 1 patient in the trametinib group; and pyrexia in 3 patients, pain, hepatic enzyme increased, anaemia, leukopenia, pancytopenia, bronchitis, anaphylactic reaction, diarrhoea, nausea, vomiting, dehydration, and infusion related reaction in 1 patient each in the chemotherapy group.

Adverse events leading to study drug discontinuation occurred in 20 of 211 patients (9%) in the trametinib group and in 9 of 99 patients (9%) in the chemotherapy group. They were flushing and

peripheral sensory neuropathy in 2 patients (2%) each and diarrhoea, pneumonia, back pain, bone marrow oedema, cerebrovascular accident, dehydration, and anaphylactic reaction in 1 patient (1%) each in the chemotherapy group. Of these, a causal relationship to the study drug could not be ruled out for flushing and peripheral sensory neuropathy in 2 patients (2%) each, diarrhoea, back pain, cerebrovascular accident, dehydration, and anaphylactic reaction in 1 patient (1%) each in the chemotherapy group.

4.(iv).(8) Foreign phase III study (Study MEK115306)

Adverse events occurred in 203 of 209 patients (97%) in the trametinib/DAB group and in 205 of 211 patients (97%) in the placebo/DAB group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 181 of 209 patients (87%) and in 189 of 211 patients (90%) in the respective groups. Adverse events with an incidence of ≥15% in either group are shown in the following table.

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

System organ classes Preferred terms (MedDRA/J ver17.0)	Number of patients (%)			
	Trametinib/DAB (n = 209)		Placebo/DAB (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 88 of 209 patients (42%) in the trametinib/DAB group and in 78 of 211 patients (37%) in the placebo/DAB group. Serious adverse events reported in ≥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 trametinib/DAB 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%), and chills and anaemia in 3 patients (1%) each in the placebo/DAB 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 trametinib/DAB 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 placebo/DAB group.

Adverse events leading to study drug discontinuation occurred in 24 of 209 patients (11%) in the trametinib/DAB group and in 14 of 211 patients (7%) in the placebo/DAB group. Adverse events leading to study drug discontinuation reported in ≥3 patients in either group were pyrexia in 5 patients (2%) and ejection fraction decreased in 3 patients (1%) in the trametinib/DAB group and ejection fraction decreased in 3 patients (1%) in the placebo/DAB group, and for all of these events, a causal relationship to the study drug could not be ruled out.

4.(iv).(9) Foreign phase III study (Study MEK116513)

Adverse events occurred in 343 of 350 patients (98%) in the trametinib/DAB group and in 345 of 349 patients (99%) in the Vem group, and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 320 of 350 patients (91%) and 342 of 349 patients (98%), respectively. Adverse events with an incidence of ≥15% in either group are shown in the following table.

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

System organ classes Preferred terms (MedDRA/J ver17.0)	Number of patients (%)			
	Trametinib/DAB (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 occurred in 131 of 350 patients (37%) in the trametinib/DAB group and in 122 of 349 patients (35%) in the Vem group. Serious adverse events reported in ≥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, and erysipelas, hepatic enzyme increased, nausea, pulmonary embolism, and renal failure in 4 patients (1%) each in the trametinib/DAB 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%), blood bilirubin increased, pyrexia, and hepatic enzyme increased in 6 patients (2%) each, AST increased in 5 patients (1%), and 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 trametinib/DAB 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 drug discontinuation were observed in 44 of 350 patients (13%) in the trametinib/DAB group and in 41 of 349 patients (12%) in the Vem group. Adverse events leading to study drug discontinuation reported by ≥4 patients in either group were pyrexia in 12 patients (3%) and ejection fraction decreased in 10 patients (3%) in the trametinib/DAB 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 any of these events.

4.(iv).(10) Japanese phase II study (Study MEK117134)

Adverse events occurred in all 20 patients, and adverse events for which a causal relationship to the study drug could not be ruled out also occurred in all patients. Adverse events with an incidence of ≥15% are shown in the following table.

Adverse events with an incidence of ≥15%

System organ classes Preferred terms (MedDRA/J ver17.0)	Number of patients (%) Trametinib (n = 20)	
	All Grades	Grade ≥3
All adverse events	20 (100)	15 (75)
Skin and subcutaneous tissue disorders		
Dermatitis acneiform	15 (75)	1 (5)
Rash	4 (20)	1 (5)
Dry skin	3 (15)	0
Gastrointestinal disorders		
Diarrhoea	8 (40)	0
Vomiting	7 (35)	0
Nausea	6 (30)	1 (5)
Stomatitis	6 (30)	0
Constipation	3 (15)	0
General disorders and administration site conditions		
Fatigue	7 (35)	0
Pyrexia	7 (35)	0
Oedema peripheral	6 (30)	0
Malaise	5 (25)	0
Metabolism and nutrition disorders		
Decreased appetite	11 (55)	1 (5)
Hypoalbuminaemia	5 (25)	0
Infections and infestations		
Pharyngitis	4 (20)	0
Paronychia	3 (15)	0
Investigations		
Blood creatine phosphokinase increased	5 (25)	2 (10)
AST increased	4 (20)	1 (5)
Blood ALP increased	3 (15)	2 (10)
Hepatobiliary disorders		
Cholangitis	5 (25)	3 (15)
Nervous system disorders		
Dizziness	3 (15)	0
Psychiatric disorders		
Insomnia	3 (15)	0

AST, Aspartate aminotransferase; ALP, Alkaline phosphatase

Serious adverse events occurred in 13 of 20 patients (65%). They were cholangitis in 4 patients (20%), biliary tract infection in 2 patients (10%), and bile duct stenosis, hepatic function abnormal, jaundice cholestatic, infection, pyelonephritis, chorioretinopathy, retinal detachment, blood bilirubin increased, platelet count decreased, oesophageal varices haemorrhage, pyrexia, and presyncope in 1 patient (5%) each. Of these, a causal relationship to the study drug could not be ruled out for chorioretinopathy, retinal detachment, and hepatic function abnormal in 1 patient each.

Adverse events leading to study drug discontinuation occurred in 3 of 20 patients (15%), which were drug-induced liver injury, small intestinal obstruction, and hepatic function abnormal and pyelonephritis in 1 patient (5%) each. Of these, a causal relationship to the study drug could not be ruled out for drug-induced liver injury and hepatic function abnormal in 1 patient each.

4.(iv).(11) Foreign phase II study (Study MEK115064)

Adverse events were reported by 2 of 4 patients (50%), but there were no adverse events for which a causal relationship to the study drug could not be ruled out.

The adverse events observed were diarrhoea, catheter site related reaction, excoriation, arthralgia, headache, ecchymosis, and palmar erythema in 1 patient (25%) each. No Grade ≥3 events occurred.

No serious adverse events occurred.

No adverse events leading to study drug discontinuation occurred.

4.(iv).(12) Foreign phase I study (Study MEK111054)

Adverse events occurred in all patients treated with trametinib, i.e., 7 patients in the 1 mg group, 96 patients in the 2 mg group, 84 patients in the 2.5 mg group, 16 patients in the 3 mg group, and 3 patients in the 4 mg group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 5 of 7 patients (71%), 94 of 96 patients (98%), 79 of 84 patients (94%), 16 of 16 patients (100%), and 3 of 3 patients (100%) in the respective groups. Adverse events with an incidence of ≥40% in any group are shown in the following table.

Adverse events with an incidence of ≥40% in any group

System organ classes Preferred terms (MedDRA/J ver14.0)	Number of patients (%)									
	1 mg (n = 7)		2 mg (n = 96)		2.5 mg (n = 84)		3 mg (n = 16)		4 mg (n = 3)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	7 (100)	2 (29)	96 (100)	47 (49)	84 (100)	50 (60)	16 (100)	9 (56)	3 (100)	2 (67)
Skin and subcutaneous tissue disorders										
Rash	2 (29)	0	75 (78)	5 (5)	63 (75)	5 (6)	14 (88)	3 (19)	1 (33)	0
Gastrointestinal disorders										
Diarrhoea	4 (57)	0	54 (56)	1 (1)	35 (42)	2 (2)	11 (69)	1 (6)	1 (33)	0
Nausea	2 (29)	0	38 (40)	1 (1)	35 (42)	1 (1)	8 (50)	0	1 (33)	0
Vomiting	1 (14)	0	27 (28)	1 (1)	24 (29)	1 (1)	7 (44)	0	1 (33)	0
General disorders and administration site conditions										
Fatigue	2 (29)	0	47 (49)	5 (5)	39 (46)	6 (7)	8 (50)	0	1 (33)	0
Oedema peripheral	0	0	40 (42)	1 (1)	37 (44)	1 (1)	9 (56)	0	2 (67)	0

Serious adverse events occurred in 1 of 7 patients (14%) in the 1 mg group, 31 of 96 patients (32%) in the 2 mg group, 29 of 84 patients (35%) in the 2.5 mg group, and 3 of 16 patients (19%) in the 3 mg group. Serious adverse events reported in ≥2 patients in any group were pulmonary embolism in 6 patients (6%), dehydration in 4 patients (4%), pneumonia, convulsion, and fatigue in 3 patients (3%) each, and pleural effusion, anaemia, ascites, and nausea in 2 patients (2%) each in the 2 mg group; pneumonia, dehydration, and cellulitis in 3 patients (4%) each, and pleural effusion and pain in 2 patients (2%) each in the 2.5 mg group; and pneumonia in 2 patients (13%) in the 3 mg group. Of these, a causal relationship to the study drug could not be ruled out for dehydration and fatigue in 1 patient each in the 2 mg group.

Adverse events leading to study drug discontinuation occurred in 1 of 7 patients (14%) in the 1 mg group, 13 of 96 patients (14%) in the 2 mg group, 10 of 84 patients (12%) in the 2.5 mg group, and 2 of 16 patients (13%) in the 3 mg group. They were small intestinal obstruction in 1 patient (14%) in the 1 mg group; ascites in 3 patients (3%), fatigue in 2 patients (2%), and convulsion, ALT increased, AST increased, blood ALP increased, blood bilirubin increased, hyperkalaemia, hyperphosphataemia, hyperuricaemia, left ventricular dysfunction, nausea, oedema peripheral, pneumatosis intestinalis, pulmonary embolism, pulmonary hypertension, rash, retinal haemorrhage, and vomiting in 1 patient (1%) each in the 2 mg group; fatigue, convulsion, cerebral haemorrhage, cerebrovascular accident, dyspnoea, ejection fraction decreased, hepatic encephalopathy, myopathy, obstruction gastric, and pneumonia in 1 patient (1%) each in the 2.5 mg group; and fatigue and chorioretinopathy in 1 patient (6%) each in the 3 mg group. Of these, a causal relationship to the study drug could not be ruled out for the following: fatigue, nausea, pneumatosis intestinalis, pulmonary hypertension, rash, retinal haemorrhage, and vomiting in 1 patient each in the 2 mg group; fatigue, dyspnoea, ejection fraction decreased, hepatic encephalopathy, and myopathy in 1 patient each in the 2.5 mg group; and fatigue and chorioretinopathy in 1 patient each in the 3 mg group.

4.(iv).(13) Foreign phase I/II study (Study BRF113220) (phase I part)

4.(iv).(13).1) Part A

Adverse events and those for which a causal relationship to the study drug could not be ruled out occurred in all 8 patients.

Adverse events with an incidence of ≥30% were rash in 6 patients (75%), nausea, vomiting, and fatigue in 5 patients (63%) each, decreased appetite in 4 patients (50%), and diarrhoea, chills, pyrexia, cough, and skin papilloma in 3 patients (38%) each. Of these, nausea in 1 patient was Grade ≥3.

Serious adverse events were observed in 5 of 8 patients (63%) and included nausea in 2 patients (25%), and 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 drug discontinuation was convulsion, which occurred in 1 of 8 patients (13%), and its causal relationship to the study drug was ruled out.

4.(iv).(13).2) Part B

Adverse events occurred in all patients treated with the study drug: 6 patients in the trametinib 1 mg QD + DAB 75 mg BID group (B-1 group); 23 patients in the trametinib 1 mg QD + DAB 150 mg BID group (B-2 group); 27 patients in the trametinib 1.5 mg QD + DAB 150 mg BID group (B-3 group); and 79 patients in the trametinib 2 mg QD + DAB 150 mg BID group (B-4 group). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 6 of 6 patients (100%), 22 of 23 patients (96%), 27 of 27 patients (100%), and 72 of 79 patients (91%) in the respective groups. Adverse events with an incidence of ≥40% in any group are shown in the following table.

Adverse events with an incidence of ≥40% in any group

System organ classes Preferred terms (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 12 of 23 patients (52%) in the B-2 group; 12 of 27 patients (44%) in the B-3 group; and 44 of 79 patients (56%) in the B-4 group. Serious adverse events reported in ≥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%), and 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 drug discontinuation occurred in 6 of 79 patients (8%) in the B-4 group. Adverse events leading to study drug discontinuation 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 in either event.

4.(iv).(13).3) Part D

Adverse events occurred in 15 of 15 patients (100%) in the DAB 75 mg BID group (D-1 group), 15 of 15 patients (100%) in the DAB 150 mg BID group (D-2 group), 41 of 41 patients (100%) in the trametinib 2 mg QD + DAB 75 mg BID group (D-3 group), and 38 of 39 patients (97%) in the trametinib 2 mg QD + DAB 150 mg BID group (D-4 group). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 15 of 15 patients (100%), 15 of 15 patients (100%), 39 of 41 patients (95%), and 37 of 39 patients (95%) in the respective groups. Adverse events with an incidence of ≥30% in any group are shown in the following table.

Adverse events with an incidence of ≥30% in any group

System organ classes Preferred terms (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 7 of 15 patients (47%) in the D-1 group, 12 of 15 patients (80%) in the D-2 group, 22 of 41 patients (54%) in the D-3 group, and 25 of 39 patients (64%) in the D-4 group. Serious adverse events reported in ≥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 drug discontinuation occurred in 4 of 15 patients (27%) in the D-2 group, 4 of 41 patients (10%) in the D-3 group, and 4 of 39 patients (10%) 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 liver function test abnormal, headache, uveitis, glioblastoma, influenza like illness, nausea, and vomiting in 1 patient each in the D-4 group.

4.(iv).(14) Foreign phase II study (Study MEK113583)

Adverse events occurred in 39 of 40 patients (98%) with a history of treatment with a BRAF inhibitor (the A group) and in 57 of 57 patients (100%) with a history of treatment with drugs other than BRAF inhibitor (the B group). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 34 of 40 patients (85%) and 55 of 57 patients (96%) in the respective groups. Adverse events with an incidence of ≥20% in either group are shown in the following table.

Adverse events with an incidence of ≥20% in either group

System organ classes Preferred terms (MedDRA/J ver14.0)	Number of patients (%)			
	A (n = 40)		B (n = 57)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	39 (98)	13 (33)	57 (100)	32 (56)
Skin and subcutaneous tissue disorders				
Rash	20 (50)	1 (3)	31 (54)	5 (9)
Dermatitis acneiform	8 (20)	0	21 (37)	4 (7)
Pruritus	8 (20)	1 (3)	20 (35)	0
Dry skin	8 (20)	0	16 (28)	0
Gastrointestinal disorders				
Diarrhoea	21 (53)	1 (3)	35 (61)	3 (5)
Nausea	19 (48)	1 (3)	22 (39)	0
Constipation	13 (33)	0	13 (23)	0
Vomiting	12 (30)	1 (3)	14 (25)	1 (2)
Abdominal pain	7 (18)	1 (3)	13 (23)	0
Dry mouth	8 (20)	0	6 (11)	0
General disorders and administration site conditions				
Fatigue	14 (35)	0	25 (44)	3 (5)
Oedema peripheral	13 (33)	1 (3)	25 (44)	2 (4)
Metabolism and nutrition disorders				
Decreased appetite	8 (20)	1 (3)	9 (16)	0
Vascular disorders				
Hypertension	0	0	12 (21)	1 (2)

Serious adverse events occurred in 4 of 40 patients (10%) in the A group and 13 of 57 patients (23%) in the B group. They were vomiting in 2 patients (5%), pulmonary embolism, decreased appetite, dehydration, diarrhoea, gastrointestinal haemorrhage, hypoxia, lethargy, nausea, and tumour haemorrhage in 1 patient (3%) each in the A group; and cellulitis in 5 patients (9%) and pulmonary embolism, blood amylase increased, cerebral haemorrhage, hypoglycaemia, lipase increased, pneumatosis, pneumonia, pyrexia, rash erythematous, sepsis syndrome, and upper respiratory tract infection in 1 patient (2%) each in the B group. Of these, a causal relationship to the study drug could not be ruled out for decreased appetite, dehydration, diarrhoea, gastrointestinal haemorrhage, lethargy, nausea, and vomiting in 1 patient each in the A group; and cellulitis in 2 patients and pneumatosis, pulmonary embolism, and rash erythematous in 1 patient each in the B group.

Adverse events leading to study drug discontinuation occurred in 4 of 57 patients (7%) in the B group, which were ejection fraction decreased in 2 patients (4%) and intestinal perforation and pulmonary embolism in 1 patient (2%) each. Of these, a causal relationship to the study drug could not be ruled out for ejection fraction decreased in 2 patients and pulmonary embolism in 1 patient (2%).

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. The inspection and assessment revealed no problem. PMDA thus 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 conducted 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 conducted at 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

Based on the submitted data, the efficacy of trametinib in the treatment of patients with unresectable malignant melanoma with a mutation in v-raf murine sarcoma viral oncogene homolog B1 (BRAF) has been demonstrated and its safety is acceptable in view of its observed benefits. Trametinib is a drug product containing a new active ingredient that inhibits tumor growth by inhibition of the phosphorylation of mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) kinase (MEK)1 and MEK2, thereby inhibiting phosphorylation of ERK, an enzyme involved in the downstream of MAPK signal transduction pathway, and thus have a clinical significance as a treatment option for unresectable malignant melanoma with *BRAF* gene mutation. Clinical positioning, dosage and administration, post-marketing investigations, etc., will be further discussed at the Expert Discussion.

This application may be approved if trametinib 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]	Mekinist Tablets 0.5 mg Mekinist Tablets 2 mg
[Non-proprietary name]	Trametinib Dimethyl Sulfoxide
[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 trametinib dimethyl sulfoxide (hereinafter referred to as trametinib) monotherapy and concomitant use of trametinib with dabrafenib mesilate (DAB) (trametinib/DAB) are both effective in patients with unresectable malignant melanoma with v-raf murine sarcoma viral oncogene homolog (BRAF) with mutations in valine-encoding codon 600 (BRAF V600 mutations), as demonstrated by the results of the following 3 foreign phase III studies.

- Study MEK114267 (METRIC study):
  The study was conducted to compare the efficacy and safety between trametinib monotherapy and investigator-selected treatment (dacarbazine or paclitaxel) (chemotherapy) in patients with unresectable malignant melanoma with BRAF V600 mutations. The results showed the superiority of trametinib to chemotherapy 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 trametinib/DAB and vemurafenib (Vem) in patients with unresectable malignant melanoma with BRAF V600 mutations. The results showed the superiority of trametinib/DAB to Vem in the overall survival (OS), the primary endpoint.

- Study MEK115306 (COMBI-D study):
  The study was conducted to compare the efficacy and safety between trametinib/DAB and concomitant use of placebo with DAB (placebo/DAB) in patients with unresectable malignant melanoma with BRAF V600 mutations. The results showed the superiority of trametinib/DAB to placebo/DAB in PFS, the primary endpoint. In addition, a statistically significant increase in OS, the secondary endpoint, was observed in the trametinib/DAB group compared with the placebo/DAB group.

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

(2) Safety

PMDA has concluded in the review of "4.(iii).B.(3) Safety" of the Review Report (1) that adverse events requiring particular caution in trametinib treatment are cardiac disorders, hepatic dysfunction, pyrexia, eye disorders, and rhabdomyolysis, and that particular caution should be exercised against possible occurrence of these adverse events in trametinib treatment.

With these premises, PMDA has concluded that trametinib is well tolerated provided that adverse events are monitored and controlled, and dose reduction, interruption, discontinuation, and other actions are appropriately taken by 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

PMDA concluded in the review of "4.(iii).B.(4) Clinical positioning" of the Review Report (1) that trametinib/DAB is positioned as a treatment option for patients with unresectable malignant melanoma with BRAF V600 mutations. PMDA concluded that trametinib monotherapy is not currently recommended because there are no available study results in Japanese patients with unresectable malignant melanoma with BRAF V600 mutations.

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

(4) Indication

PMDA concluded in the review of "4.(iii).B.(5) Indication" of the Review Report (1) that the indication should be "unresectable malignant melanoma with *BRAF* mutations," that the Clinical Studies section of the package insert should include the types of *BRAF* mutations in patients investigated in the Japanese phase I/II study (Study MEK116885), COMBI-V study, COMBI-D study, etc., and that the Precautions for Indications section should include the following cautions.

- Trametinib should be administered to patients with known *BRAF* mutations through the test performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic should be used in the test.

- The physician should thoroughly understand the description in the Clinical Studies section and become fully aware of the efficacy and safety of trametinib before selecting patients eligible to be treated.

- The efficacy and safety of trametinib as an 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 the Precautions for Indications section, to which the applicant agreed.

(5) Dosage and administration

PMDA concluded in the review of "4.(iii).B.(6) Dosage and administration" of the Review Report (1) that the Dosage and administration and Precautions for Dosage and Administration sections of trametinib should be include the following descriptions.

[Dosage and administration]
The usual adult dosage is 2 mg of trametinib administered orally once daily under fasted conditions in concomitant use with dabrafenib. The dose may be adjusted according to the patient's condition.

[Precautions for Dosage and Administration]

- It is reported that postprandial administration of trametinib causes a decrease in C_{max} and AUC. In order to avoid food effect, patient should refrain from receiving trametinib from 1 hour before meal to 2 hours after meal.

- If adverse drug reaction occurs after the use of trametinib, trametinib 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, trametinib 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 1-level lower dose.
Grade 4	In principle, administration should be discontinued. If deemed desirable for the patient, administration may be resumed at a 1-level lower dose after improvement to Grade ≤1.

*: Grade assessed by NCI-CTCAE v4.0

Guide for dose adjustment

Dose adjustment level	Dose
Usual dose	2 mg (once daily)
1-level dose reduction	1.5 mg (once daily)
2-level dose reduction	1 mg (once daily)
3-level dose reduction	Discontinue

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

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

On the above basis, PMDA instructed the applicant to revise the descriptions in the Dosage and Administration and Precautions for Dosage and Administration sections accordingly, and the applicant agreed.

(6) Risk management plan (draft)

In order to investigate the safety etc., of trametinib in routine clinical use after market launch, the applicant plans to conduct an all-case post-marketing surveillance in all patients treated with trametinib/DAB, with the target sample size of 200 patients and 1-year follow-up period.

PMDA concluded in the review of "4.(iii).B.(7) Post-marketing investigations" of the Review Report (1), that, because of the extremely limited safety information currently available for Japanese patients treated with trametinib, a post-marketing surveillance should be conducted in all patients treated with trametinib in order to collect safety information in a prompt and unbiased manner, 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 trametinib/DAB combination therapy 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 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 trametinib/DAB), a similar sample size as that of the trametinib/DAB group in the foreign clinical study.

- In light of the time to the onset of adverse events described as primary survey 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 new matters requiring investigation occur during the surveillance, sample size, additional surveys, etc., should be re-considered.

Also, on the basis of above discussions, PMDA concluded that the draft risk management plan should be revised at present to include safety and efficacy specifications and that pharmacovigilance activities and risk minimization activities should be conducted in addition as described in the following table.

Safety and efficacy specifications in risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Cardiac disorders • Eye disorders • Hepatic dysfunction • Rhabdomyolysis • Pyrexia	• Decreased fertility • Effects on embryo-fetal development • Deep vein thrombosis and pulmonary embolism • Interstitial lung disease • Cerebrovascular disorders (e.g., cerebral haemorrhage, cerebrovascular accident) • Renal impairment	• Safety in patients with hepatic dysfunction
Efficacy specifications		
• Efficacy in routine clinical use		

Outline of additional pharmacovigilance activities and risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey	• Provide information obtained in the early post-marketing phase vigilance • Prepare and distribute materials for healthcare professionals in clinical settings • Prepare and supply materials for patients

Outline of specified use-results survey plan (draft)

Objective	To evaluate safety etc., of trametinib in routine clinical use
Method	All-case surveillance by central registration method
Patient population	All patients treated with trametinib
Follow-up period	1 year
Target sample size	200 patients treated with trametinib/DAB
Main investigation items	Priority investigation items: Cardiac disorders, hepatic dysfunction, pyrexia, eye disorders, spinocellular carcinoma, secondary malignant tumor other than spinocellular carcinoma, and rhabdomyolysis Other investigation items: Patient characteristics, use status of trametinib and DAB, concomitant drugs and therapies, adverse events (including changes in laboratory values), etc.

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 trametinib is provided appropriately after market launch, and (ii) the proper use of trametinib is ensured under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions capable of handling emergencies appropriately. Since trametinib is an orphan drug, the re-examination period is 10 years. The drug substance is classified as a poisonous drug and the drug product is 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 2 mg of trametinib administered orally once daily under fasted conditions in combination with dabrafenib. 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 in all 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 actions 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]

Trametinib should be administered only to patients considered eligible to be treated with trametinib and only under the supervision of a physician with sufficient knowledge and experience in cancer chemotherapy at a medical institution well equipped and staffed to manage emergencies. Before initiating treatment with trametinib, the attending physician should fully explain the benefits and risks of trametinib to the patient or the family members, and obtain informed consent from them.

[Contraindication]

Patients with a history of hypersensitivity to any ingredient of trametinib

[Precautions for Indications]

1. Trametinib should be administered to patients with known *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 become fully aware of the efficacy and safety of trametinib before selecting patients eligible to be treated with trametinib.

3. The efficacy and safety of trametinib as an adjuvant chemotherapy have not been established.

[Precautions for Dosage and Administration]

1. Postprandial administration of trametinib has been reported to cause a decrease in C_{max} and AUC. Trametinib should not be administered from 1 hour before meal to 2 hours after meal to avoid food effect.

2. If an adverse drug reaction occurs during trametinib treatment, treatment should be interrupted, discontinued, or continued at a reduced dose referring to the following criteria. If spinocellular carcinoma (squamous cell carcinoma of skin) or new primary malignant melanoma occurs, trametinib may be continued without interruption or dose reduction after appropriate actions such as surgical resection.

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 1-level lower dose.
Grade 4	In principle, administration should be discontinued. If deemed desirable for the patient, administration may be resumed at a 1-level lower dose after improvement to Grade ≤1.

1) Grade assessed by NCI-CTCAE v4.0

Guide for dose adjustment

Dose adjustment level	Dose
Usual dose	2 mg (once daily)
1-level dose reduction	1.5 mg (once daily)
2-level dose reduction	1 mg (once daily)
3-level dose reduction	Discontinue

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