Report on the Deliberation Results

November 30, 2018

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

Brand Name	Mektovi Tablets 15 mg
Non-proprietary Name	Binimetinib (JAN*)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	April 25, 2018

Results of Deliberation

In its meeting held on November 29, 2018, 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 product is not classified as a biological product or a specified biological product. The re-examination period is 10 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics of patients treated with the product. The applicant is also required to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

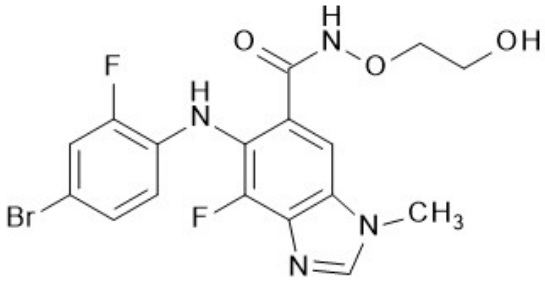
Review Report

November 19, 2018
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Mektovi Tablets 15 mg
Non-proprietary Name	Binimetinib
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	April 25, 2018
Dosage Form/Strength	Tablets: Each tablet contains 15 mg of Binimetinib.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{17}H_{15}BrF_2N_4O_3$

Molecular weight: 441.23

Chemical name: 5-[(4-Bromo-2-fluorophenyl)amino]-4-fluoro-*N*-(2-hydroxyethoxy)-1-methyl-1*H*-benzimidazole-6-carboxamide

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 322 of 2013 [*25 yaku*]; PSEHB/PED Notification No. 0330-3 dated March 30, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with unresectable malignant melanoma with B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) gene mutations, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The occurrence of eye disorders, cardiac dysfunction, hepatic dysfunction, rhabdomyolysis, cutaneous malignancy, hypertension, haemorrhage, and palmar-plantar erythrodysaesthesia syndrome need to be further investigated via post-marketing surveillance.

Indication

Unresectable malignant melanoma with *BRAF* gene mutation

Dosage and Administration

In combination with encorafenib, the usual adult dosage is 45 mg of binimetinib administered orally twice daily. The dose may be reduced according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics of patients treated with the product. The applicant is also required to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.

Attachment

Review Report (1)

October 12, 2018

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

Products Submitted for Approval

(a) Brand Name Braftovi Capsules 50 mg

Non-proprietary Name Encorafenib

Applicant Ono Pharmaceutical Co., Ltd.

Date of Application April 25, 2018

Dosage Form/Strength Capsules: Each capsule contains 50 mg of encorafenib.

Proposed Indication Unresectable malignant melanoma with *BRAF* gene mutation

Proposed Dosage and Administration

In combination with binimetinib, the usual adult dosage is 450 mg of encorafenib administered orally once daily.

(b) Brand Name Mektovi Tablets 15 mg

Non-proprietary Name Binimetinib

Applicant Ono Pharmaceutical Co., Ltd.

Date of Application April 25, 2018

Dosage Form/Strength Tablets: Each tablet contains 15 mg of binimetinib.

Proposed Indication Unresectable malignant melanoma with *BRAF* gene mutation

Proposed Dosage and Administration

In combination with encorafenib, the usual adult dosage is 45 mg of binimetinib administered orally twice daily at an interval of approximately 12 hours.

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) gene mutations have been found in approximately 60% and 20% to 30%, respectively, of patients with malignant melanoma in Western countries and in Japan (*Nature*. 2002;417:949-54, *J Dermatol Sci*. 2012;66:240-2, etc.). BRAF is involved in the activation of mitogen-activated protein kinase (MAPK) signal transduction pathway, and mutations in *BRAF* gene are considered to constitutively activate MAPK signal transduction pathway including mitogen-activated protein kinase/extracellular signal-regulated kinase kinase (MEK) in the downstream, resulting in the enhancement of tumor cell growth, suppression of apoptosis, etc. (*Nature Med*. 2013;19:1401-9, *Nat Rev Cancer*. 2017;17:676-91).

Encorafenib (ENCO), a low molecular weight compound discovered by Novartis (Switzerland), is considered to suppress the growth of tumor with *BRAF* gene mutations by inhibiting the kinase activity of BRAF.

Binimetinib (BINI), a low molecular weight compound discovered by Array BioPharma (US), is considered to suppress the growth of tumor with *BRAF* gene mutations by inhibiting the kinase activity of MEK.

1.2 Development history, etc.

A global phase I study (Study CLGX818X2101 [Study X2101]) administering a single dose of ENCO to patients with advanced solid cancer was initiated by Novartis (Switzerland) in September 2011, and a foreign phase I study (Study ARRY-162-0601 [Study 162-0601]) administering a single dose of BINI to healthy adults was initiated by Array BioPharma (US) in [redacted] 20[redacted]. Also, a foreign phase Ib/II study (Study CMEK162X2110 [Study X2110]) administering combination of encorafenib and binimetinib (ENCO/BINI) to patients with advanced solid cancer with "BRAF mutation involving amino acid substitution of valine to other amino acid at codon 600" (BRAF V600 mutation) was initiated in May 2012 by Novartis (Switzerland) and Array BioPharma (US). Subsequently, a global phase III study (Study CMEK162B2301 [Study B2301]) administering ENCO/BINI to patients with unresectable malignant melanoma with *BRAF* gene mutation was initiated in [redacted] 2013 by Novartis (Switzerland) and Array BioPharma (US).

In the US and in the EU, applications for ENCO and BINI were submitted in June (US) and July (EU) of 2017, with Study B2301 as the pivotal study. ENCO and BINI were approved in June 2018 in the US for the following indication: "BRAFTOVI is indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test." and "MEKTOVI is indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test." They were also approved in September 2018 in the EU for the following indication: "Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation." and "Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation."

As of September 2018, ENCO and BINI are approved in 32 countries or regions for the indication for malignant melanoma.

In Japan, enrollment of patients in Study X2101 and Study B2301 was initiated in [redacted] 20[redacted] and in [redacted] 20[redacted], respectively.

ENCO and BINI were designated as orphan drugs in March 2018 with the intended indication for "*BRAF*^{V600} gene mutation-positive malignant melanoma" and "NRAS proto-oncogene, GTPase (*NRAS*) or *BRAF*^{V600} gene mutation-positive malignant melanoma," respectively (Orphan Drug Designation No. 323 and 322 of 2013 [*25 yaku*]).

An application exclusively for ENCO/BINI has now been submitted for the indication of malignant melanoma with *BRAF* gene mutation with the results of Study B2301 as the pivotal data.

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

2.1 ENCO

2.1.1 Drug substance

2.1.1.1 Characterization

The drug substance is white to practically white powder, and the determined general properties of the drug substance include description, solubility, hygroscopicity, melting point, optical rotation, dissociation constant, and distribution coefficient.

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

2.1.1.2 Manufacturing process

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

The strategy for quality control was developed by the following investigations, etc., using a quality-by-design (QbD) approach (Table 1):

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) and investigation of the acceptable range of process parameters, based on the results of experiments related to quality risk assessment and quality attributes

Table 1. Outline of the quality control strategy for the drug substance

CQA	Control method
Content	Manufacturing process and specifications
Description	Manufacturing process and specifications
Identification	Manufacturing process and specifications
Related substances	Manufacturing process and specifications
Optical isomers	Manufacturing process and specifications
Residual solvents	Manufacturing process and specifications
[redacted]	Manufacturing process
Water content	Manufacturing process and specifications
Particle size	Manufacturing process and specifications
[redacted]	Manufacturing process

The following processes were identified as critical steps: (a) Processes for [redacted] reaction [redacted] group [redacted] group, (b) processes for [redacted] reaction of [redacted] compound and [redacted] compound, (c) processes for [redacted] reaction of [redacted] group, (d) processes for [redacted] reaction of [redacted] group, and (e) [redacted] process of [redacted] drug substance.

In-process control parameters and the control values were established for all manufacturing processes of the drug substance, except [redacted] process and [redacted] process.

2.1.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR), purity (related substances [liquid chromatography (LC)] and residual solvents [gas chromatography (GC)]), water content, particle size, and assay (LC).

2.1.1.4 Stability of drug substance

Table 2 shows stability studies conducted on the drug substance. A photostability testing showed that the drug substance is photostable.

Table 2. Stability studies of drug substance

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 pilot scale batches	30°C	75%RH	Polyethylene bag (double-layered) + metallic drum	24 months
Accelerated testing		40°C	75%RH		6 months

On the basis of the above, a retest period of 36 months was proposed for the drug substance when stored at room temperature in double-layered polyethylene bags placed in metallic drums, according to the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)" (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Q1E Guideline). Long-term testing will be continued up to [redacted] months.

2.1.2 Drug product

2.1.2.1 Description and composition of drug product and formulation development

The drug product is immediate-release hard capsules, each containing 50 mg of the drug substance. The drug product also contains, as excipients, copolyvidone, polyoxyethylene (160) polyoxypropylene (30) glycol, microcrystalline cellulose, succinic acid, crospovidone, light anhydrous silicic acid, and magnesium stearate.

2.1.2.2 Manufacturing process

The drug product is manufactured through a process comprised of blending, [redacted], [redacted], mixing, capsule-filling, and packaging/labeling.

The strategy for quality control was developed by the following investigations, etc., using a QbD approach (Table 3):

- Identification of CQAs
- Identification of CPPs and material attributes that might affect the CQAs of the drug product, and investigation of the acceptable range of process parameters, based on the quality risk assessment and design of experiments

Table 3. Outline of quality control strategy for the drug product

CQA	Control method
Strength	Specifications
Appearance	Manufacturing process and specifications
[redacted]	Manufacturing process
[redacted]	Manufacturing process
Identification	Specifications
Related substances	Manufacturing process and specifications
Water content	Manufacturing process and specifications
Uniformity of dosage units	Manufacturing process and specifications
Microbial limit	Specifications
Dissolution	Manufacturing process and specifications
[redacted] of drug substance	Manufacturing process

[redacted] and [redacted] are identified as the critical steps, and in-process control parameters and control values are defined in [redacted] and [redacted] processes.

2.1.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (ultraviolet-visible absorption spectroscopy and LC), purity (related substances [LC]), water content, uniformity of dosage unit (content uniformity [LC]), microbial limit, dissolution (LC), and assay (LC).

2.1.2.4 Stability of drug product

Table 4 shows the stability studies conducted on the drug product. [redacted][1)] did not meet the acceptance criteria at [redacted] months after the start of the pre-validation accelerated testing, showing reduced dissolution. A photostability testing showed that the drug product is photostable.

[1)] Although [redacted] is a CQA affecting the dissolution of the drug product, [redacted] is not included in the specifications because (1) [redacted] is controlled by the process control system for the drug product and (2) dissolution and [redacted] (CQA affecting [redacted]) are controlled by the specifications for the drug product.

Table 4. Stability studies of drug product

	Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Tests for application	Long-term testing	3 pilot-scale batches	25 ± 2°C	60 ± 5%RH	PTP (nylon/ aluminum/ polyvinyl chloride and aluminum foil)	24 months
	Intermediate testing		30 ± 2°C	75 ± 5%RH		24 months
	Accelerated testing		40 ± 2°C	75 ± 5%RH		6 months
Pre-validation*	Long-term testing		25 ± 2°C	60 ± 5%RH		12 months
	Intermediate testing		30 ± 2°C	75 ± 5%RH		12 months
	Accelerated testing		40 ± 2°C	75 ± 5%RH		6 months

* During the stability studies for application, the dissolution test was changed from the old method (;dissolution medium, mol/L solution [pH]; rotational speed, revolutions per minute; method for measurement,) to the proposed method (Paddle method; dissolution medium, mol/L solution [pH]; rotational speed, revolutions per minute; method for measurement, LC) from months after the start of the test. Therefore, a pre-validation stability study was conducted using the proposed test from the start.

On the basis of the above, a shelf life of 27 months was proposed for the drug product when packaged in press through packaging (PTP) (nylon/aluminum/polyvinyl chloride and aluminum foil) and stored at room temperature according to ICH Q1E Guideline, taking account of the following. Long-term testing will be continued up to months.

- did not meet the acceptance criteria at months after the start of the pre-validation accelerated testing, showing clear changes in the quality attributes and reduced dissolution.
- All test parameters including and dissolution met the specifications up to 24 months when the intermediate testing for application was conducted, showing no clear changes in quality attributes.
- No statistical analysis was performed related to the extension of the shelf-life of the drug product.

2.2 BINI

2.2.1 Drug substance

2.2.1.1 Characterization

The drug substance is white to grayish-white powder, and the determined general properties of the drug substance include description, solubility, hygroscopicity, melting point, dissociation constant, and distribution coefficient. The drug substance exists in 4 crystalline forms (anhydride, , , and), but only Crystalline Form A (anhydride) is produced in the manufacturing process on a commercial scale. The stability study demonstrated that Crystalline Form A (anhydride) does not change to any other form.

The chemical structure of the drug substance has been elucidated by mass spectrometry, IR, NMR (^{1}H-NMR, ^{13}C-NMR), and single-crystal X-ray diffractometry.

2.2.1.2 Manufacturing process

The drug substance is synthesized using , , and as the starting materials.

The strategy for quality control was developed by the following investigations, etc., using a QbD approach (Table 5):

- Identification of CQAs
- Identification of CPPs and investigation of the acceptable range of process parameters, based on the results of experiments related to quality risk assessment and quality attributes.

Table 5. Outline of the quality control strategy for the drug substance

CQA	Control method
Content	Manufacturing process and specifications
Description	Manufacturing process and specifications
Identification	Manufacturing process and specifications
Related substances	Manufacturing process and specifications
Residual solvents	Manufacturing process and specifications
[redacted]	Manufacturing process
Water content	Manufacturing process and specifications
Particle size	Manufacturing process and specifications
[redacted]	Manufacturing process
Microbial limit	Manufacturing process and specifications

The following processes were identified as critical steps: (a) Processes for [redacted] reaction of [redacted] compound and [redacted] using [redacted], (b) processes for removal of [redacted] and [redacted] reaction of [redacted] group, (c) processes for [redacted] reaction of [redacted] group, (d) [redacted] process of the [redacted] drug substance, and (e) [redacted] and [redacted] processes of the drug substance.

In-process control parameters and the control values were established for all manufacturing processes of the drug substance, except [redacted] process and [redacted] process.

2.2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR), purity (related substances [LC] and residual solvents [GC]), water content, microbial limit, particle size, and assay (LC).

2.2.1.4 Stability of drug substance

Table 6 shows stability studies conducted on the drug substance. A photostability testing showed that the drug substance is photolabile.

Table 6. Stability studies of drug substance

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	2 commercial-scale batches, 1 pilot-scale batch	30°C	75%RH	Polyethylene bag (double-layered) + metallic drum	48 months
Accelerated testing	2 commercial-scale batches, 1 pilot-scale batch	40°C	75%RH		6 months

On the basis of the above, a retest period of 60 months was proposed for the drug substance when stored at room temperature protected from light in double-layered polyethylene bags placed in metallic drums, according to ICH Q1E Guideline. Long-term testing will be continued up to [redacted] months.

2.2.2 Drug product

2.2.2.1 Description and composition of drug product and formulation development

The drug product is immediate-release film-coated tablets, each containing 15 mg of the drug substance. The drug product also contains, as excipients, lactose hydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, light anhydrous silicic acid, and [redacted].

2.2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of mixing, tableting, film-coating, and packaging/labeling. [redacted] is identified as the critical step, and in-process control parameters and control values are defined in [redacted], [redacted], and [redacted] processes.

2.2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (thin-layer chromatography and LC), purity (related substances [LC]), water content, uniformity of dosage unit (content uniformity [LC]), microbial limit, dissolution (LC), and assay (LC).

2.2.2.4 Stability of drug product

Table 7 shows the stability studies conducted on the drug product. A photostability testing showed that the drug product is photostable.

Table 7. Stability studies of drug product

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 pilot-scale batches	25 ± 2°C	60 ± 5%RH	PTP (polyvinylidene chloride/polyvinyl chloride and aluminum foil)	48 months
Accelerated testing		40 ± 2°C	75% ± 5%RH		6 months

On the basis of the above, a shelf life of 60 months was proposed for the drug product when packaged in PTP (polyvinylidene chloride/polyvinyl chloride and aluminum foil) and stored at room temperature, according to ICH Q1E Guideline. Long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

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

2.R.1 Determination of shelf life of ENCO formulation

The applicant submitted reference data supporting 3-month extension of the shelf life of ENCO formulation in the form of the following long-term testing, taking account of the objective of ICH Q1E guideline:

- Long-term testing on 2 [redacted] packaged batches manufactured on a pilot scale (up to [redacted] and [redacted] months, respectively): In this study, all measurement items including dissolution met the specifications except [redacted] which was not subjected to measurement.

In the above long-term testing, dissolution was studied using the old testing method that has a lower detectability than the proposed testing method. Therefore, PMDA asked the applicant to explain the appropriateness to determine the shelf-life of ENCO as 27 months [see Section 2.1.2.4].

The applicant's explanation:

Taking account of the following, the dissolution of ENCO formulation is unlikely to deviate from the specification at 27 months after the manufacture. It is therefore appropriate to determine the shelf life of ENCO formulation to be 27 months.

- No change over time was observed either in the dissolution or CQAs of the dissolution ([redacted] and [redacted]) in (a) the long-term testing for application from [redacted] to 24 months and the intermediate testing or in (b) the pre-validation long-term testing up to 12 months from the start of the testing and the intermediate testing, all conducted using the proposed testing method.

PMDA accepted the explanation of the applicant.

2.R.2 New excipient

ENCO formulation contains succinic acid, a new excipient, in an amount exceeding that of the previous uses for oral administration.

2.R.2.1 Specifications and stability

PMDA concluded that since succinic acid used meets the specifications for Japanese Pharmaceutical Excipients, there is no problem in the specifications and the stability of succinic acid used.

2.R.2.2 Safety

On the basis of the submitted data, PMDA concluded that succinic acid is unlikely to pose any safety problem at the amount used in the proposed formulation.

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

3.1 ENCO

3.1.1 Primary pharmacodynamics

3.1.1.1 Inhibitory effect of RAF (CTD 4.2.1.1-1, 4.2.1.1-6)

The inhibitory effect of ENCO and M42.5A, a metabolite of ENCO, against human BRAF V600E, wild-type BRAF, and wild-type Raf-1 proto-oncogene, serine/threonine kinase (CRAF; recombinant proteins) was investigated by fluorescence resonance energy transfer (FRET) method or by using the uptake of γ-^{33}P-labeled adenosine triphosphate (ATP) as the index. Table 8 shows IC_{50} of ENCO and M42.5A.

Table 8. Inhibitory effect of ENCO and M42.5A against RAF

Kinase	IC_{50} (nmol/L)			
	n	ENCO	n	M42.5A
BRAF V600E	13	0.35 ± 0.16	3	9.3 ± 7.3
Wild-type BRAF	1	0.47	3	15.5 ± 7.8
Wild-type CRAF	1	0.30	3	9.1 ± 4.5

Mean ± standard deviation (SD), individual value for n = 1

3.1.1.2 Inhibitory effect against kinases other than RAF (CTD 4.2.1.1-2, 4.2.1.1-3)

The inhibitory effect of ENCO against 439 types of kinases (recombinant proteins) other than RAF was investigated by quantitative polymerase chain reaction (PCR). Serine/threonine kinase 36 (STK36) was the only kinase that was inhibited ≥50% by 0.01 μmol/L ENCO.

3.1.1.3 Inhibitory effect against MEK and ERK phosphorylation (CTD 4.2.1.1-4, 4.2.1.1-7)

Using human malignant melanoma-derived A375 cell line with "BRAF mutation involving amino acid substitution of valine to glutamic acid at codon 600" (BRAF V600E mutation), the inhibitory effect of

ENCO against MEK phosphorylation was investigated by electro-chemiluminescence immunoassay. IC_{50} (n = 1) at 0, 1, and 3 hours after removal of ENCO was 2.4, 3.0, and 4.2 nmol/L, respectively.

Using A375 cell line, the inhibition of ENCO against extracellular signal-regulated kinase (ERK) phosphorylation was investigated by In-Cell enzyme-linked immunosorbent assay (ELISA).[2)] IC_{50} of ENCO (n = 4, mean ± standard deviation [SD]) was 3.0 ± 0.2 nmol/L.

Using human malignant melanoma-derived Malme-3M cell line with BRAF V600E mutation, the inhibition of M42.5A against ERK phosphorylation was investigated by In-Cell ELISA. IC_{50} of M42.5A (n = 2, individual values) was 73 and 79 nmol/L, respectively.

3.1.1.4 Growth-inhibitory effect against malignant melanoma-derived cell lines

3.1.1.4.1 *In vitro* (CTD 4.2.1.1-4, 4.2.1.1-7)

The growth-inhibition of ENCO against A375 cell line was investigated using viable cell-derived ATP as the index. IC_{50} of ENCO (n = 5, mean ± SD) was 4.4 ± 1.1 nmol/L.

The growth-inhibition of M42.5A against Malme-3M cell line was investigated using viable cell-derived reductase activity as the index. IC_{50} of M42.5A (n = 2, individual values) was 112 and 125 nmol/L, respectively.

3.1.1.4.2 *In vivo* (CTD 4.2.1.1-8)

Using nude mice (n = 5/group) subcutaneously implanted with A375 cell line, the tumor growth-inhibition of ENCO was investigated. ENCO 0.6, 6.0, 60, or 300 mg/kg was administered orally BID for 14 days starting from Day 11 after the day of implantation (which was defined as "Day 0 of the study"), and tumor volume was calculated. On Day 24, a statistically significant tumor growth inhibition was observed in the ENCO 6.0, 60, and 300 mg/kg groups compared with the control (20% polyethylene glycol [PEG] 300 solution containing 3% vitamin E d-α-tocopheryl polyethylene glycol succinate [ETPGS]) group ($P < 0.05$, Dunn test).

3.1.2 Secondary pharmacodynamics

3.1.2.1 Effect on receptors, transporters, ion channels, and enzymes (CTD 4.2.1.2-1)

The effect of ENCO 10 μmol/L on 143 types of receptors, transporters, ion channels, and enzymes was investigated by scintillation proximity assay (SPA) and other methods. ENCO inhibited phosphodiesterase 4D (PDE4D) with IC_{50} (n = 3, mean ± SD) of 4.4 ± 1.4 μmol/L.

3.1.3 Safety pharmacology

3.1.3.1 Effect on central nervous system (CTD 4.2.1.3-1, 4.2.1.3-4)

A single dose of ENCO 100 mg/kg was administered orally to rats (n = 10/group), and the effect of ENCO on the central nervous system was investigated by functional observation battery (FOB). ENCO had no effect on the central nervous system.

2) ELISA performed by allowing the antibody to directly react with immobilized cells

A single dose of ENCO 50, 100, or 200 mg/kg was administered orally to monkeys (n = 4/group), and the effect of ENCO on body temperature was investigated. ENCO had no effect on body temperature.

3.1.3.2 Effect on cardiovascular system

3.1.3.2.1 Effect on hERG potassium current (CTD 4.2.1.3-2)

Using human fetal kidney-derived HEK293 cell line introduced with human ether-a-go-go related gene (hERG), the effect of ENCO 10, 30, or 100 μmol/L on hERG potassium current was investigated. ENCO at 10, 30, and 100 μmol/L inhibited hERG potassium current by 13.5% ± 0.4%, 26.6% ± 1.3%, and 58.7% ± 2.7% (n = 3, mean ± SD), respectively.

3.1.3.2.2 Effect on heart rate, blood pressure, and electrocardiogram (CTD 4.2.1.3-4)

A single dose of ENCO 50, 100, or 200 mg/kg was administered orally to monkeys (n = 4/group), and the effect of ENCO on heart rate, blood pressure, and electrocardiogram was investigated. ENCO increased heart rate and shortened PR interval and QT interval (QT).

The applicant explained that ENCO does not have any serious effect on cardiac function due to the following observations: (1) Observed changes in heart rate were mild and within the range of physiological variations. (2) 3-month repeated-dose toxicity study in monkeys did not detect any histopathological changes in the heart nor abnormalities in electrocardiogram and heart rate [see Section 5.1.2].

3.1.3.3 Effect on respiratory system (CTD 4.2.1.3-1)

A single dose of ENCO 100 mg/kg was administered orally to rats (n = 5/group), and the effect of ENCO on respiratory rate, tidal volume, and minute ventilation was investigated. ENCO had no effect.

3.2 BINI

3.2.1 Primary pharmacodynamics

3.2.1.1 Inhibitory effect of MEK phosphorylation (CTD 4.2.1.1-1)

The inhibitory effect of BINI against phosphorylation of human MEK1 and MEK2 (recombinant proteins) was investigated using the uptake of γ-^{33}P-labeled ATP as the index. IC_{50} of BINI (n = 1) against MEK1 and MEK2 was 16 and 46 nmol/L, respectively.

3.2.1.2 Inhibitory effect against kinases other than MEK (CTD 4.2.1.1-3)

The inhibitory effect of BINI against 218 types of kinases (recombinant proteins) other than MEK was investigated using the uptake of γ-^{33}P-labeled ATP as the index. BINI 10 μmol/L did not inhibit any of the kinases tested by ≥50%.

3.2.1.3 Inhibitory effect against ERK phosphorylation (CTD 4.2.1.1-2, 4.2.1.1-4)

The inhibitory effect of BINI and M3, a metabolite of BINI, against phosphorylation of human ERK (recombinant protein) by activated MEK1 was investigated using the uptake of γ-^{33}P-labeled ATP as the index. IC_{50} of BINI and M3 (n = 4 and 1; mean ± SD, individual value for n = 1) was 12.1 ± 5.6 and 7.1 nmol/L, respectively.

Using human malignant melanoma-derived A375, UACC-62, RPMI-7951, and COLO 800 cell lines with BRAF V600E mutation, the inhibition of BINI against ERK phosphorylation was investigated by In-Cell ELISA.[2)] IC_{50} of BINI (n = 1) in each cell line was 27.4, 14.4, 125.8, and 7.6 nmol/L, respectively.

3.2.1.4 Growth-inhibitory effect against malignant tumor-derived cell lines

3.2.1.4.1 *In vitro* (CTD 4.2.1.1-4)

The growth-inhibitory effect of BINI against 8 types of human malignant melanoma-derived cell lines with BRAF V600 mutation was investigated using viable cell-derived reductase activity as the index. Table 9 shows IC_{50} values of BINI.

Table 9. Growth-inhibitory effect of BINI against human malignant melanoma-derived cell lines

Cell line	Type of BRAF mutation	IC_{50} (nmol/L)
A375	V600E	34.4 ± 9.3
UACC-62	V600E	34.1 ± 0.7
RPMI-7951	V600E	4,359.1 ± 4,717.6
MDA-MB-435S	V600E	5,046.6 ± 7,005.2
IGR-39	V600E	9,272.0 ± 1,261.0
COLO 800	V600E	93.6 ± 28.2
WM-115	V600D	99.8 ± 16.0
IGR-1	V600K	372.2 ± 20.2

n = 3, mean ± SD

3.2.1.4.2 *In vivo* (CTD 4.2.1.1-7)

Using nude mice (n = 11/group) subcutaneously implanted with A375 cell line, the tumor growth-inhibition of BINI was investigated. BINI 1, 3, 10, or 30 mg/kg was administered orally BID for 21 days starting from Day 12 after the day of implantation (which was defined as Day 0 of the study), and tumor volume was calculated. On Day 23, a statistically significant tumor growth inhibition was observed in the BINI 3, 10, and 30 mg/kg groups compared with the control (1 w/v% carboxymethylcellulose [CMC] solution containing 0.5 vol% polysorbate 80) group ($P < 0.05$, Dunnett multiple comparison).

3.2.2 Secondary pharmacodynamics

3.2.2.1 Effect on receptors, transporters, ion channels, and enzymes (CTD 4.2.1.2-1)

The effect of BINI 10 μmol/L on 60 types of receptors, transporters, ion channels, and enzymes was investigated by SPA and other methods. BINI did not inhibit nor activate any of the receptors, transporters, ion channels, or enzymes tested by ≥50%.

3.2.3 Safety pharmacology

3.2.3.1 Effect on central nervous system (CTD 4.2.1.3-1, 4.2.1.3-4)

A single dose of BINI 10, 30, or 100 mg/kg was administered orally to rats (n = 10/group), and the effect of BINI on the central nervous system was investigated by FOB and by measurement of locomotor activity. No effect of BINI was observed.

A single dose of BINI 1, 3, or 10 mg/kg was administered orally to monkeys (n = 6/group), and the effect of BINI on body temperature was investigated. No effect of BINI was observed.

3.2.3.2 Effect on cardiovascular system

3.2.3.2.1 Effect on hERG potassium current (CTD 4.2.1.3-2)

Using HEK293 cell line introduced with hERG, the effect of BINI 0.3, 1, 3, 10, or 30 μmol/L on hERG potassium current was investigated. BINI at 10 and 30 μmol/L inhibited hERG potassium current by 8.0% ± 1.8% and 30.4% ± 1.6% (n = 3 or 4, mean ± standard error [SE]), respectively, with IC_{50} of >30 μmol/L.

3.2.3.2.2 Effect on heart rate, blood pressure, and electrocardiogram (CTD 4.2.1.3-4)

A single dose of BINI 1, 3, or 10 mg/kg was administered orally to monkeys (n = 6/group), and the effect of BINI on heart rate, blood pressure, and electrocardiogram was investigated. No effect of BINI was observed.

3.2.3.3 Effect on respiratory system (CTD 4.2.1.3-5)

A single dose of BINI 10, 30, or 100 mg/kg was administered orally to rats (n = 12/group), and the effect of BINI on respiratory rate, tidal volume, minute ventilation, and blood gas was investigated. No effect of BINI was observed.

3.2.3.4 Effect on gastrointestinal system (CTD 4.2.1.3-6, 4.2.1.3-7)

A single dose of BINI 10, 30, or 100 mg/kg was administered orally to rats (n = 10/group), and the effect of BINI on gastric secretion and gastrointestinal transport was investigated. No effect of BINI was observed.

3.2.3.5 Effect on renal/urinary system (CTD 4.2.1.3-8)

A single dose of BINI 10, 30, or 100 mg/kg was administered orally to rats (n = 10/group), and the effect of BINI on renal/urinary system was investigated by clinical chemistry and urinalysis (urine volume, urinary electrolytes, fractional electrolyte clearance, specific gravity, and pH). No effect of BINI was observed.

3.3 ENCO/BINI

3.3.1 Primary pharmacodynamics

3.3.1.1 Growth-inhibitory effect against malignant tumor-derived cell lines

3.3.1.1.1 *In vitro* (CTD 4.2.1.1-9)

The growth-inhibitory effect of ENCO/BINI against 16 types of human malignant tumor-derived cell lines with or without BRAF V600 mutation was investigated using the amount of viable cell-derived ATP as the index. Table 10 shows IC_{50} values of ENCO and BINI, and the combined effect of ENCO and BINI.[3)]

[3)] The combined effect of ENCO/BINI was evaluated according to the following criteria (*Nat Biotechnol*. 2009;27:659-66):
Synergistic, SS >2.0 and CI <0.5
Additive/synergistic, SS >2.0 and CI >0.5; or SS >1.0 and <2.0 and CI <0.5
Additive, SS <1.0 and CI <0.5; or SS <2.0 and CI >0.5

Table 10. Growth-inhibitory effect against human malignant melanoma-derived cell lines

Cell line	Type of BRAF mutation	IC_{50} (nmol/L)		SS	CI	Effect of concomitant use
		ENCO	BINI			
A375	V600E	5.8	20.0	1.20	0.87	Additive/synergistic
COLO 741		32.6	1,190.4	1.45	0.27	Additive/synergistic
COLO 800		7.9	50.5	2.67	0.84	Additive/synergistic
IGR-37		17.6	82.8	1.03	0.70	Additive/synergistic
K029AX		12.8	78.8	2.59	0.73	Additive/synergistic
LOX IMVI		>2,700	>2,700	5.99	0.28	Synergistic
A2058		1,486.1	978.0	2.07	0.34	Synergistic
IGR-39		>2,700	>2,700	0.70	—	—
RPMI-7951		>2,700	>2,700	1.02	—	—
SK-MEL-24		776.0	892.2	1.87	0.66	Additive
UACC-62		3.7	47.0	1.26	0.93	Additive/synergistic
IGR-1	V600K	167.6	893.0	3.81	0.02	Synergistic
COLO 792	None	>2,700	182.5	0.90	1.29	Additive
HMCB		>2,700	>2,700	2.86	0.04	Synergistic
MeWo		>2,700	>2,700	2.60	0.25	Synergistic
SK-MEL-31		1,032.0	>2,700	0.93	0.80	Additive

n = 1; SS, synergy score; CI, combination index; —, Not calculated.

3.3.1.1.2 *In vivo* (CTD 4.2.1.1-10)

Using nude mice subcutaneously implanted with a tissue slice of HMEX1906 tumor derived from a patient with malignant melanoma (n = 8/group), the tumor growth-inhibition of ENCO/BINI and survival of mice were investigated. ENCO 3 mg/kg and BINI 3 or 10 mg/kg were administered orally BID for a maximum of 117 days starting from Day 29 after the day of implantation (which was defined as Day 0 of the study), and tumor volume was calculated. On Day 50, a statistically significant tumor growth inhibition was observed in the ENCO alone group, the BINI alone group, and the ENCO/BINI group compared with the control (0.5 w/v% CMC solution containing 0.5 vol% polysorbate 80) group ($P < 0.05$, Tukey's test) (Figure 1). A statistically significant prolongation in survival was observed in the ENCO/BINI group (ENCO 3 mg/kg + BINI 10 mg/kg) compared with the ENCO alone group and the BINI alone group ($P < 0.05$, log-rank test).

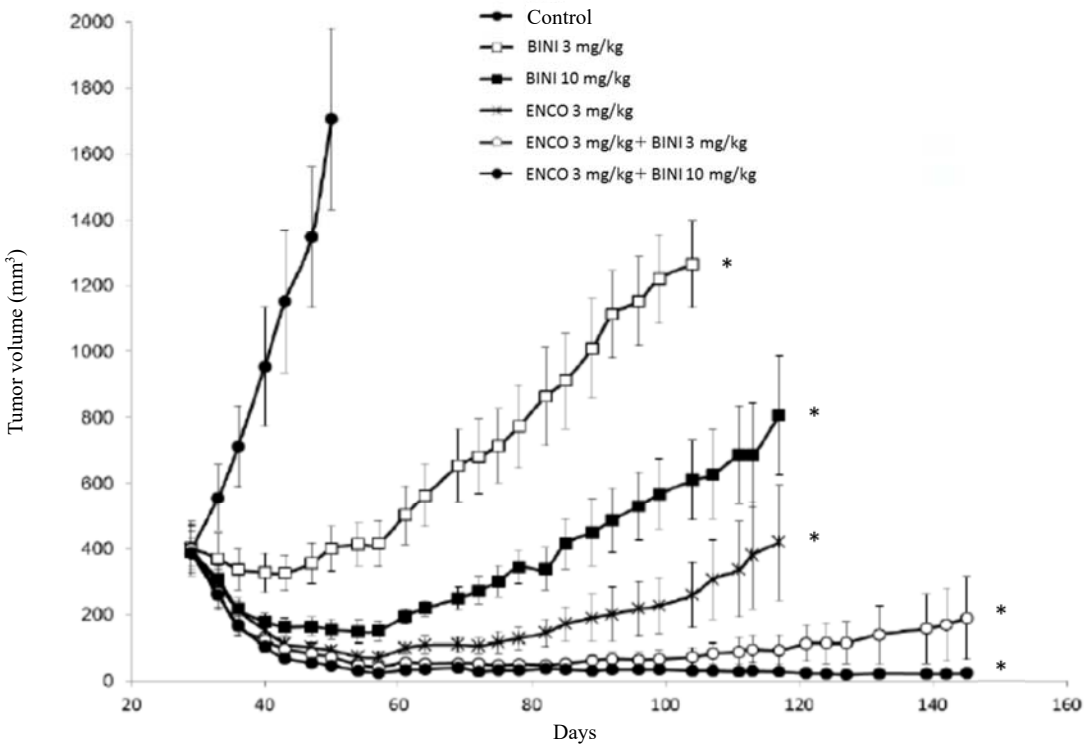


Figure 1. Tumor growth-inhibitory effect of ENCO and BINI in mice subcutaneously implanted with a HMEX1906 tumor tissue slice

n = 8; mean ± SE; *, $P < 0.05$ against the control group (Tukey's test)

3.R Outline of the review conducted by PMDA

As a result of the review of the submitted data, PMDA accepted the applicant's explanation on the nonclinical pharmacology of ENCO and BINI, except for those discussed in the following sections.

3.R.1 Mechanism of action of ENCO or BINI alone and of ENCO/BINI in combination, and their efficacy against malignant melanoma with *BRAF* gene mutation

The applicant's explanation about (a) the mechanism of action of ENCO or BINI alone and of ENCO/BINI in combination and (b) their efficacy against malignant melanoma with *BRAF* gene mutation:

BRAF is involved in the activation of MAPK pathway, and *BRAF* gene mutation is considered to constitutively activate signal transduction via MAPK pathway which includes MEK in the downstream, leading to enhanced tumor cell growth, apoptosis suppression, etc. (*Nature Med*. 2013;19:1401-9, *Nat Rev Cancer*. 2017;17:676-91).

ENCO and BINI are low molecular weight compounds that inhibit kinase activity of BRAF and MEK, respectively, and they are considered to inhibit the growth of tumors with *BRAF* gene mutation [see Sections 3.1.1.4 and 3.2.1.4] by inhibiting the phosphorylation of signal transduction molecules on MAPK pathway (e.g., ERK) [see Sections 3.1.1.1, 3.1.1.3, 3.2.1.1, and 3.2.1.3].

In addition to the mechanism of action of ENCO and BINI described above, *BRAF* gene mutations observed in malignant melanoma are mostly BRAF V600E mutation or "BRAF mutation involving amino acid substitution of valine to lysine at codon 600" (BRAF V600K mutation), accounting for 62%

and 21%, respectively, of the mutations (*Cancer*. 2017;123:1372-81). In view of the observation that both ENCO and BINI inhibited the growth of malignant melanoma-derived cell lines with the above mutations [see Sections 3.1.1.4 and 3.2.1.4], ENCO and BINI are expected to demonstrate efficacy against malignant melanoma with *BRAF* gene mutation.

Given the following observations, ENCO/BINI therapy is expected to have greater efficacy than the ENCO or BINI monotherapy against malignant melanoma with *BRAF* gene mutation:

- Reactivation of MAPK pathway is observed in ≥70% of patients with malignant melanoma that has become resistant to BRAF inhibitors (*Cancer Discov*. 2014;4:80-93), and concomitant use of a BRAF inhibitor and a MEK inhibitor is expected to delay the acquisition of resistance caused by the reactivation of MAPK pathway.
- Compared with ENCO or BINI monotherapy, ENCO/BINI therapy enhanced the growth-inhibition against malignant melanoma-derived cell lines with *BRAF* gene mutation [see Section 3.3.1].

No difference was observed in the pharmacological characteristics (a) between ENCO and dabrafenib mesilate (DAB) or vemurafenib (VEM), both of which are BRAF inhibitors approved in Japan and (b) between BINI and trametinib dimethyl sulfoxide (TRA), a MEK inhibitor approved in Japan.

PMDA's view:

PMDA generally accepted the explanation of the applicant. However, the following remain unclear currently: (a) Efficacy of ENCO and BINI against malignant melanoma with *BRAF* gene mutation other than BRAF V600 mutation, and (b) whether the pharmacological characteristics are similar between ENCO and DAB or VEM and between BINI and TRA. Since the above information may be useful in selecting appropriate patients to be treated with ENCO and BINI in clinical use, further investigations are warranted, and once available, new information should be provided appropriately to health professionals.

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

4.1 ENCO

The pharmacokinetics (PK) of ENCO was investigated in mice, rats, and monkeys. Plasma protein binding, drug-metabolizing enzymes, transporters, etc. of ENCO were investigated using biomaterials derived from humans and animals.

4.1.1 Absorption

4.1.1.1 Single-dose studies

Plasma ENCO concentration was investigated in the following animals (Table 11). Bioavailability (BA) of ENCO following oral administration was 42.6%, 42%, and 22%, respectively, in mice, rats, and monkeys:

- Male mice receiving a single dose of ENCO 2 mg/kg intravenously or 10 mg/kg orally
- Male rats receiving a single dose of ^{14}C-labeled ENCO (^{14}C-ENCO) 5 mg/kg intravenously or 50 mg/kg orally
- Male monkeys receiving a single dose of ^{14}C-ENCO 3 mg/kg intravenously or 20 mg/kg orally

Table 11. PK parameters of ENCO (following intravenous or oral administration in each animal species)

Animal species	Dose (route of administration)	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_{inf} (ng•h/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	Vss (L/kg)
Mice	2 mg/kg (i.v.)	3	—	—	7,715 ± 690	0.86 ± 0.03	4.34 ± 0.37	0.10 ± 0.01
	10 mg/kg (p.o.)	3	14,271 ± 2,346	0.5 (0.5, 0.5)	16,430 ± 2,346	1.42 ± 0.06	—	—
Rats	5 mg/kg (i.v.)	3	43,500 ± 3,900	0.08 (0.08, 0.08)	58,900 ± 2,800	62 ± 26	1.42 ± 0.07	0.31 ± 0.024
	50 mg/kg (p.o.)	3	36,400 ± 12,900	2 (2, 4)	245,000 ± 95,600	7.6 ± 1.4	—	—
Monkeys	3 mg/kg (i.v.)	2	2,450, 3,560	0.08, 0.08	2,310, 2,530	0.67, 1.4	20, 22	0.899, 1.12
	20 mg/kg (p.o.)	3	1,010 ± 378	2 (2, 2)	2,930 ± 644	1.4 ± 0.27	—	—

Arithmetic mean ± SD (individual values for n = 2); *, Median (range); —, Not calculated.

4.1.1.2 Repeated-dose studies

ENCO 6, 20, or 60 mg/kg was administered to male and female rats orally QD for 3 months, and plasma ENCO concentration was investigated (Table 12). C_{max} and AUC_{24h} increased roughly in proportion to dose over the range of dose investigated. C_{max} and AUC_{24h} on Day 90 of administration were higher than those on Day 1. C_{max} and AUC_{24h} in females were higher than those in males. The applicant explained that the observed sex difference in PK of ENCO might have been caused by the sex difference in the expression level of cytochrome P450 (CYP) in rats (*Drug Metab Rev*. 1998;30:441-98), given the finding that ENCO is eliminated mainly by metabolism [see Section 4.1.4.1].

Table 12. PK parameters of ENCO (3-month repeated oral administration in male and female rats)

Day of administration	Dose (mg/kg)	C_{max} (ng/mL)		t_{max} (h)		AUC_{24h} (ng•h/mL)	
		Male	Female	Male	Female	Male	Female
1	6	9,820	16,800	1	1	40,900	96,800
	20	27,500	48,300	1	1	141,000	288,000
	60	57,800	102,000	0.5	1	303,000	879,000
90	6	10,400	18,600	1	1	45,200	114,000
	20	42,100	54,500	1	0.5	178,000	414,000
	60	100,000	150,000	1	1	614,000	1,110,000

PK parameters were calculated based on the mean plasma ENCO concentration (n = 2) at each measuring time point.

ENCO 20 or 60 mg/kg was administered orally QD for 3 months to male and female monkeys, and plasma ENCO concentration was investigated (Table 13). The applicant explained that there is no clear sex difference in PK of ENCO, and that repeated administration has no clear effect on either C_{max} or AUC_{24h}, taking account of the variability of C_{max} and AUC_{24h}.

Table 13. PK parameters of ENCO (3-month repeated oral administration in male and female monkeys)

Day of administration	Dose (mg/kg)	n	C_{max} (ng/mL)		t_{max}* (h)		AUC_{24h} (ng•h/mL)	
			Male	Female	Male	Female	Male	Female
1	20	4	3,590 ± 4,070	8,270 ± 1,410	1.00 (1.00, 1.00)	0.75 (0.500, 1.00)	5,830 ± 6,390	11,100 ± 3,980
	60	6	10,400 ± 5,610	12,700 ± 6,600	1.00 (0.500, 1.00)	1.00 (1.00, 1.00)	24,200 ± 17,100	43,000 ± 31,000
23	20	4	1,740 ± 1,840	3,190 ± 2,460	1.00 (0.500, 1.00)	0.75 (0.500, 1.00)	2,730 ± 2,630	4,940 ± 3390
	60	6	12,100 ± 9,130	12,800 ± 9,130	1.00 (0.500, 1.00)	1.00 (0.500, 3.00)	23,500 ± 17,800	31,400 ± 20,800
86	20	4	1,640 ± 1,500	2,930 ± 4,540	1.00 (0.500, 1.00)	0.500 (0.500, 3.00)	3,120 ± 2,450	4,280 ± 4,620
	60	6	6,790 ± 4,440	7,790 ± 7,340	1.00 (1.00, 3.00)	2.00 (1.00, 3.00)	20,300 ± 19,200	23,900 ± 20,400

Arithmetic mean ± SD; *, Median (range)

4.1.1.3 *In vitro* membrane permeability

Membrane permeability of ENCO was investigated using human colon cancer-derived Caco-2 cell line. The apparent permeability in apical to basolateral direction ($P_{app\ A\rightarrow B}$) of ^{14}C-ENCO 4.8 and 25 μmol/L was 67.4 × 10^{-5} and 76.0 × 10^{-5} cm/min, respectively, in the presence of 1.0 μmol/L LY335979, a P-glycoprotein (P-gp) inhibitor. On the other hand, $P_{app\ A\rightarrow B}$ of ^{14}C-labeled mannitol 3.9 μmol/L, a reference compound with a low membrane permeability, and ^{3}H-labeled propranolol 4.5 μmol/L, a reference compound with a high membrane permeability, was 4.0 × 10^{-5} and 79.2 × 10^{-5} cm/min, respectively. The applicant explained that the above results suggest that ENCO has a high membrane permeability.

4.1.2 Distribution

4.1.2.1 Tissue distribution

A single dose of ^{14}C-ENCO 50 mg/kg was administered orally to male pigmented rats, and tissue distribution of radioactivity was investigated by quantitative whole-body autoradiography. The radioactivity was distributed over a wide range of tissues, and reached the highest level within 2 hours after administration in most of the tissues including blood. The maximum level of radioactivity in bile, liver, and renal pelvis (157,000, 70,800, and 57,600 ng Eq./g, respectively) was higher than the maximum level in blood (48,500 ng Eq./g). $t_{1/2}$ of radioactivity in melanin-containing tissues, i.e., pigmented skin and uvea (3.58 and 5.61 hours, respectively), did not show any tendency of prolongation compared with $t_{1/2}$ in other tissues (1.36-47.2 hours). No radioactivity was detected in tissues other than liver at 168 hours after administration. The applicant explained that the above results suggest that ENCO and its metabolites have only low affinities for melanin.

4.1.2.2 Plasma protein binding

^{14}C-ENCO 50-50,000 ng/mL was incubated with plasma of mice, rats, dogs, monkeys, and humans at 37°C for 3 hours, and plasma protein binding of ENCO was investigated by ultracentrifugation. Plasma protein binding rate of ENCO was almost constant regardless of ENCO concentration in all animal species investigated; the mean binding rate at all concentrations measured was 98.6%, 98.1%, 82.7%, 74.6%, and 86.1%, respectively, in mice, rats, dogs,[4)] monkeys, and humans.

4) The sample of 50 ng/mL, which showed an outlier value (18.8%), was excluded from the calculation of the mean value.

4.1.2.3 Distribution in blood cells

^{14}C-ENCO 50-50,000 ng/mL was incubated with blood of rats, dogs, monkeys, and humans at 37°C for 30 minutes, and distribution of ENCO in blood cells was investigated. The blood/plasma concentration ratio of the radioactivity was almost constant regardless of ENCO concentration in all animal species; the mean ratio at all concentrations tested was 0.61, 0.81, 0.76, and 0.75, respectively, in rats, dogs, monkeys, and humans. The applicant explained that the above results suggest that ENCO is distributed mainly in plasma.

4.1.2.4 Placental and fetal transfer

The applicant explained that ENCO is considered to be crossed the placenta and transferred into fetuses, given the following results:

- ENCO 0.5, 5, or 20 mg/kg was administered orally QD to pregnant rats from Gestation Day 6 to 17, and plasma ENCO concentration in the maternal animals and their offspring was investigated. Following the administration of ENCO at 0.5, 5, and 20 mg/kg, the mean plasma ENCO concentration in the offspring at 1 hour after administration on Gestation Day 17 was 27.5, 237, and 583 ng/mL, respectively, which was 1.5% to 1.7% of plasma ENCO concentration in maternal animals.
- ENCO 5, 25, or 75 mg/kg was administered orally QD to pregnant rabbits from Gestation Day 7 to 20, and plasma ENCO concentration in the maternal animals and their offspring was investigated. Following the administration of ENCO at 5, 25, and 75 mg/kg, the mean plasma ENCO concentration in the offspring at 3 hours after administration on Gestation Day 20 was 73.4, 357, and 1,400 ng/mL, respectively, which was 0.40% to 0.78% of the plasma ENCO concentration in maternal animals.

4.1.3 Metabolism

4.1.3.1 *In vitro*

^{14}C-ENCO ([a] 2.5 and [b] 12.5 μmol/L) was incubated with hepatocytes of rats, monkeys, and humans at 37°C for 24 hours, and intrinsic clearance and metabolites of ENCO were investigated. The intrinsic clearance calculated from the elimination speed of unchanged ENCO in rats, monkeys, and humans was (a) 123, 686, and 54.2 μL/h/10^{-6} cells and (b) 48.2, 276, and 35.4 μL/h/10^{-6} cells, respectively. Main metabolites were M23.8 and M32.7 (*N*-dealkylated forms) in rats; M23.8, M32.7, M42.5A (*N*-dealkylated forms), and M36.5 (hydroxylated form) in monkeys. In human samples, M17.3 (glucuronide conjugate of M32.7) was detected as the main metabolite, together with M23.8, M32.7, M36.5, M42.5A, M42.5B, and M46.3 (hydroxylated forms). The applicant explained that the above results suggest that the main metabolic pathways of ENCO in humans are CYP-catalyzed hydroxylation and *N*-dealkylation, and glucuronidation after *N*-dealkylation.

The applicant's explanation about the enzymes involved in ENCO metabolism in humans:
The following results suggest that mainly CYP3A4 is involved in ENCO metabolism in humans. The applicant plans to conduct a clinical study (Study ARRAY-818-103 [Study 818-103]) to investigate pharmacokinetic interactions between ENCO and an inducer (modafinil) and a substrate (midazolam) of CYP3A. Pharmacokinetic interactions between ENCO and CYP3A inhibitors are described in Section "6.2.4.1 Drug-drug interactions between ENCO and posaconazole or diltiazem hydrochloride (diltiazem)."

- ^{14}C-ENCO (38 μmol/L) was incubated with microsomes prepared from insect cells expressing human CYP isoforms (CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, CYP4A11, CYP4F2, CYP4F3A, CYP4F3B, or CYP4F12) at 37°C for 30 minutes in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH). As a result, metabolites of ENCO were detected in the presence of CYP1A1, CYP2C19, CYP2D6, or CYP3A4. The contribution rate of CYP2C19, CYP2D6, and CYP3A4 to ENCO metabolism, calculated from the rate of formation of metabolites, was 16.0%, 0.71%, and 83.3%, respectively.
- ^{14}C-ENCO (64 μmol/L) was incubated with human liver microsomes in the presence or absence of an inhibitor[5)] of CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A) at 37°C for 30 minutes. The inhibition rate against ENCO metabolism was 71.9% and 76.3% in the presence of ketoconazole and azamulin, respectively, and ≤36.5% in the presence of other inhibitors.

The following results suggest that uridine diphosphate glucuronosyl transferase (UGT)1A1, UGT1A3, UGT1A4, UGT1A8, UGT1A9, and UGT2B7 are involved in ENCO glucuronidation in humans:

- ^{14}C-ENCO (38 μmol/L) was incubated with microsomes prepared from insect cells expressing human UGT isoform (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, or UGT2B17) at 37°C for 30 minutes in the presence of uridine diphosphate glucuronic acid (UDPGA). Glucuronide conjugates of ENCO were detected in the presence of UGT1A1, UGT1A3, UGT1A4, UGT1A8, UGT1A9, and UGT2B7.

4.1.3.2 *In vivo*

A single dose of ^{14}C-ENCO was administered (a) intravenously at 5 mg/kg, or (b) orally at 50 mg/kg, to bile duct-cannulated or non-cannulated male rats, and metabolites of ENCO in plasma, urine, feces, and bile were investigated. The following results were obtained:

- In plasma samples collected from bile duct non-cannulated male rats up to 24 hours after administration, mainly unchanged ENCO, M23.8, M32.7, and M42.5A were detected (percentage to total radioactivity in plasma was (a) 85%, 4.6%, 3.3%, and 1.7%, and (b) 85%, 3.8%, 2.3%, and 1.9%, respectively).
- In urine samples collected from bile duct non-cannulated male rats up to (a) 72 hours or (b) 48 hours after administration, mainly M23.8 and M32.7 were detected (percentage to the administered radioactivity was (a) 13.6% and 5.23%, and (b) 6.7% and 2.4%, respectively). The unchanged ENCO also was detected (percentage to the administered radioactivity was (a) 0.2% and (b) 0.05%).
- In urine samples collected from bile duct-cannulated male rats up to 48 hours after administration, mainly M23.8 and M32.7 were detected (percentage to the administered radioactivity was (a) 5.66% and 6.7%, and (b) 3.55% and 2.21%, respectively). The unchanged ENCO also was detected (percentage to the administered radioactivity was (a) 0.08% and (b) 0.04%).
- In feces collected from bile duct non-cannulated male rats up to 48 hours after administration, mainly the unchanged ENCO and M32.7 were detected (percentage to the administered radioactivity was (a) 9.96% and 36.1%, and (b) 45.7% and 22.8%, respectively).

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5) Furafylline, montelukast, sulfaphenazole, and quinidine were used as inhibitors of CYP1A2, CYP2C8, CYP2C9, and CYP2D6, respectively. Ticlopidine was used as the inhibitor of both CYP2B6 and CYP2C19. Ketoconazole and azamulin were used as inhibitors of CYP3A.

- In feces collected from bile duct-cannulated male rats up to 48 hours after administration, mainly the unchanged ENCO and M32.7 were detected (percentage to the administered radioactivity was (a) 5.5% and 0.92%, and (b) 57.8% and 2.0%, respectively).
- In bile samples collected from bile duct-cannulated male rats up to 24 hours after administration, mainly M32.7 and M23.8 were detected (percentage to the administered radioactivity was (a) 20.6% and 6.18%, and (b) 11.1% and 3.86%, respectively). The unchanged ENCO also was detected (percentage to total administered radioactivity was (a) 1.33% and (b) 0.87%).

A single dose of ^{14}C-ENCO was administered (a) intravenously at 3 mg/kg or (b) orally at 20 mg/kg, and metabolites of ENCO in plasma, urine, and feces were investigated. The following results were obtained:

- In plasma samples collected up to 24 hours after administration, mainly the unchanged ENCO, M22.5A,[6)] M23.8, M32.7, and M42.5A were detected (percentage to total radioactivity in plasma was (a) 40%, 23%, 7.8%, 7.7%, and 2.4%, and (b) 10%, 42%, 12%, 6.1%, and 4.9%, respectively.)
- In urine samples collected up to 48 hours after administration, mainly M23.8, M32.7, and M28.3 (metabolite formed by hydroxylation and *N*-dealkylation) were detected (percentage to the administered radioactivity was (a) 3.98%, 2.96%, and 1.5%, and (b) 4.74%, 1.86%, and 2.84%, respectively).
- In feces collected up to (a) 48 hours or (b) 72 hours after administration, mainly M36.5, M32.7, and M30.6 (oxidized form of M36.5) were detected (percentage to the administered radioactivity was (a) 16.3%, 10.3%, and 8.17%, and (b) 14.5%, 8.69%, and 4.0%, respectively).

4.1.4 Excretion

4.1.4.1 Urinary, fecal, and biliary excretion

The applicant explained that ENCO is eliminated mainly by metabolism, based on the following results:

- Following a single-dose administration of ^{14}C-ENCO to male rats (a) intravenously at 5 mg/kg or (b) orally at 50 mg/kg, the urinary and fecal excretion rate of radioactivity (percentage relative to the administered radioactivity) up to 168 hours after administration was (a) 24.3% and 74.1% and (b) 12.2% and 85.1%, respectively. The urinary and fecal excretion rate of the unchanged ENCO (percentage relative to the administered radioactivity) was (a) 0.20% and 9.96% and (b) 0.05% and 45.7%, respectively.
- Following a single-dose administration of ^{14}C-ENCO to male monkeys (a) intravenously at 3 mg/kg or (b) orally at 20 mg/kg, the urinary and fecal excretion rate of radioactivity (percentage relative to the administered radioactivity) up to 168 hours after administration was (a) 14.4% and 68.2% and (b) 17.4% and 59.7%, respectively. The urinary and fecal excretion rate of the unchanged ENCO (percentage relative to the administered radioactivity) was (a) 0.08% and 2.43% and (b) 0.16% and 6.03%, respectively.
- Following a single-dose administration of ^{14}C-ENCO to bile duct-cannulated male rats (a) intravenously at 5 mg/kg or (b) orally at 50 mg/kg, the biliary excretion rate of radioactivity (percentage relative to the administered radioactivity) up to 48 hours after administration was (a) 41.5% and (b) 28.2%. The biliary excretion rate of the unchanged ENCO (percentage relative to the administered radioactivity) was (a) 1.33% and (b) 0.87%.

6) Multiple reactions including *N*-dealkylation, hydroxylation, hydrolysis, and oxidative deamination are involved in the formation.

The applicant also explained that the contribution of enterohepatic circulation to PK of ENCO is considered to be minimal from the following results: Following a single-dose administration of ^{14}C-ENCO to male rats intravenously at 5 mg/kg or orally at 50 mg/kg, plasma ENCO concentration did not show multimodal changes over time suggestive of enterohepatic circulation.

4.1.4.2 Excretion in milk

Excretion of ENCO in milk was not investigated. The applicant explained that ENCO may be transferred into milk given the physicochemical property of ENCO (partition coefficient in 1-octanol/water [pH 7.8-7.9] is 1.8), because lipophilic compounds are easily transferred into milk (*Japanese Journal of Pediatric Medicine*. 1993;25:52-7).

4.1.5 Pharmacokinetic interactions

4.1.5.1 Enzyme inhibition

The applicant's explanation about the pharmacokinetic interactions of ENCO mediated by inhibition of metabolic enzymes:

Given the following results and C_{max} of ENCO (17.9 μmol/L, [see Section 6.2.11.1]) on Day 1 of administration at the proposed dose to Japanese patients, ENCO is unlikely to cause pharmacokinetic interaction mediated by the inhibition of CYP2A6 or CYP2E1 in clinical use. On the other hand, ENCO may cause pharmacokinetic interaction mediated by the inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A.

- Human liver microsomes were incubated with a substrate[7)] of CYP isoform (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A) in the presence of ENCO (0.5-100 μmol/L) and NADPH, and the inhibition of ENCO against the metabolism of the substrate of each CYP isoform was investigated. ENCO inhibited the metabolism of the substrates of the following CYP isoforms with IC_{50} value indicated in the parentheses: (a) substrates of CYP1A2 (22 μmol/L), CYP2B6 (1 μmol/L), CYP2C9 (5 μmol/L), CYP2C19 (50 μmol/L), and CYP2D6 (25 μmol/L), (b) substrates of CYP2C8 (30 and 20 μmol/L), and (c) substrates of CYP3A (8 and 15 μmol/L). On the other hand, ENCO had no clear inhibition against metabolism of the substrates of other CYP isoforms tested.
- Human liver microsomes and ENCO (1-50 μmol/L) were preincubated in the presence of NADPH, followed by incubation with a substrate[8)] of CYP isoform (CYP1A2, CYP2C9, CYP2D6, or CYP3A), and the time-dependent inhibition of ENCO against metabolism of the substrate of each CYP isoform was investigated. ENCO inhibited the metabolism of the substrate of CYP3A in a time-dependent manner with inhibitor concentration at 50% of maximum inhibition rate (K_I) and maximum inactivation rate constant (k_{inact}) of 20.5 μmol/L and 0.0527 min^{-1}, respectively. In contrast, ENCO had no clear inhibition against metabolism of the substrates of other CYP isoforms tested.

Given the following results and C_{max} of ENCO (17.9 μmol/L, [see Section 6.2.11.1]) on Day 1 of administration at the proposed dose to Japanese patients, ENCO may cause pharmacokinetic interaction mediated by the inhibition of UGT1A1 in clinical use.

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7) Phenacetin, coumarin, bupropion, diclofenac, S-mephenytoin, bufuralol, and chlorzoxazone were used as substrates of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP2E1, respectively. Paclitaxel and amiodarone were used as substrates of CYP2C8. Midazolam and testosterone were used as substrates of CYP3A.

8) Phenacetin, diclofenac, bufuralol, and midazolam were used as the substrate of CYP1A2, CYP2C9, CYP2D6, and CYP3A, respectively.

- Human liver microsomes were incubated with (a) a substrate[9)] of UGT1A1 or BINI at (b) 1, (c) 5, or (d) 25 μmol/L in the presence of ENCO (0.5-100 μmol/L) and UDPGA, and the inhibition of ENCO against metabolism of the substrate of UGT1A1 and BINI was investigated. ENCO inhibited the metabolism of the substrate of UGT1A1 and BINI with IC_{50} of (a) 7, (b) 1, (c) 4, and (d) 4 μmol/L, respectively.
- Microsomes prepared from insect cells expressing human UGT1A1 were incubated with (a) a substrate[9)] of UGT1A1 or BINI at (b) 1, (c) 5, or (d) 25 μmol/L in the presence of ENCO (0.5-100 μmol/L) and UDPGA, and the inhibition of ENCO against metabolism of the substrate of UGT1A1 and BINI was investigated. ENCO inhibited the metabolism of the substrate of UGT1A1 and BINI with IC_{50} of (a) 4, (b) 3.5, (c) 3.5, and (d) 3.5 μmol/L, respectively.

4.1.5.2 Enzyme induction

The applicant's explanation about pharmacokinetic interactions mediated by metabolic enzyme induction by ENCO:

Given the following results and C_{max} of ENCO (17.9 μmol/L, [see Section 6.2.11.1]) on Day 1 of administration at the proposed dose to Japanese patients, ENCO may cause pharmacokinetic interaction mediated by the induction of CYP1A2, CYP2B6, CYP2C9, or CYP3A by ENCO in clinical use.

- Human primary cultured hepatocytes were incubated for 48 hours in the presence of ENCO (1-100 μmol/L), and messenger ribonucleic acid (mRNA) expression and enzyme activity of CYP isoforms ([a] CYP1A2, [b] CYP2B6, [c] CYP2C9, and [d] CYP3A4) were investigated. ENCO induced mRNA expression and enzyme activity of (a) to (d) above, resulting in the increase in mRNA expression and enzyme activity by up to (a) 39.2- and 3.76-fold, (b) 9.44- and 2.26-fold, (c) 5.41- and 2.61-fold, and, (d) 167- and 4.97-fold, respectively, compared with the vehicle (0.1% dimethyl sulfoxide [DMSO]) group, within the concentration range investigated.

- Human primary cultured hepatocytes were incubated for 48 hours in the presence of ENCO (0.5-100 μmol/L), and mRNA expression and enzyme activity of CYP3A4 was investigated. ENCO induced mRNA expression and enzyme activity of CYP3A4, resulting in the increase in mRNA expression and enzyme activity by up to 167- and 3.64-fold, respectively, compared with the vehicle (0.1% DMSO) group within the concentration range investigated. ENCO induced the expression of CYP3A4 mRNA with EC_{50} of 10.2 μmol/L and with E_{max} of 169-fold.

4.1.5.3 Transporters

The applicant's explanation about pharmacokinetic interactions of ENCO mediated by transporters:

The following results, etc., demonstrated that ENCO is not a substrate for breast cancer resistance protein (BCRP), multidrug resistance associated protein (MRP)2, organic cation transporter (OCT)1, organic anion transporting polypeptide (OATP)1B1, OATP1B3, or OATP2B1, but a substrate for P-gp. However, since absorption rate of ENCO is suggested to be ≥86% [see Section 6.2.1.2], indicating only minimal contribution of P-gp in the absorption of ENCO through the gastrointestinal tract, concomitant use of ENCO and a P-gp inhibitor is unlikely to cause pharmacokinetic interactions in clinical use.

- Using Caco-2 cell line, P-gp-, BCRP-, or MRP2-mediated transport of ^{14}C-ENCO (4.8 μmol/L) was investigated. The efflux ratio (ratio of permeability coefficient in the direction of secretion to that in

9) Estradiol was used as the substrate of UGT1A1.

the direction of absorption) was 39.0 in the absence of P-gp, BCRP, or MRP2 inhibitor, and 1.67, 18.9, and 16.7 in the presence of P-gp inhibitor (LY335979 1 μmol/L), BCRP inhibitor (Ko143 1 μmol/L), or MRP2 inhibitor (MK571 10 μmol/L), respectively.

- Using human hepatocytes, OCT1-, OATP1B1-, OATP1B3-, or OATP2B1-mediated transport of ENCO (28 μmol/L) was investigated. Inhibitors[10)] of OCT1, OATP1B1, OATP1B3 and OATP2B1 did not show clear inhibition of intracellular uptake of ENCO.

Given the following results and C_{max} of ENCO (17.9 μmol/L, [see Section 6.2.11.1]) on Day 1 of administration at the proposed dose to Japanese patients, ENCO is unlikely to cause pharmacokinetic interactions mediated by P-gp or MRP2 inhibition in clinical use. On the other hand, ENCO may cause pharmacokinetic interactions mediated by inhibition of BCRP, OATP1B1, OATP1B3, OCT1, OCT 2, organic anion transporter (OAT)1, or OAT 3.

- Using human breast cancer-derived MDA435T0.3 cell line expressing human P-gp, human ovarian cancer-derived IGROV1 cell line expressing human BCRP, and dog kidney-derived MDCKII cell line expressing human MRP2, the inhibition of ENCO (0.1-50 μmol/L[11)]) against P-gp-, BCRP-, and MRP2-mediated transport of each substrate[12)] was investigated. ENCO inhibited the transport of the substrate of BCRP with estimated IC_{50} of 10 to 25 μmol/L. On the other hand, ENCO had no clear inhibition against the transport of the substrates of P-gp and MRP2.
- Using HEK293 cell line expressing human OATP1B1, OATP1B3, or OCT1, the inhibition of ENCO (1-100 μmol/L) against OATP1B1-, OATP1B3-, and OCT1-mediated transport of each substrate[13)] was investigated. ENCO inhibited the transport of the substrates of OATP1B1, OATP1B3, and OCT1 with IC_{50} of 5.35, 6.16, and 12.7 μmol/L, respectively.
- Using HEK293 cell line expressing human OAT1, OAT3, or OCT2, the inhibition of ENCO (1-50 μmol/L[14)]) against OAT1-, OAT3-, or OCT2-mediated transport of each substrate[15)] was investigated. ENCO inhibited the transport of the substrates of OAT1, OAT3, and OCT2 with IC_{50} of 4.20, 0.92, and 2.05 μmol/L, respectively.

4.2 BINI

PK of BINI was investigated in mice, rats, and monkeys. Plasma protein binding, drug-metabolizing enzymes, transporters, etc. of BINI were investigated using biomaterials derived from humans and animals.

4.2.1 Absorption

4.2.1.1 Single dose studies

Plasma BINI concentration was investigated in the following animals (Table 14). BA of BINI following oral administration was 29% to 54%, 47.1%, and 48.2%, respectively, in mice, rats, and monkeys:

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10) Inhibitors used were decynium 22 against OCT1, rifamycin SV against OATP1B1 and OATP1B3, atorvastatin against OATP1B1 and OATP2B1, and MK-571 against OATP1B1, OATP1B3, and OATP2B1. All inhibitors were used at 10 μmol/L.

11) MRP2 was used at 5 and 50 μmol/L.

12) Rhodamine 123 (0.1 μmol/L), bodipy FL prazosin (0.05 μmol/L), and ^{14}C-labeled valsartan (10 μmol/L) were used as substrates for P-gp, BCRP, and MRP2, respectively.

13) ^{3}H-labeled estradiol-17β-glucuronide (1.4 μmol/L) was used as the substrate for OATP1B1 and OATP1B3. ^{3}H-labeled 1-methyl-4-phenylpyridinium iodide (8.8 nmol/L) was used as the substrate for OCT1.

14) OAT1-medidated transport was investigated using ENCO at 1 to 25 μmol/L.

15) ^{3}H-labeled *p*-aminohippuric acid (0.29 μmol/L), ^{3}H-labeled estrone-3-sulfate (0.028 μmol/L), and ^{14}C-labeled metformin (6.6 μmol/L) were used as substrates for OAT1, OAT3, and OCT2, respectively.

- Female mice receiving a single dose of BINI 1 mg/kg intravenously or 3, 10, 30, 100, or 300 mg/kg orally
- Male rats receiving a single dose of ^{14}C-labeled BINI (^{14}C-BINI) 1 mg/kg intravenously or 4 mg/kg orally
- Male monkeys receiving a single dose of ^{14}C-BINI 1 mg/kg intravenously or 3 mg/kg orally
- Male monkeys receiving a single dose of BINI 1, 3, or 10 mg/kg orally

Following oral administration in female mice, C_{max} and AUC_{inf} of BINI increased less than in proportion to dose within the dose range tested. The applicant explained the less than dose-proportional increase was caused by the limited absorption at higher doses due to the poor solubility of BINI resulting in incomplete dissolution within the gastrointestinal tract.

Following oral administration in male monkeys, both C_{max} and AUC_{last} increased roughly in proportion to dose within the dose range tested.

Table 14. PK parameters of BINI (single intravenous or oral administration in each animal species)

Animal species	Dose (route of administration)	n	C_{max} (ng/mL)	t_{max} *2 (h)	AUC_{inf} (ng•h/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	Vss (L/kg)
Mice*1	1 mg/kg (i.v.)	3	—	—	2,916	4.8	5.72	0.29
	3 mg/kg (p.o.)	3	606	0.25	3,727	—	—	—
	10 mg/kg (p.o.)	3	1,887	1	13,672	—	—	—
	30 mg/kg (p.o.)	3	6,800	2	47,256	—	—	—
	100 mg/kg (p.o.)	3	20,967	2	122,653*3	—	—	—
	300 mg/kg (p.o.)	3	28,967	8	252,376*3	—	—	—
Rats	1 mg/kg (i.v.)	3	6,990 ± 1,350	0.08 (0.08, 0.08)	5,920 ± 1,140	6.6 ± 0.94	2.88 ± 0.57	0.618 ± 0.327
	4 mg/kg (p.o.)	3	2,690 ± 1,580	0.25 (0.25, 0.5)	11,100 ± 4,640	4.7 ± 0.25	—	—
Monkeys	1 mg/kg (i.v.)	2	4,660, 5,820	0.083, 0.083	3,310, 3,360	13.5, 6.87	5.0, 5.0	1.24, 0.88
	3 mg/kg (p.o.)	3	846 ± 221	0.5 (0.5, 1)	4,820 ± 581	9.04 ± 1.69	—	—
Monkeys	1 mg/kg (p.o.)	3	49 ± 12	2 (0.5, 6)	564 ± 30*3	8.48 ± 0.72	—	—
	3 mg/kg (p.o.)	3	330 ± 239	2 (1, 4)	2,500 ± 701*3	7.70 ± 0.95	—	—
	10 mg/kg (p.o.)	3	898 ± 483	2 (0.5, 4)	7,870 ± 1,390*3	7.93 ± 0.27	—	—

Arithmetic mean ± SD (individual values for n = 2); *1, PK parameters were calculated based on the mean plasma BINI concentration (n = 3) at each measuring time point; *2, Median (range); *3, AUC_{last}; —, Not calculated.

4.2.1.2 Repeated-dose studies

BINI 1, 3, or 10 mg/kg was administered orally QD for 5 days to male monkeys, and plasma BINI concentration was investigated (Table 15). C_{max} and AUC_{12h} of BINI tended to decrease on Day 5 after administration compared with Day 1. The applicant explained that the decrease was caused by repeated administration of BINI that induced UGT1A1, a metabolic enzyme of BINI [see Section 4.2.3.1], in view of the findings that BINI induces CYP3A [see Section 4.2.5.2] and that, in monkeys, drugs with CYP3A4-inducing activity are capable of inducing multiple UGT isoforms including UGT1A1 (*Drug Metab Pharmacokinet*. 2008;23:45-53).

Table 15. PK parameters of BINI (5-day repeated oral administration in male monkeys)

Day of administration	Dose (mg/kg)	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{12h} (ng•h/mL)
1	1	3	72 ± 23	2.00 ± 1.73	417 ± 29
	3	3	297 ± 76	1.50 ± 0.87	1,280 ± 350
	10	3	877 ± 410	1.00 ± 0.866	4,380 ± 1,690
5	1	3	70 ± 25	2.00 ± 1.73	490 ± 96
	3	3	227 ± 89	0.67 ± 0.289	1,180 ± 514
	10	2	398, 834	0.50, 0.50	1,920, 3,460

Arithmetic mean ± SD (individual values for n = 2)

4.2.1.3 *In vitro* membrane permeability

Membrane permeability of BINI was investigated using Caco-2 cell line. $P_{app\ A\rightarrow B}$ of ^{14}C-BINI 12 μmol/L was 63.2 × 10^{-5} cm/min in the presence of 2.0 μmol/L GF120918 (inhibitor of P-gp and BCRP). In addition, $P_{app\ A\rightarrow B}$ of ^{14}C-labeled mannitol 3.9 μmol/L, a reference compound with a low membrane permeability, and ^{3}H-labeled propranolol 4.5 μmol/L, a reference compound with a high membrane permeability, was 4.0 × 10^{-5} and 79.2 × 10^{-5} cm/min, respectively. The applicant explained that the above results suggest that BINI has a moderate to high membrane permeability.

4.2.2 Distribution

4.2.2.1 Tissue distribution

A single dose of ^{14}C-BINI 30 mg/kg was administered orally to male pigmented and albino rats, and tissue distribution of radioactivity was investigated by quantitative whole-body autoradiography. In pigmented rats, the radioactivity was distributed over a wide range of tissues, and reached the highest level within 2 hours after administration in most of the tissues including blood. The maximum level of radioactivity in small intestine, bile, renal medulla, renal cortex, bladder, and liver (209.2, 122.6, 21.1, 18.7, 16.4, and 13.9 μg Eq./g, respectively) was higher than the maximum level in blood (13.6 μg Eq./g). The tissue distribution of radioactivity was similar between pigmented rats and albino rats. The maximum radioactivity concentration in the pigmented skin (6.8 μg Eq./g) was higher than the concentration in the white skin (3.7 μg Eq./g), and was eliminated more gradually than in the white skin. In contrast, the time-course change in radioactivity concentration in the uvea was similar between pigmented rats and albino rats, and radioactivity concentration at 168 hours after administration was below the lower limit of quantitation (0.336 μg Eq./g).

Synthetic melanin was incubated with ^{14}C-BINI (0.4-50 μmol/L) for 1 hour, and affinity of BINI to melanin was investigated by measuring the concentration of unbound BINI. Results showed that BINI has 2 binding sites of high and low affinity for synthetic melanin; the maximum binding/dissociation constant ratio was 1.11 and 0.52, respectively. The applicant explained that the affinity of BINI to melanin is low, taking into account that the maximum binding/dissociation constant ratio of ^{14}C-labeled chloroquine, a high-affinity compound, to melanin was ≥53.

4.2.2.2 Plasma protein binding

^{14}C-BINI (50-10,000 ng/mL) was incubated with plasma of mice, rats, dogs, monkeys, and humans at 37°C for 3 hours, and plasma protein binding of BINI was investigated by ultracentrifugation. Plasma protein binding rate of BINI was almost constant in all investigated animal species regardless of BINI concentration; the mean binding rate at all concentrations measured was 96.5%, 98.5%, 84.0%, 96.4%, and 97.2%, respectively, in mice, rats, dogs, monkeys, and humans.

BINI (2 μmol/L) was incubated with human serum albumin (HSA) solution (40 g/L) or with mixture of HSA (40 g/L) and α1-acid glycoprotein (AGP) (3 g/L) at 37°C for 6 hours, and binding of BINI to each protein was investigated. The binding rate of BINI in HSA solution and the mixture of HSA and AGP was 90.4% and 89.4%, respectively. The applicant explained that the above results suggest that BINI binds mainly to HSA in human plasma.

4.2.2.3 Distribution in blood cells

^{14}C-BINI (50-10,000 ng/mL) was incubated with blood of mice, rats, dogs, monkeys, and humans at 37°C for 30 minutes, and distribution of BINI in blood cells was investigated. The blood/plasma concentration ratio of the radioactivity was almost constant in all investigated animal species regardless of BINI concentration; the mean ratio at all concentrations tested was 0.719, 0.652, 0.994, 0.787, and 0.718, respectively, in mice, rats, dogs, monkeys, and humans. The applicant explained that the above results suggest that BINI is distributed mainly in plasma.

4.2.2.4 Placental and fetal transfer

Placental and fetal transfer of BINI was not investigated. The applicant explained that BINI may be crossed the placenta and transferred into fetuses given the physicochemical property of BINI (molecular weight 441.23, partition coefficient in 1-octanol/0.01 mol/L hydrochloric acid [pH 2.0] is 1.239), because low molecular weight compounds and lipophilic compounds are easily crossed the placenta (*Acta Obstetrica et Gynecologica Japonica*. 2006;58:77-85).

4.2.3 Metabolism

4.2.3.1 *In vitro*

BINI (5 μmol/L) was incubated[16)] with hepatocytes or liver microsomes of mice, rats, monkeys, and humans at 37°C, and metabolites of BINI were investigated. In all animal species tested, M3 (*N*-demethylated form) and glucuronide conjugate were observed in hepatocytes, and M3 was observed in liver microsomes.

^{14}C-BINI (45.9 μmol/L) was incubated[17)] with human hepatocytes or liver microsomes at 37°C, and metabolites of BINI were investigated. In the study using hepatocytes, the main metabolites were M10.2 and M10.9 (glucuronide conjugates), and sum of M10.2 and M10.9 accounted for 45.1%, and M3 accounted for 2.4%, of the unchanged BINI eliminated. In the study using liver microsomes, the main metabolite was M10.9. The applicant explained that the above results suggest the main route of BINI metabolism in humans is glucuronidation.

The applicant's explanation about the enzymes involved in BINI metabolism in humans:
The following results suggest that the main CYP isoforms involved in BINI metabolism in humans are CYP1A2 and CYP2C19. However, since glucuronide conjugate was the main metabolite observed in the study using human hepatocytes, CYP1A2 and CYP2C19 are considered to contribute only minimally

16) Incubated for 3 hours in the study using hepatocytes, and for 1 hour in the presence of NADPH in the study using liver microsomes.
17) Incubated for 24 hours in the study using hepatocytes, and for 30 minutes in the presence of NADPH and UDPGA in the study using liver microsomes.

to metabolism of BINI, and PK of BINI is unlikely to be affected by CYP1A2- or CYP2C19-mediated pharmacokinetic interaction.

- ^{14}C-BINI (45.9 μmol/L) was incubated with microsomes prepared from insect cells expressing human CYP isoform (CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, CYP4A11, CYP4F2, CYP4F3A, CYP4F3B, or CYP4F12) at 37°C for 30 minutes in the presence of NADPH. M3 was detected in the presence of CYP1A1, CYP1A2, or CYP2C19. The amount of M3 formed in the presence of CYP1A1 was much smaller than the amount formed in the presence of CYP1A2 or CYP2C19. The contribution rate of CYP1A2 or CYP2C19 to BINI metabolism, calculated from the rate of M3 formation, was 50% for both.
- Human liver microsomes and ^{14}C-BINI (10 μmol/L) were incubated at 37°C for 30 minutes in the presence or absence of an inhibitor[5)] of CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A). The inhibition rate against BINI metabolism was 62.2% and 41.4% in the presence of furafylline and ticlopidine, respectively, and ≤8.6% in the presence of other inhibitors.

The following results suggest that mainly UGT1A1 is involved in the glucuronide conjugation of BINI in humans. In Study CMEK162X1101 (Study X1101) [see Section 6.2.2.1], the exposure to BINI (AUC_{inf}) following oral administration of BINI (45 mg BID) was 2,690 ng•h/mL in UGT1A1 extensive metabolizers, 2,320 ng•h/mL in intermediate metabolizers, and 3,480 ng•h/mL in poor metabolizers,[18)] showing no clear relationship between exposure to BINI and genetic polymorphism of UGT1A1, which suggests that UGT1A1-mediated pharmacokinetic interactions are unlikely to occur in clinical use.

- ^{14}C-BINI (5 or 50 μmol/L) was incubated with recombinant human UGT isoform (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B10, UGT2B15, or UGT2B17) at 37°C for 30 minutes in the presence of UDPGA. M10.2 and M10.9 were detected in the presence of UGT1A1, UGT1A3, UGT1A4, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, or UGT2B7. M10.2 was detected most abundantly in the presence of UGT2B7. M10.9 was detected most abundantly in the presence of UGT1A1, and next abundantly in the presence of UGT1A3 or UGT1A9.
- Human liver microsomes and ^{14}C-BINI (20 μmol/L) were incubated at 37°C for 30 minutes in the presence or absence of atazanavir (inhibitor of UGT1A1 and UGT1A3) and in the presence of UDPGA. Atazanavir inhibited the metabolism of BINI to M10.9 by ≥93.7%, but had no clear inhibition against metabolism to M10.2.
- BINI (10-1,000 μmol/L[19)]) was incubated with microsomes prepared from insect cells expressing UGT isoform (UGT1A1, UGT1A3, or UGT1A9) mainly involved in the formation of M10.9, the metabolite most abundantly detected in studies using human liver cells, at 37°C for 30 minutes in the presence of UDPGA, and contribution rate of each UGT isoform to BINI metabolism was estimated from the rate of M10.9 formation. The contribution rate of UGT1A1, UGT1A3, and UGT1A9 to BINI metabolism was estimated to be 90%, 3.0%, and 7.0%, respectively.

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18) Patients who lacked both UGT1A1*28 and UGT1A1*6 were defined as extensive metabolizers; patients who had UGT1A1*28 or UGT1A1*6 in heterozygotic form were defined as intermediate metabolizers; and patients who had UGT1A1*28 or UGT1A1*6 in homozygotic form and patients who had UGT1A1*28 and UGT1A1*6 in compound heterozygotic form were defined as poor metabolizers.

19) Investigated 10 to 500 μmol/L for UGT1A1 and 50 to 750 μmol/L for UGT1A9.

4.2.3.2 *In vivo*

A single dose of ^{14}C-BINI was administered (a) intravenously at 1 mg/kg or (b) orally at 4 mg/kg to bile duct-cannulated or non-cannulated male rats, and metabolites in plasma, urine, feces, and bile were investigated. The following results were obtained:

- In the plasma samples collected from bile duct non-cannulated male rats up to 48 hours after administration, mainly the unchanged BINI and M4 (amide form) were detected (percentage relative to total radioactivity in plasma was (a) 83.4% and 4.52% and (b) 75.4% and 8.52%, respectively).
- In the urine samples collected from bile duct non-cannulated male rats up to 48 hours after administration, mainly the unchanged BINI and M10.9 were detected (percentage relative to administered radioactivity was (a) 15.0% and 21.7% and (b) 5.02% and 13.4%, respectively).
- In feces collected from bile duct non-cannulated male rats up to (a) 72 hours or (b) 48 hours after administration, mainly the unchanged BINI and M4 (amide form) were detected (percentage relative to administered radioactivity was (a) 15.6% and 18.8% and (b) 21.8% and 34.2%, respectively).
- In the bile samples collected from bile duct-cannulated male rats up to 24 hours after administration, mainly M10.9 was detected (percentage relative to administered radioactivity was (a) 45.0% and (b) 35.3%). The unchanged BINI also was detected (percentage to administered radioactivity was (a) 1.8% and (b) 1.0%).

A single dose of ^{14}C-BINI was administered (a) intravenously at 1 mg/kg or (b) orally at 3 mg/kg to male monkeys, and metabolites in plasma, urine, and feces were investigated. The following results were obtained:

- In plasma samples collected up to (a) 24 hours or (b) 48 hours, mainly the unchanged BINI and M10.2 were detected (percentage relative to total radioactivity in plasma was (a) 47.2% and 42.1% and (b) 49.7% and 20.5%, respectively).
- In urine samples collected up to 72 hours after administration, mainly the unchanged BINI and M10.2 were detected (percentage relative to administered radioactivity was (a) 2.04% and 8.75% and (b) 5.33% and 12.7%, respectively).
- In feces samples collected up to (a) 72 hours or (b) 96 hours after administration, mainly M4 was detected (percentage relative to administered radioactivity was (a) 10.6% and (b) 22.5%). The unchanged BINI also was detected (percentage to administered radioactivity was (a) 8.72% and (b) 16.0%).

4.2.4 Excretion

4.2.4.1 Urinary, fecal, and biliary excretion

The applicant explained that BINI is eliminated mainly by metabolism, based on the following results:

- Following a single-dose administration of ^{14}C-BINI (a) intravenously at 1 mg/kg or (b) orally at 4 mg/kg to biliary duct non-cannulated male rats, the urinary and fecal excretion rates of radioactivity up to 168 hours after administration (percentage relative to administered radioactivity) was (a) 45.6% and 44.7% and (b) 23.1% and 69.4%, respectively. The urinary and fecal excretion rates of the unchanged BINI (percentages relative to administered radioactivity) were (a) 15.0% and 15.6% and (b) 5.02% and 21.8%, respectively.
- Following a single-dose administration of ^{14}C-BINI (a) intravenously at 1 mg/kg or (b) orally at 3 mg/kg to male monkeys, urinary and fecal excretion rates of radioactivity (percentage relative to administered radioactivity) up to 168 hours after administration was (a) 40.3% and 39.4% and

(b) 42.6% and 50.5%, respectively, and urinary and fecal excretion rates of the unchanged BINI (percentages relative to the administered radioactivity) was (a) 2.04% and 8.72% and (b) 5.33% and 16.0%, respectively.

- Following a single-dose administration of ^{14}C-BINI (a) intravenously at 1 mg/kg or (b) orally at 4 mg/kg to bile duct-cannulated male rats, the biliary excretion rate of radioactivity up to 48 hours after administration (percentage relative to the administered radioactivity) was (a) 49.9% and (b) 39.4%, and the biliary excretion rate of the unchanged BINI was (a) 1.8% and (b) 1.0%,.

The applicant explained that the contribution of enterohepatic circulation to PK of BINI is considered to be minimal from the following and other results: Following a single-dose administration of ^{14}C-BINI intravenously at 1 mg/kg or orally at 4 mg/kg, plasma BINI concentration did not show multimodal changes over time suggestive of enterohepatic circulation.

4.2.4.2 Excretion in milk

Excretion of BINI in milk was not investigated. The applicant explained that BINI may be transferred into milk given the physicochemical property of BINI (partition coefficient in 1-octanol/0.01 mol/L hydrochloric acid [pH 2.0] is 1.239), because lipophilic compounds are easily transferred into milk (*Japanese journal of pediatric medicine*. 1993;25:52-7).

4.2.5 Pharmacokinetic interactions

4.2.5.1 Enzyme inhibition

The applicant's explanation about the pharmacokinetic interactions of BINI mediated by inhibition of metabolic enzymes:

Given the following results and C_{max} of BINI (1.82 μmol/L, [see Section 6.2.2.1]) under the steady state after administration at the proposed dose to Japanese patients, BINI is unlikely to cause pharmacokinetic interaction mediated by the inhibition of CYP1A2 or CYP2C9 in clinical use. On the other hand, BINI may cause pharmacokinetic interactions mediated by inhibition of CYP2B6.

- Human liver microsomes were incubated with a substrate[20)] of CYP isoform (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A) in the presence of BINI (0.5-100 μmol/L) and NADPH, and the inhibition of BINI against metabolism of the substrate of each CYP isoform was investigated. BINI inhibited the metabolism of the substrates of CYP1A2, CYP2B6, and CYP2C9 with IC_{50} of 50, 6, and 52 μmol/L, respectively. On the other hand, BINI had no clear inhibition against metabolism of the substrates of other CYP isoforms tested.

Also, given the following results and C_{max} of BINI (1.82 μmol/L, [see Section 6.2.2.1]) under the steady state after administration at the proposed dose to Japanese patients, BINI is unlikely to cause pharmacokinetic interaction mediated by the inhibition of UGT1A in clinical use:

- Human liver microsomes were incubated with a substrate[21)] of UGT1A in the presence of BINI (0.05-25 μmol/L) and UDPGA, and the inhibition of BINI against metabolism of the substrate of UGT1A was investigated. The inhibition rate of BINI was 20.3% at 25 μmol/L.

[20)] Phenacetin, coumarin, bupropion, amodiaquine, diclofenac, S-mephenytoin, bufuralol, and chlorzoxazone were used as substrates for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1, respectively. Testosterone and midazolam were used as substrates for CYP3A.

[21)] SN-38, the active metabolite of irinotecan hydrochloride, was used as the substrate for UGT1A.

4.2.5.2 Enzyme induction

The applicant's explanation about pharmacokinetic interactions mediated by metabolic enzyme induction by BINI:

Given the following results and C_{max} of BINI (1.82 μmol/L, [see Section 6.2.2.1]) under the steady state after administration at the proposed dose to Japanese patients, BINI is unlikely to cause pharmacokinetic interactions mediated by induction of CYP1A2, CYP2B6, or CYP2C9 in clinical use. On the other hand, BINI may cause pharmacokinetic interactions mediated by CYP3A induction.

- Human primary cultured hepatocytes were incubated for 48 hours in the presence of BINI (0.1-20 μmol/L), and mRNA expression level and enzyme activity of CYP isoforms (CYP1A2, CYP2B6, CYP2C9, or CYP3A) were investigated. BINI induced mRNA expression and enzyme activity of CYP3A4, resulting in the increase in mRNA expression and enzyme activity by up to 37.2- and 4.08-fold, respectively, compared with the vehicle (0.1% DMSO) group within the concentration range investigated. BINI (20 μmol/L) induced mRNA expression of CYP1A2, CYP2B6, CYP2C9 by 4.75% to 6.38%, 2.70% to 17.2%, and 47.9% to 72.7%, respectively, compared with the level induced by the positive control,[22)] but did not clearly induce enzyme activities.
- Human primary cultured hepatocytes were incubated for 48 hours in the presence of BINI (0.01-30 μmol/L), and the activity of BINI to induce the mRNA expression of CYP3A4 was investigated. EC_{50} and E_{max} were 3.56 to 15.4 μmol/L and 7.39 to 11.9 times baseline, respectively.

4.2.5.3 Transporters

The applicant's explanation about pharmacokinetic interactions of BINI mediated by transporters:

The following results, etc., demonstrated that BINI is not a substrate for OCT1, OATP1B1, OATP1B3, or OATP2B1, but a substrate for P-gp and BCRP:

- Using Caco-2 cell line, P-gp- or BCRP-mediated transport of ^{14}C-BINI (12 μmol/L) was investigated. The efflux ratio of BINI was 11.5 in the absence of inhibitors of P-gp and BCRP, 2.37 in the presence of P-gp inhibitor LY335979 (1 μmol/L), 8.39 in the presence of BCRP inhibitor Ko143 (1 μmol/L), and 1.23 in the presence of GF120918, inhibitor of both P-gp and BCRP (2 μmol/L).
- Using Caco-2 cell line, P-gp-mediated transport of BINI (1, 10, and 100 μmol/L) was investigated. In the absence of P-gp inhibitor, the efflux ratio of BINI at 1, 10, and 100 μmol/L was 6.3, 5.8, and 2.1, respectively, showing a decrease with the increase in BINI concentration. In the presence of P-gp inhibitor verapamil (100 μmol/L), efflux ratio of BINI (10 μmol/L) was 1.7.
- Using human hepatocytes, transport of ^{14}C-BINI (8.7 μmol/L) mediated by OCT1, OATP1B1, OATP1B3, or OATP2B1 was investigated. Inhibitors of OCT1, OATP1B1, OATP1B3, or OATP2B1[10)] did not clearly inhibit the intracellular uptake of ^{14}C-BINI.

Given the following results and C_{max} of BINI (1.82 μmol/L, [see Section 6.2.2.1]) under the steady state after administration at the proposed dose to Japanese patients, BINI, in clinical use, is unlikely to cause pharmacokinetic interactions mediated by inhibition of P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, bile salt export pump (BSEP), multidrug and toxin extrusion (MATE)1, or MATE2-K.

- Using porcine kidney-derived LLC-PK1 cell line expressing human P-gp, IGROV1 cell line expressing human BCRP, or HEK 293 cell line expressing human OCT1 or MATE2-K, the inhibition

22) Positive controls used were omeprazole (50 μmol/L) for CYP1A2, phenobarbital (1,000 μmol/L) for CYP2B6, and rifampicin (10 μmol/L) for CYP2C9.

of BINI ([a] 0.1-100, [b] 0.1-50, [c] 1-100, and [d] 1.57-50 μmol/L) against the transport of each substrate[23] mediated by (a) P-gp, (b) BCRP, (c) OCT1, and (d) MATE2-K was investigated. BINI did not show any clear inhibition against P-gp-, BCRP-, OCT1-, or MATE2-K-mediated transport.

- Using HEK293 cell line expressing human OATP1B1, OATP1B3, OCT2, OAT1, or OAT3, the inhibition of BINI ([a] 5-200, [b] 1-100, [c] 1-50, [d] 0.1-50 μmol/L) against transport of each substrate[24] mediated by transporters (a) OATP1B1 and OATP1B3, (b) OCT2, (c) OAT1, and (d) OAT3 was investigated. BINI inhibited the transport mediated by OATP1B1, OATP1B3, OCT2, OAT1, and OAT3 with IC_{50} of 23.6, 29, 18.1, 27, and 1.87 μmol/L, respectively.
- Using membrane vesicles prepared by insect cells expressing human BSEP, the inhibition of BINI against BSEP-mediated transport of taurocholic acid was investigated. BINI did not clearly inhibit BSEP-mediated transport of taurocholic acid.
- Using HEK293 cell line expressing human MATE1, the inhibition of BINI against MATE1-mediated transport of ^{14}C-labeled metformin was investigated. BINI did not clearly inhibit MATE1-mediated transport.

4.R Outline of the review conducted by PMDA

On the basis of the submitted data and the results of the reviews in the following sections, PMDA concluded that the applicant's discussions on the nonclinical pharmacokinetics of ENCO and BINI are acceptable.

4.R.1 Pharmacokinetic interactions of ENCO

In vitro studies suggested that ENCO causes pharmacokinetic interactions mediated by the following metabolic enzymes and transporters in clinical use:

- Inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2 [see Sections 4.1.5.1 and 4.1.5.3]
- Induction of CYP1A2, CYP2B6, CYP2C9, and CYP3A [see Section 4.1.5.2]

The applicant's explanation about pharmacokinetic interactions of ENCO with the above metabolic enzymes and transporters:

- In the pooled analysis of part 1 of the global phase III study (Study B2301), the foreign phase II study (Study CLGX818X2109 [Study X2109]), and the foreign phase Ib/II study (Study X2110), there were no particular safety concerns in concomitant use with substrates of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2, which suggests that concomitant use of these substrates with ENCO is unlikely to pose any problem in clinical use.
- Since substrates of CYP2B6 are unlikely to be concomitantly administered with ENCO clinically, concomitant use of a substrate of CYP2B6 with ENCO is unlikely to pose any problems in clinical use.

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[23] Digoxin (10 μmol/L), bodipy FL prazosin (0.05 μmol/L), ^{3}H-labeleedd methyl-4-phenylpyridinium (8.8 nmol/L), and ^{14}C-labeled metformin (14.8 μmol/L) were used as substrates for P-gp, BCRP, OCT1, and MATE2-K, respectively.

[24] ^{3}H-labeled estradiol-17β-glucuronide (1.1 μmol/L) was used as the substrate for OATP1B1 and OATP1B3. ^{14}C-labeled metformin (14.2 μmol/L), ^{3}H-labeled cidofovir (1.4 μmol/L), and ^{3}H-labeled estrone-3-sulfate (0.75 μmol/L) were used as substrates for OCT2, OAT1, and OAT3, respectively.

- PK of BINI, a substrate of UGT1A1 [see Section 4.2.3.1], was not clearly affected by combination with ENCO [see Sections 6.2.2.4 and 6.2.3.1], which suggests that concomitant use of ENCO with a substrate of UGT1A1 in clinical use is unlikely to pose any problem.

The applicant plans to conduct a clinical study (Study 818-103) to investigate pharmacokinetic interactions of ENCO with an inducer (modafinil) and a substrate (midazolam) of CYP3A.

PMDA's view:
The applicant's explanation is generally acceptable. Since information on pharmacokinetic interactions of ENCO mediated by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2 is critical for the proper use of ENCO, such information, including that obtained from Study 818-103, etc., should be collected continuously, and when useful information become available, the information should be provided to healthcare professionals in an appropriate manner.

4.R.2 Pharmacokinetic interactions of BINI

In vitro studies suggested that BINI causes pharmacokinetic interactions mediated by the following metabolic enzymes and transporters in clinical use:
- BINI inhibits CYP2B6 [see Section 4.2.5.1].
- BINI serves as a substrate for P-gp and BCRP [see Section 4.2.5.3].

The applicant's explanation about pharmacokinetic interactions of BINI with the above metabolic enzyme and transporters:
- Since substrates of CYP2B6 are unlikely to be concomitantly administered with BINI clinically, concomitant use of a substrate of CYP2B6 with BINI is unlikely to pose any problems in clinical use.
- In the pooled analysis of the global phase III study (Study CMEK162A2301 [Study A2301]) and the foreign phase II study (Study CMEK162X2201 [Study X2201]), there were no particular safety concerns in combination with a P-gp inhibitor, which suggests that concomitant use of a P-gp inhibitor with BINI is unlikely to pose any problem in clinical use.
- It is practically impossible currently to plan a clinical drug interaction study using a typical BCRP inhibitor. The *in vitro* observation that BINI serves as a substrate for BCRP will be communicated appropriately to healthcare professionals using the package insert, etc.

PMDA's view:
The applicant's explanation is generally acceptable. Since information on pharmacokinetic interactions of BINI mediated by CYP2B6, P-gp, and BCRP is critical for the proper use of BINI, such information should be collected continuously, and when useful information becomes available, the information should be provided to healthcare professionals in an appropriate manner.

It is also suggested that BINI induces CYP3A [see Section 4.2.5.2], which will be described in Section "6.2.4.2 Drug-drug interaction between BINI and midazolam."

5. Toxicity and Outline of the Review Conducted by PMDA

5.1 ENCO

In *in vivo* studies of ENCO, 0.5 w/v% CMC solution containing 0.5 vol% polysorbate 80 was used as vehicle, unless specified otherwise.

5.1.1 Single-dose toxicity

A single-dose toxicity study was conducted in cynomolgus monkeys (Table 16). No single-dose toxicity study in rats was conducted. Instead, approximate lethal dose in rats was evaluated based on the acute toxicity after the first dose in a micronucleus study in rats.

The approximate lethal dose was determined to be >2,000 mg/kg in rats and >200 mg/kg in cynomolgus monkeys.

Table 16. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male rats (Wistar Han)	p.o.	0,[a] 200, 1,000, 2,000	Acute toxicity was evaluated by a micronucleus test. No toxic changes.	>2,000	4.2.3.3.2-1
Male cynomolgus monkeys	p.o.	0[b] →50 (QD) →100 (QD) →100 (BID)	Acute toxicity was evaluated by the dose-titration study administering a single dose of BINI at 3- to 4-day intervals. ≥100: Vomiting	>200	Reference 4.2.3.1-1

a) Only vehicle was administered; b) Only vehicle (mixture of PEG400, polyoxyethylene castor oil, and oleic acid [56:29:15]) was administered.

5.1.2 Repeated-dose toxicity

Repeated-dose toxicity studies (1- and 3-month) were conducted in rats and cynomolgus monkeys (Table 17). Main toxicological target organs were skin and male reproductive organs in rats and gastrointestinal tract and eyes in cynomolgus monkeys.

In the 3-month repeated-dose toxicity studies in rats and cynomolgus monkeys, the plasma exposure (AUC_{24h}) of ENCO at the no observed adverse effect level (NOAEL) or at the lowest observed adverse effect level (LOAEL)[25] (6 mg/kg/day in rats, 20 mg/kg/day in cynomolgus monkeys) was 45.2 μg•h/mL in male rats, 114 μg•h/mL in female rats, and 3.7 μg•h/mL in cynomolgus monkeys, which was 3.3 times, 8.3 times, and less than the clinical exposure,[26] respectively.

[25] In the 3-month repeated-dose toxicity study in rats, the NOAEL was <6 mg/kg/day. Therefore, plasma exposure at the LOAEL was used for evaluation.

[26] AUC_{tau} (13.8 μg•h/mL) on Day 15 in 28-day oral administration of ENCO (450 mg QD) to patients with malignant melanoma with *BRAF* gene mutation in Study X2101 [see Section 6.2.1.1].

Table 17. Repeated-dose toxicity studies

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Wistar Han)	p.o.	1-month (QD) + 1-month recovery	0,[a)] 20, 100, 400[b)]	Death/moribund sacrifice: 400 (1/16 males, 11/16 females), aggravation of clinical signs (emaciation, coldness of skin, hunched posture, salivation, decreased locomotor activity, ptosis, piloerection, etc.), hyperaemia/erosion/ulcer of anterior/glandular stomach, congestion/hypertrophy/bleeding/vacuolation of adrenal cortex, atrophy of lymph nodes, decreased thymic lymphocyte count, decreased bone marrow cell count, vacuolation/necrosis of renal tubular epithelial cells, vacuolation/necrosis of liver, decreased hematopoiesis/atrophy/vacuolation of spleen, and vacuolation of parathyroid gland ≥20: Reduced body weight gain, tail injury, abnormalities of limb plantar skin[c)] (scale/swelling/reddening/squamous cell hyperplasia/hyperkeratosis/infiltration of inflammatory cells, etc.), degeneration of seminiferous tubules/vacuolation of Sertoli cells/decreased spermatid count, decreased weight/decreased sperm count/cell debris in epididymis ≥100: Increased white blood cell/neutrophil/lymphocyte/eosinophil counts, decreased serum TG, hyperplasia/hyperkeratosis of anterior stomach 400: Decreased food consumption, decreased body weight, dehydration, decreased serum phosphate/creatinine/total protein/globulin, increased serum A/G ratio, decreased prostate weight Reversibility: Yes [d)]	<20	4.2.3.2-1
Male and female rats (Wister Han)	p.o.	3-month (QD) + 1-month recovery	0,[a)] 6, 20, 60	≥6: Reduced body weight gain, abnormalities of limb/tail skin (crust/desiccation/scale/squamous epithelium hyperplasia/hyperkeratosis, etc.), increased eosinophil/reticulocyte counts, increased serum cholesterol, degeneration of seminiferous tubules, decreased sperm count/cell debris in epididymis ≥20: Decreased food consumption, increased white blood cell count, increased serum urea nitrogen/TG/glucose, decreased weight/reduction in size of epididymis, softening/size reduction of testis, squamous cell hyperplasia/hyperkeratosis of anterior stomach 60: Salivation, increased neutrophil count, vaginal fluid secretion, decreased testicular weight Reversibility: Yes	<6	4.2.3.2-2

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female cynomolgus monkeys	p.o.	1-month (QD) + 1-month recovery	0,[e] 5, 20, 100	≥20: Bloody stool,[f] vomiting[f] 100: Decreased body weight, decreased food consumption, soft feces, diarrhoea Reversibility: Yes	20	4.2.3.2-3
Male and female cynomolgus monkeys	p.o.	3-month (QD) + 10-week recovery	0,[g] 20,[h] 60[h]	60: Decreased body weight, salivation, vomiting, blistering lesion in macular region of retina, separation/detachment of rods, conical outer layer, and pigment epithelial cells Reversibility: Yes	20	4.2.3.2-5

a) Only vehicle was administered.
b) In females, death or moribund state occurred frequently from Day 8 of administration. Administration was discontinued on Day 10 and surviving animals were necropsied or withdrawn from the administration.
c) In females of the 400 mg/kg/day group, the event was observed after they had entered the recovery period.
d) For effects on male reproductive organs (degeneration, vacuolation, etc., of seminiferous tubules), the changes were not reversible after a 1-month recovery period in this study. However, reversibility was observed in the 3-month repeated-dose toxicity study administering ENCO for a longer period, and no toxicity to spermatogonia or spermatocytes was observed, from which it was concluded that the effects on male reproductive organs are reversible.
e) Only vehicle (mixture of PEG400, polyoxyethylene castor oil, and oleic acid [56:29:15]) was administered.
f) This event was observed only once in 1 female during the administration period, and no effect on body weight, clinical signs, etc., was observed, from which the event was considered to have little toxicological significance.
g) Only the placebo ([redacted]) was administered
h) [redacted] of ENCO was used as the test substance.

5.1.3 Genotoxicity

The applicant conducted *in vitro* genotoxicity studies consisting of a bacterial reverse mutation assay and a chromosomal aberration assay in mammalian cells; and the *in vivo* genotoxicity study consisting of a micronucleus assay in rodents (Table 18). All tests were negative, from which it was concluded that ENCO is unlikely to have genotoxicity.

Table 18. Genotoxicity studies

Type of study		Test system	Metabolic activation (treatment duration)	Concentration (μg/plate or μg/mL) Dose (mg/kg/day)	Results	Attached document CTD
In vitro	Bacterial reverse mutation assay (Ames)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA97a, TA102	S9−/+	0,[a] 156.3, 312.5, 625, 1,250, 2,500, 5,000	Negative	4.2.3.3.1-1
	Chromosomal aberration assay using cultured mammalian cells	Primary cultured human peripheral blood lymphocytes	S9− (3 hours)	0,[a] 75, 100, 250, 400[b]	Negative	4.2.3.3.1-2
			S9+ (3 hours)	0,[a] 50, 200, 400, 550[b]		
			S9− (20 hours)	0,[a] 5, 40, 50, 60[b]		
In vivo	Micronucleus assay in rodents	Male rat (Wistar Han) bone marrow		0,[c] 200, 1,000, 2,000 (p.o., QD, 2 days)	Negative	4.2.3.3.2-1

a) Only vehicle (DMSO) was added; b) Cell growth was suppressed by ≥50%; c) Only vehicle was administered.

5.1.4 Carcinogenicity

Because ENCO is an antineoplastic drug intended to treat patients with advanced cancer, no carcinogenicity study was conducted.

5.1.5 Reproductive and developmental toxicity

Because ENCO is an antineoplastic drug intended to treat patients with advanced cancer, no studies were conducted on the fertility and early embryonic development to implantation.

The applicant's explanation about possible effect of ENCO on fertility:
In the repeated-dose toxicity study in rats, the effect on male reproductive organs (degeneration of seminiferous tubules in testis, decreased sperm count in epididymis, etc.) was observed from the dose corresponding to 3.3 times the clinical exposure, and the NOAEL for these findings was not determined [see Section 5.1.2], suggesting the possibility that ENCO affects fertility of males. These results will be provided to healthcare professionals using the package insert to alert them to the possible effect of ENCO on male fertility.

In the repeated-dose toxicity studies in rats and cynomolgus monkeys, administration of ENCO up to the dose corresponding to 80 and 1.7 times the clinical exposure, respectively, and the administration did not have any effect on male reproductive organs [see Section 5.1.2]. In *BRAF* gene-deficient mice, no embryonal death occurred during the early pregnancy (*Nat Genet*. 1997;16:293-7). These results suggest that ENCO is unlikely to affect female fertility.

Studies on embryo-fetal development were conducted in rats and rabbits (Table 19). In both rats and rabbits, decreased fetal body weight and skeletal variations (incomplete ossification of parietal bone and frontal bone) were observed.

At the NOAEL for embryo-fetal development (5 mg/kg/day in rats, 25 mg/kg/day in rabbits), plasma exposure (C_{max} and AUC_{24h}) of ENCO was 12.7 μg/mL and 90.2 μg·h/mL, respectively in rats and 83.8 μg/mL and 1,010 μg·h/mL, respectively in rabbits, which were 2.9 and 6.5 times higher in rats, and 19.4 and 73 times higher in rabbits, than the clinical exposure.[27)]

[27)] C_{max} (4.33 μg/mL) and AUC_{tau} (13.8 μg·h/mL) on Day 15 in 28-day oral administration of ENCO (450 mg QD) to patients with malignant melanoma with *BRAF* gene mutation in Study X2101 [see Section 6.2.1.1].

Table 19. Reproductive toxicity studies

Type of study	Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Embryo-fetal development studies	Female rats (Wistar Han)	p.o.	Gestation Day 6-17 (QD)	0,[a] 0.5, 5, 20	Maternal animals: 20: Reduced body weight gain[b] Fetuses: 20: Decreased body weight, skeletal anomalies (incomplete ossification of parietal bone/interparietal bone, unossification/incomplete ossification/bipartite ossification of thoracic vertebral bodies, etc.)	Maternal animals (general toxicity): 20 Embryo-fetal development: 5	4.2.3.5.2-1
	Female rabbits (NZW)	p.o.	Gestation Day 7-20 (QD)	0,[a] 5, 25, 75	Maternal animals: Moribund sacrifice: 75 (4/20 rabbits), complete loss of appetite, mucous stools, watery stools, ptosis, emaciation, watery substances in cecum/colon/rectum, black spots in lung, swelling/darkening of mediastinal lymph nodes, gallbladder wall thickening, white spots in liver, black content in vagina 75: Decreased food consumption, reduced body weight gain, decreased feces, and smaller feces Fetuses: ≥5: Incomplete ossification of hyoid bone [c] ≥25: Dumbbell ossification of thoracic vertebral bodies [c] 75: Decreased body weight, incomplete ossification of frontal bone/pubis/13th ribs, supernumerous presacral vertebrae, visceral abnormalities[d] (dilated aortic arch/ascending aorta, ventricular septal defect, round heart, missing spleen, smaller pulmonary lobe)	Maternal animals (general toxicity): 25 Embryo-fetal development: 25	4.2.3.5.2-3

a) Only vehicle was administered.
b) Transient reduction in body weight gain was observed during the early stage of administration. On Gestation Day 21, the body weight was lower by approximately 2% compared with the control group. Therefore, the finding was considered to be of little toxicological significance.
c) The incidence was within the range of the historical data in the study facility (incomplete ossification of hyoid bone, [redacted]%; dumbbell ossification, [redacted]%). Therefore, the finding was considered to be of little toxicological significance.
d) The incidence of each finding was slightly higher than the historical data of the study facility. However, the percentages of the number of fetuses and maternal animals with anomaly in the 75 mg/kg/day group were within the range of the historical data, and the finding was observed only in 1 each of fetus in 1 or 2 maternal animals, from which these findings were considered not to be caused directly by ENCO.

5.1.6 Local tolerance

A local tolerance study was conducted (Table 20). ENCO caused no skin irritation in rabbits.

Table 20. Local tolerance study

Test system	Application site	Testing method	Main finding	Attached document CTD
Male rabbits (NZW)	Skin	ENCO 0.5 g was applied for 4 hours, and the dermal application site was evaluated for skin irritation at 1, 24, 48, and 72 hours after application	None	4.2.3.6-1

5.1.7 Other toxicity studies

5.1.7.1 Skin sensitization

A skin sensitization study was conducted (Table 21). Although mild skin irritation was observed, it was concluded that ENCO does not sensitize skin.

Table 21. Skin sensitization test

Type of test	Test system	Testing method	Main findings	Attached document CTD
Local lymph node test	Female mice (Balb/c)	ENCO 0.5, 5, 50% solution was applied to the back of ear auricle once daily for 3 days, and auricle weight, auricular lymph node weight, and cell count in auricular lymph node were measured at 24 hours after the final application.	≥5%: Swelling of auricular lymph node 50%: Increased auricular weight Mild skin irritation was observed, but no skin sensitization was observed.	4.2.3.7.7-1

5.1.7.2 Photosafety

An *in vitro* phototoxicity study was conducted (Table 22). It was concluded that ENCO is phototoxic.

Table 22. Photosafety study

Type of test	Test system	Testing method	Main findings	Attached document CTD
Phototoxicity test	Mouse fibroblasts Balb/c 3T3	0.06-185.18 µmol/L (with UV-A irradiation) 0.06-185.18 µmol/L (without UV-A irradiation)	Phototoxic (photo-irritation factor, >82)	Reference 4.2.3.7.7-2

The applicant's explanation about the possibility that the phototoxicity of ENCO poses problems in clinical use:

The incidence of phototoxicity-related adverse events[28)] in Study B2301 which recommended taking photoprotective measures was lower in the group receiving ENCO/BINI or ENCO than in the group receiving VEM which is known to have a risk of causing photosensitivity in clinical use (4.7% in the ENCO/BINI group, 4.7% in the ENCO group, 37.6% in the VEM group), suggesting that the phototoxicity of ENCO is unlikely to pose any problem in clinical use. Nevertheless, results of the phototoxicity studies will be provided to healthcare professionals using the package insert.

28) Events classified as "Photosensitivity and photodermatosis conditions" in MedDRA high level term (HLT) were investigated.

5.2 BINI

In *in vivo* studies of BINI, 1 w/v% CMC solution containing 0.5 vol% polysorbate 80 was used as vehicle, unless specified otherwise.

5.2.1 Single-dose toxicity

Single dose toxicity studies were conducted in mice and rats (Table 23). No single-dose toxicity study in cynomolgus monkeys was conducted. Instead, acute toxicity was evaluated based on the results following the first dose in the repeated-dose toxicity study.

The approximate lethal dose was determined to be >2,000 mg/kg in mice, >300 mg/kg in rats, and >10 mg/kg in cynomolgus monkeys.

Table 23. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male mice (ICR)	p.o.	0,[a)] 500, 1,000, 2,000	Acute toxicity was evaluated by a micronucleus test. No toxic changes.	>2,000	4.2.3.3.2-1
Male and female rats (SD)	p.o.	0,[a)] 30, 100, 300	≥30: Depilation, decreased serum chloride, increased serum phosphate/AST/ALT, mineralization of glandular stomach/ovary ≥100: Reduced body weight gain, decreased food consumption, decreased serum Na, increased neutrophil count	>300	4.2.3.1-1
Male and female cynomolgus monkeys	p.o.	0,[a)] 1, 3, 10	Acute toxicity was evaluated in 1-month repeated-dose toxicity study. No toxic changes.	>10	4.2.3.2-3

a) Only vehicle was administered.

5.2.2 Repeated-dose toxicity

Repeated-dose toxicity studies in rats (1 and 6 months) and in cynomolgus monkeys (1 and 9 months) were conducted (Table 24). Main toxicological target organs were skin and bones in rats and gastrointestinal tract in cynomolgus monkeys. In rats, mineralization was observed in the aorta, heart, kidneys, pituitary gland, etc.

In the 6-month repeated-dose toxicity study in rats and the 9-month repeated-dose toxicity study in cynomolgus monkeys, the plasma exposure (AUC_{24h}) of BINI at the NOAEL or the LOAEL[29)] (1 mg/kg/day in rats, 0.2 mg/kg/day in cynomolgus monkeys) was 6.2 μg•h/mL in male rats, 11 μg•h/mL in female rats, and 0.2 μg•h/mL in cynomolgus monkeys, which was less, 1.5 times larger, and less, than the clinical exposure,[30)] respectively.

29) In the 6-month repeated-dose toxicity study in rats, the NOAEL in male rats was <1 mg/kg/day. Therefore, plasma exposure at the LOAEL was used for evaluation.

30) AUC_{24h} (7.34 μg•h/mL) estimated from AUC_{tau} on Day 15 of administration (3.67 μg•h/mL) in 28-day oral administration of BINI (45 mg BID) to Japanese patients with solid cancer in Study X1101 [see Section 6.2.2.1].

Table 24. Repeated-dose toxicity studies

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (SD)	p.o.	1-month (QD) + 1-month recovery	0,[a] 10,[b] 30,[b] 100[b]	Death: 30 (1/15 males), 100 (1/15, in both males and females) Aortic wall hypertrophy,[c] subacute inflammation of heart,[c] mineralization of cardiac muscles/colon/lung[c] ≥10: Decreased lymphocyte count, increased serum phosphate/AST/ALT/globulin/urea nitrogen, decreased serum A/G ratio, exudate/regenerative hyperplasia of epidermis, mineralization of glandular stomach/pituitary gland/ovary, hypertrophy/hyperplasia of adrenal cortex ≥30: Depilation, crust, abrasion, increased neutrophil/monocyte count, decreased serum albumin/Ca, decreased weight of heart/pituitary gland/spleen, increased adrenal weight, erosion/ulcer/inflammation, etc., of skin, mineralization of heart/tongue/kidney/Harderian gland 100: Decreased serum total protein, increased lung weight, decreased thymus weight, mineralization of aorta/spleen/submandibular gland/duodenum/brain, focal necrosis of femoral bone marrow, growth plate thickening/osteopenia/fibrous bone hyperplasia of femur, hyperplasia of pancreatic acinar cells Reversibility: Yes (except mineralization of stomach/kidney, etc.)	<10	4.2.3.2-1[d]
Male and female rats (SD)	p.o.	6-month[e] (QD) + 1-month recovery	0,[a] 1, 3, 10	≤1: Depilation[f] ≤3: Decreased serum parathyroid hormone, crust, abrasion, erosion/ulcer of skin, exudate/inflammation of epidermis, decreased spleen weight 10: Increased serum phosphate/urea nitrogen, decreased serum cholesterol, regenerative hyperplasia of epidermis Reversibility: Yes	<1 (males) 1 (females)	4.2.3.2-2[d],[g]

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female cynomolgus monkeys	p.o.	1-month (QD) + 1-month recovery	0,[a] 1, 3, 10	Moribund sacrifice: 10 (1/5, both in males and females), decreased food consumption, decreased body weight, decreased activity, hunched posture, abdominal bloating, dehydration, decreased body temperature, mucosal decoloration, bleeding/ulcer/fibrosis of colon/rectal mucosa 10: Stool abnormalities (watery stool, etc.), vomiting, lethargy, effect on erythroid parameters (decreased red blood cell count/hemoglobin concentration, etc.), increased neutrophil/monocyte count, decreased lymphocyte count, decreased serum albumin/A/G ratio, increased serum globulin/C-reactive protein, distention of cecum/colon due to watery content and gas, mucosal epithelium degeneration/inflammatory cell infiltration/regenerative hyperplasia of cecum/colon/rectum, increased erythroid cells in bone marrow Reversibility: Yes	3	4.2.3.2-3[d]
Male and female cynomolgus monkeys	p.o.	9-month[h] (QD) + 3-month recovery	0,[a] 0.2, 2, 5	Moribund sacrifice: 5 (1/10 females), decreased food consumption, decreased body weight, decreased locomotor activity, hunched posture, emaciation, swelling of lymph nodes, thymic atrophy, erosion of cecum, decreased bone marrow cells, eosinophilia in adrenal cortex, degranulation of pancreatic acinar cells, decreased thymic cell count ≥2: Decreased serum albumin, inflammatory cell infiltration/regenerative hyperplasia of cecum/colon mucosa 5: Watery stool, effects on erythroid parameters (decreased red blood cell count/hemoglobin concentration, etc.), increased platelet/neutrophil/monocyte counts, decreased serum A/G ratio, increased serum urea nitrogen/phosphate/globulin, watery content in colon, degeneration of mucosal epithelium in cecum/colon/rectum, increased erythroid cells in bone marrow Reversibility: Yes	0.2	4.2.3.2-4[d]

a) Only vehicle was administered.
b) Due to a clerical error in the study protocol, BINI was administered at 30, 100, or 300 mg/kg/day, respectively, to the 10, 30, or 100 mg/kg/day groups on Day 1 to 3 of administration.
c) The event was observed in the 100 mg/kg/day group only.
d) Since GLP conformance could not be confirmed for toxicokinetics measurements, plasma exposure was handled as reference data.
e) Data include necropsy and histopathology after 3 months of administration and at1-month recovery after 3 months of administration.
f) In the 1 mg/kg/day group, the event was observed only in males.
g) Since GLP conformance could not be confirmed for measurements of serum parathyroid hormone and 1,25-dihydroxy vitamin D concentrations, they were handled as reference data.
h) In the 0, 0.2, and 5 mg/kg/day groups, data include those of necropsy and histopathology at Month 3 and 4 of administration.

5.2.3 Genotoxicity

The applicant conducted *in vitro* genotoxicity studies consisting of a bacterial reverse mutation assay and a forward mutation test using cultured mammalian cells, and the *in vivo* genotoxicity study consisting of a micronucleus assay in rodents (Table 25). All tests were negative, from which it was concluded that BINI is unlikely to have genotoxicity.

Table 25. Genotoxicity studies

Type of test		Test system	Metabolic activation (treatment duration)	Concentration (μg/plate or μg/mL) Dose (mg/kg/day)	Results	Attached document CTD
In vitro	Bacterial reverse mutation assay (Ames)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 *Escherichia coli* WP2*uvr*A	S9−/+	0,[a] 15, 50, 150, 500, 1,500,[b] 5,000[b]	Negative	4.2.3.3.1-1
	Forward mutation test using cultured mammalian cells	L5178Y mouse lymphoma cells	S9−/+ (4 hours)	0,[a] 75, 100, 150, 200, 300[b]	Negative	4.2.3.3.1-2
			S9− (24 hours)	0,[a] 50, 100, 125, 150, 250[b]		
In vivo	Micronucleus assay in rodents	Male mouse (ICR) bone marrow		0, 500, 1,000, 2,000 (p.o., QD, single dose)	Negative	4.2.3.3.2-1

a) Only vehicle (DMSO) was added; b) Precipitation of the study substance was observed.

5.2.4 Carcinogenicity

Because BINI is an antineoplastic drug intended to treat patients with advanced cancer, no carcinogenicity study was conducted.

5.2.5 Reproductive and developmental toxicity

Because BINI is an antineoplastic drug intended to treat patients with advanced cancer, no studies were conducted on the fertility and early embryonic development to implantation.

The applicant's explanation about possible effect of BINI on fertility:

MEK plays an important role in folliculogenesis and ovulation (*Zoolog Sci.* 2003;20:193-201, etc.), and MAPK signal transduction pathway is involved in the sperm fertility and motility as well as in the maintenance of the function of Sertoli cells critical for spermatogenesis (*Stem Cells.* 2013;31:2517-27, etc.). However, BINI is unlikely to affect the male and female fertility clinically, given the following findings:

- In the 6-month repeated-dose toxicity study in rats [see Section 5.2.2], BINI had no effect on either male or female reproductive organs up to the maximum dose which corresponds to 8.2 times the clinical exposure.
- In the 9-month repeated-dose toxicity study in cynomolgus monkeys [see Section 5.2.2], BINI had no effect on either male or female reproductive organs up to the maximum dose which corresponds to 0.37 times the clinical exposure. Although the effect at doses exceeding the clinical exposure was not investigated, the inhibition of BINI on MEK was observed at the maximum dose,[31] allowing evaluation of the effect due to the pharmacological action.

[31] At the dose of 5 mg/kg/day, ERK phosphorylation was inhibited by 60% in peripheral mononuclear cells.

Studies on embryo-fetal development were conducted in rats and rabbits (Table 26). Decreased fetal body weight was observed in both rats and rabbits, unossified sternebrae were observed in rats, and decreased number of live fetuses, ventricular septal defect, etc., were observed in rabbits.

At the NOAEL for embryo-fetal development (10 mg/kg/day in rats, 2 mg/kg/day in rabbits), plasma exposure[32)] (C_{max} and AUC_{24h}) of BINI was 6.05 μg/mL and 56.5 μg·h/mL, respectively in rats and 1.00 μg/mL and 5.26 μg·h/mL, respectively in rabbits, which was 7.5 and 7.7 times higher in rats, and 1.2 times higher and less in rabbits, than the clinical exposure.[33)]

[32)] Plasma exposure (AUC_{24h} and C_{max}) estimated from the plasma exposure (AUC_{24h} and C_{max}) on Day 27 of administration in the 1-month repeated-dose toxicity study in rats and from the plasma exposure in the 3 and 10 mg/kg/day groups on Day 1 or 13 of administration in the dose-finding study in rabbits.

[33)] AUC_{24h} (7.34 μg▪h/mL) estimated from C_{max} (0.805 μg/mL) and AUC_{tau} (3.67 μg▪h/mL) on Day 15 of administration in 28-day oral administration of BINI (45 mg BID) to Japanese patients with solid cancer in Study X1101 [see Section 6.2.2.1].

Table 26. Reproductive toxicity studies

Type of study	Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Embryo-fetal development studies	Female rats (SD)	p.o.	Gestation Day 6-17 (QD)	0,[a] 10, 30, 100	Maternal animals: ≥10: Decreased food consumption[b] ≥30: Reduced body weight gain 100: Decreased uterine weight Fetuses ≥30: Decreased body weight, unossified sternebrae	Maternal animals (general toxicity): 10 Embryo-fetal development: 10	4.2.3.5.2-1
	Female rabbits (NZW)	p.o.	Gestation Day 6-18 (QD)	0,[a] 3, 10, 30, 100	Maternal animals: Death: 30 (2/5 rabbits), 100 (5/5 rabbits) Decreased body weight, decreased locomotor activity, fluid accumulation in thoracic cavity, reddening/black spots in glandular stomach ≥3: Decreased feces ≥10: Reduced body weight gain, decreased food consumption, abortion ≥30: Emaciation Fetuses: No effect[d]	—[c]	4.2.3.5.2-2
	Female rabbits (NZW)	p.o.	Gestation Day 6-18 (QD)	0,[a] 2, 10, 20	Maternal animals: Death or moribund sacrifice: 20 (6/23 rabbits), respiration abnormal, fluid accumulation in thoracic cavity, reddening of lung, browning/reddening/surface roughness of stomach/large intestine/trachea, uterine prolapse ≥2: Decreased food consumption, decreased uterine weight ≥10: Decreased body weight, fecal abnormalities (decreased feces, loose stools, etc.), decreased locomotor activity, abortion 20: Coldness of skin, coarse fur, periocular secretion Fetuses: ≥10: Decreased body weight, decreased live fetuses, increased post-implantation losses 20: Ventricular septal defect, vascular abnormalities of aortic arch/pulmonary artery, etc.	Maternal animals (general toxicity): 2[e] Embryo-fetal development: 2	4.2.3.5.2-3

a) Only vehicle was administered.
b) This was a transient change observed only during the early stage of administration and no effect was observed on body weight gain during the gestation period, from which it was concluded that the finding is of little toxicological significance.
c) This study was a dose-finding study, and the NOAEL was not calculated.
d) The effect on fetuses was not investigated in the ≥30 mg/kg/day groups due to death of maternal animals, abortion, or total resorption of litters. Only external examination of fetuses was performed in the ≤10 mg/kg/day group.
e) Decreased food consumption was transient, and no decrease in the number of live fetuses or in fetal body weight was observed, from which the findings observed in the 2 mg/kg/day group were considered to be of little toxicological significance.

5.2.6 Local tolerance

Local tolerance studies in rats and rabbits were conducted (Table 27). BINI caused stomach irritation in rats, and did not cause skin irritation in rabbits.

Table 27. Local tolerance studies

Test system	Application site	Testing method	Main findings	Attached document CTD
Male rats (SD)	Stomach	BINI 0,[a] 2, 6, or 20 mg/mL (corresponding to BINI 0, 10, 30, or 100 mg/kg, respectively) was administered orally in a single dose, and the number and size of gastric mucosal lesions were measured separately for each type of lesion at 4 hours after administration.	20: Increased number of superficial mucosal lesion/hemorrhagic mucosal ulcer	4.2.3.6-1
Male rabbits (NZW)	Skin	BINI 0.5 g was applied for 4 hours, and the application site was evaluated at 1, 24, 48, and 72 hours after application.	None	4.2.3.6-2

a) Only vehicle was administered.

5.2.7 Other studies

5.2.7.1 Photosafety

An *in vitro* phototoxicity study and an *in vivo* photosensitization study were conducted (Table 28). It was concluded that BINI is both phototoxic and photo-sensitizing.

Table 28. Photosafety studies

Study	Test system	Testing method	Main findings	Attached document CTD
Phototoxicity testing	Mouse fibroblasts Balb/c 3T3	BINI 0.3906-50 μg/mL (UV-A irradiated) BINI 3.125-400 μg/mL (UV-A non-irradiated)	Phototoxic (photo-irritation factor: 18.8)	4.2.3.7.7-1
Photosensitization testing	Female mice (Balb/c)	BINI (0,[a] 10, 30, or 100 mg/kg/day) was administered orally QD for 3 days and, at 24 hours after the final dose, auricular weight, auricular lymph node weight, and cell count in auricular lymph node were compared between groups receiving UV-A irradiation and those not receiving the irradiation.	Photosensitizing (UV-A irradiation group: ≥30: erythema in auricle/tail, increased weight/cell count of auricular lymph node)	4.2.3.7.7-2

a) Only vehicle was administered.

The applicant's explanation about the possibility that the phototoxicity and photo-sensitization induced by BINI poses problems in clinical use:

The incidence of phototoxicity- or photosensitization-related adverse events[28)] in Study B2301 which recommended taking photoprotective measures was lower in the group receiving ENCO/BINI than in the group receiving VEM which is known to have a risk of causing photosensitivity in clinical use (4.7% in the ENCO/BINI group, 37.6% in the VEM group), suggesting that the phototoxicity and photosensitization induced by BINI are unlikely to pose any problem in clinical use. Nevertheless, results of the phototoxicity and photosensitization studies will be provided to healthcare professionals using the package insert.

5.3 ENCO/BINI

Because ENCO and BINI are antineoplastic drugs intended to treat patients with advanced cancer, no toxicity studies on ENCO/BINI therapy were conducted according to the "Nonclinical Evaluation for

Anticancer Pharmaceuticals (PFSB/ELD Notification No. 0604-(1) dated June 4, 2010)" (ICH S9 Guideline).

The applicant explained the possibility that combination of ENCO and BINI aggravates the effect on (a) skin and (b) gastrointestinal tract, the toxicological target organs of both drugs, as follows:

(a) ENCO caused skin disorder associated with hyperplasia of squamous epithelium [see Section 5.1.2]. In contrast, BINI did not directly enhance the growth of squamous cells although it caused skin erosion and ulcer [see Section 5.2.2]. Given the report that concomitant use with a MEK inhibitor reduces hyperplastic changes caused by a RAF inhibitor (*N Engl J Med*. 2014;371:1877-88, etc.), ENCO/BINI is unlikely to aggravate hyperplastic changes of skin in clinical use.

(b) ENCO caused loose stools, diarrhoea, vomiting, etc. [see Section 5.12] and BINI caused injurious changes in colonic mucosa [see Section 5.2.2]. Similar findings were observed with other BRAF and MEK inhibitors (see "Review Report on Tafinlar Capsules 50 mg and Tafinlar Capsules 75 mg, dated January 21 2016" and "Review Report on Mekinist Tablets 0.5 mg and Mekinist Tablets 2.0 mg, dated January 21, 2016"). Also, abnormalities in MAPK signal transduction pathway are involved in the occurrence of colitis (*Tissue Barriers*. 2015;3:1-2). These observations suggest the possibility that the effect on the gastrointestinal tract observed during the ENCO or BINI monotherapy may have been caused by the suppression of MAPK signal transduction pathway and that ENCO/BINI therapy may aggravate the effect on the gastrointestinal tract. However, in clinical studies,[34)] there was no clear difference in the incidence of adverse drug reactions associated with gastrointestinal disorder between the ENCO/BINI group and each monotherapy group (55.8% in the ENCO/BINI group, 54.8% in the ENCO alone group, 54.1% in the BINI alone group), suggesting that ENCO/BINI therapy is unlikely to aggravate gastrointestinal disorder in clinical use.

In addition, the applicant's explanation about the effect of ENCO and BINI on the retina:
ENCO caused changes suggestive of exudative retinal detachment at the macular region [see Section 5.1.2]. This finding is similar to central serous retinopathy observed in the clinical study of TRA, a MEK inhibitor (*J Clin Oncol*. 2012;30:3277-86). Although BINI did not show retinal toxicity in toxicity studies [see Section 5.2.2], retinal detachment was observed in clinical studies [see Section 7.R.3.2]. These results suggest the possibility that ENCO/BINI therapy may enhance retinal toxicity. Therefore, information on retinal detachment observed with ENCO will be provided to healthcare professionals using the package insert.

5.R Outline of the review conducted by PMDA

On the basis of the data submitted and on the results of the reviews in the following sections, PMDA concluded that the applicant's discussions on the toxicity of ENCO and BINI are acceptable.

5.R.1 Organ mineralization caused by BINI

PMDA asked the applicant to explain the possibility that organ mineralization observed in the repeated-dose toxicity studies of BINI may pose safety problems in clinical use.

34) Pooled analysis of data obtained from the ENCO/BINI groups in Studies B2301, X2109, and X2110; the ENCO single agent groups in Studies B2301, X2102, and X2101; and the BINI single agent groups in Studies A2301 and X2201.

The applicant's explanation:

In the 1-month repeated-dose toxicity study in rats, mineralization of glandular stomach, pituitary gland, etc., was observed in the ≥10 mg/kg/day groups [see Section 5.2.2]. This observation is considered to be due to the pharmacological effect of BINI, given the following findings: (1) mineralization accompanied by increased serum phosphate level was observed in mice lacking FGF-23, the ligand of fibroblast growth factor (FGF) receptor in the upstream of MAPK signal transduction pathway (*Matrix Biol*. 2004;23:421-32), and (2) mineralization accompanied by increased serum phosphate level was observed in rats administered with other MEK inhibitors (*Toxicol Sci.* 2012;125:187-95, etc.). However, the mineralization observed in the repeated-dose toxicity study of BINI is unlikely to pose safety problems in clinical use, for the reasons shown below. Information on the mineralization observed in rats will be provided to healthcare professionals using the package insert.

- No mineralization was observed in the repeated-dose toxicity studies of BINI in cynomolgus monkeys [see Section 5.2.2].
- Mineralization induced by MEK inhibitors may be specific to rats (*Toxicol Sci*. 2010;125:187-95).
- ENCO/BINI therapy did not cause hyperphosphatemia in Studies B2301, X2109, and X2110.
- In the pooled analysis of Studies A2301 and X2201, the incidence of hyperphosphatemia in the BINI monotherapy group was as low as 0.9%, and the observed hyperphosphatemia was Grade ≤2. Also, the maximum product of serum phosphate concentration and serum calcium concentration was 54.7 mg^2/dL^2 in patients showing hyperphosphatemia, which was below 70 mg^2/dL^2, the approximate lower limit requiring the control of mineralization risk (*Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing.* 2010;15:1-22).

PMDA accepted the explanation of the applicant.

5.R.2 Bone toxicity of BINI

PMDA asked the applicant to explain the possibility that bone toxicity observed in the repeated-dose toxicity studies of BINI may pose safety problems in clinical use.

The applicant's explanation:

In the 1-month repeated-dose toxicity study in rats, bone toxicity (growth plate thickening, osteopenia, and fibrous bone hyperplasia of the femur) was observed in the maximum dose (100 mg/kg/day) group [see Section 5.2.2]. The observed bone toxicity is likely to be due to the suppression of bone formation within the cartilage in the epiphyseal growth plate caused by the pharmacological effect of BINI, considering the following findings: (1) Thickening of growth plate in the femur was observed in mice lacking FGFR-3 in the upstream of MAPK signal transduction pathway (*Toxicol Pathol*. 2005;33:449-55), and (2) similar findings were observed in rodents administered with other MEK inhibitors (*Bone*. 2014;59:151-61, etc.). However, the bone toxicity observed in the repeated-dose toxicity study of BINI is unlikely to pose safety problems in clinical use, for the following reasons:

- No bone toxicity was observed in the repeated-dose toxicity study of BINI in cynomolgus monkeys [see Section 5.2.2].
- The percentage of the period of bone growth relative to the mean life-span is higher in rats than in humans (*Contemp Top Lab Anim Sci*. 2002;41:21-6), and rats were in their bone growth period when they received BINI. In humans, in contrast, epiphyseal closure is complete when they are around 18

years old. Since BINI is considered to exhibit its bone toxicity by affecting the epiphyseal growth plate, it is unlikely to affect the bone in adults, the target population for treatment with BINI.
- No bone toxicity-related adverse drug reactions were observed in clinical studies administering BINI alone or in combination with ENCO.

PMDA accepted the explanation of the applicant.

5.R.3 Administration of ENCO and BINI to pregnant women or women who may be pregnant

PMDA asked the applicant to explain the administration of ENCO and BINI to pregnant women or women who may be pregnant.

The applicant's explanation:
Given the following, both ENCO and BINI possibly affect human embryos and fetuses. Therefore, it is desirable to avoid administering these drugs to pregnant women or women who may be pregnant. However, in light of the fact that unresectable malignant melanoma, the target disease for treatment with ENCO and BINI, is a fatal disease, it is considered acceptable to administer these drugs to pregnant women, etc., upon evaluating the benefits and risks of the treatment in each patient, on the assumption that the healthcare professional thoroughly explains to the patient and her family members the possible adverse effects of ENCO and BINI on the fetus. Information on the effect of ENCO and BINI on embryos and fetuses will be provided to healthcare professionals using the package insert.
- ENCO was shown to cause low body weight and delayed ossification in rats from doses not causing toxicity in maternal animals [see Section 5.1.5].
- BINI was shown to be teratogenic in rabbits, and the plasma exposure to BINI at the NOAEL for embryo-fetal development (2 mg/kg/day) was less than the clinical exposure [see Section 5.2.5].

PMDA accepted the applicant's explanation.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Oral formulations of ENCO are available as [redacted] and capsules, and PK, etc., of ENCO was investigated using both formulations (Table 29). The proposed commercial formulation is the same as the 50-mg capsules used in clinical studies. In addition, 50-mg capsules and 100-mg capsules are [redacted]. No clear difference was observed in the dissolution behavior between these formulations when they were subjected to the specified dissolution test.

Table 29. ENCO formulations used in clinical studies

Formulation	Studies
[redacted]	Global phase I study (Study X2101), foreign phase I study (Study A2101)
Capsules (10, 25, 50, and 100 mg)	Global phase I study (Study X2101), global phase III study (Study B2301[*1]), foreign phase I studies (Studies 818-101,[*2] 818-105,[*2] 818-102,[*3] and 162-105[*3]), foreign phase Ib/II study (Study X2110), foreign phase II studies (Studies X2109[*4] and X2102[*1])

[*1], 50- and 100-mg capsules were used; [*2], 50-mg capsules were used; [*3], 100-mg capsules were used; [*4], 25-, 50-, and 100-mg capsules were used.

Oral formulations of BINI are available as [redacted], [redacted], and tablets, and PK, etc., of BINI was investigated using these formulations (Table 30).

Table 30. BINI formulations used in clinical studies

Formulation		Studies
[redacted]		Foreign phase I studies (Studies 162-0601 and 162-0602)
[redacted] (5, 10 mg)		Foreign phase I studies (Studies 162-104[*3] and 162-0602[*4])
Tablets	Formulation in the early development (5, 10, 20 mg)	Foreign phase I studies (Studies 162-111 and 162-104[*5])
	Early prototype formulation (10, 20 mg)	Foreign phase I study (Study 162-111)
	Formulation in the late development[*1] (15 mg)	Japanese phase I study (Study X1101), foreign phase I study (Study A2101J), foreign phase Ib/II study (Study X2110), foreign phase II study (Study X2201)
	Formulation in the late development[*2] (15 mg)	Foreign phase I studies (Studies A2101J and 162-111), foreign phase Ib/II study (Study X2110), foreign phase II study (Study X2201)
	Proposed commercial formulation (15 mg)	Japanese phase I study (Study X1101), global phase III studies (Studies A2301 and B2301), foreign phase I studies (Studies A2103, A2104, A2105, 162-105, and 162-106), foreign phase Ib/II study (Study X2110), foreign phase II study (Study X2109)

*1, Formulation prepared by changing the amount of [redacted] and [redacted] in the early stage prototype formulation; *2, The same formulation as the formulation in the late development, except for [redacted]; *3, 5-mg [redacted] was used; *4, 10-mg [redacted] was used; *5, 5 mg tablets were used.

6.1.1 Analytical methods

Table 31 shows the testing methods for *BRAF* gene mutation used by the central laboratory facility in each clinical study. Partial change application for "THxID BRAF kit" of bioMérieux Japan Ltd. was submitted on June 5, 2018 as an *in vitro* diagnostic to support evaluation of eligibility of patients for ENCO/BINI treatment.

Table 31. Testing methods used in clinical studies

Testing method	Studies
Next-generation sequencing	Japanese phase I study (Study X1101), global phase I study (Study X2101), foreign phase Ib/II study (Study X2110), foreign phase II studies (Studies X2102 and X2109)
PCR by "THxID BRAF kit"	Global phase III study (Study B2301)
PCR by methods of OncoCarta, Inostics, and Auragen	Foreign phase I study (Study 162-111)
PCR by method of MolecularMD	Foreign phase II study (Study X2201)

6.1.2 Assay

The amount of (a) ENCO and (b) BINI in human plasma was determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS). The lower limit of quantitation was (a) 1 ng/mL and (b) 1[35] and 5[36]ng/mL, respectively.

6.1.3 Foreign clinical studies

6.1.3.1 Foreign phase I study (CTD 5.3.1.1-1, Study ARRAY-818-102 [Study 818-102] [[redacted] to [redacted] 20[redacted]])

A 2-treatment, 2-period crossover study was conducted in 40 healthy adults (31 subjects included in PK analysis) to investigate the effect of food on PK of ENCO. ENCO 100 mg was administered orally in a

35) Samples collected in Studies X2109, B2301, A2102, A2101J, A2103, A2105, 162-105, A2104, 162-106, and A2301 were measured.
36) Samples collected in Studies 162-0601, 162-0602, 162-104, 162-111, X1101, X2201, and X2110 were measured.

single dose under fasted conditions[37)] or at 30 minutes after a high-fat diet (fat accounted for approximately 50% of the total calorie [approximately 800-1,000 kcal]), and plasma ENCO concentration was investigated. A washout period of ≥7 days was allowed between treatment periods.

Median t_{max} of ENCO following administration under fasted conditions and after a high-fat diet was 1.5 and 3.5 hours, respectively. The geometric mean ratio [90% confidence interval (CI)] of the C_{max} and AUC_{inf} of ENCO following administration after a high-fat diet relative to that following administration under fasted conditions was 0.640 [0.577, 0.709] and 0.959 [0.916, 1.00], respectively.

The applicant's explanation about the effect of food on PK of ENCO, based on the above results:
Consumption of a high-fat diet may cause a decrease in gastric emptying speed, resulting in delayed t_{max} and decreased C_{max}. However, given the coefficient of variation of C_{max} (31.8% and 36.4%, respectively, following administration under fasted conditions and after a high-fat diet, respectively), the decrease in C_{max} following administration under fed conditions is unlikely to pose any problem in clinical use. It is therefore unnecessary to include dietary conditions in the dosage regimen of ENCO.

6.1.3.2 Foreign phase I study (CTD 5.3.3.4-3, Study CMEK162A2103 [Study A2103] [[redacted] to [redacted] 20[redacted]])

A 6-treatment, 3-period crossover study was conducted in 12 healthy adults (12 subjects included in PK analysis) to investigate the effect of food on PK of BINI. BINI 45 mg was administered orally in a single dose under fasted conditions[37)] or at 30 minutes after a high-fat diet (fat accounted for 52% of total calorie [1,000 kcal]) or a low-fat diet (fat accounted for 23% of total calorie [334 kcal]), and plasma BINI concentration was investigated. A washout period of 8 days was allowed between treatment periods.

Median t_{max} of BINI following administration under fasted condition, after a high-fat diet, and after a low-fat diet was 0.875, 2.03, and 1.25 hours, respectively. The applicant explained that the delay in t_{max} following administration under fed condition compared with the administration under fasted condition was due to the decreased gastric emptying speed. The geometric mean ratio [90% CI] of the C_{max} and AUC_{inf} of BINI following (a) administration after a high-fat diet and (b) administration after a low-fat diet relative to those following administration under fasted conditions was (a) 0.828 [0.713, 0.962] and 0.993 [0.929, 1.06] and (b) 1.29 [1.11, 1.50] and 1.00 [0.935, 1.07], respectively. The applicant explained that it is unnecessary to include dietary conditions in the dosage regimen of BINI, based on the above results.

6.1.3.3 Foreign phase I study (CTD 5.3.3.4-2, Study ARRAY-162-105 [Study 162-105] [[redacted] 20[redacted] to [redacted] 20[redacted]])

A 2-treatment, 3-period, open-label study was conducted in 30 healthy adults (30 subjects included in PK analysis) to investigate the effect of a proton pump inhibitor rabeprazole on PK of ENCO or BINI. ENCO and BINI were administered according to the regimen shown below. A washout period of 7 days and 29 days were allowed between Period 1 and Period 2 and between Period 2 and Period 3, respectively.

Period 1: ENCO 300 mg or BINI 45 mg was administered orally in a single dose.

37) ENCO was administered after fasting for ≥10 hours, and subjects were fasted for ≥4 hours after administration.

Period 2: Rabeprazole 20 mg was administered orally QD for 5 days, and ENCO 100 mg or BINI 45 mg was administered orally in a single dose on Day 5 of rabeprazole administration.
Period 3: ENCO 100 mg was administered orally in a single dose.

The geometric mean ratio [90% CI] of C_{max} and AUC_{inf} of (a) ENCO or (b) BINI following concomitant use with rabeprazole to that following the administration of (a) ENCO 100 mg or (b) BINI 45 mg alone was (a) 0.942 [0.593, 1.50] and 0.966 [0.766, 1.22], and (b) 0.826 [0.692, 0.984] and 1.04 [0.930, 1.17], respectively. The applicant explained that increased gastric pH associated with the administration of a proton pump inhibitor is unlikely to have any clear effect on PK of ENCO or PK, based on the above results.

6.2 Clinical pharmacology

PK of ENCO in healthy adults and in patients with cancer was investigated following the administration of ENCO alone, and following the concomitant use with BINI, posaconazole, or diltiazem. PK of BINI in healthy adults and in patients with cancer was investigated following the administration of BINI alone, and following the concomitant use with ENCO. Also, the effect of BINI on PK of midazolam was investigated.

6.2.1 ENCO

6.2.1.1 Global phase I study (CTD 5.3.3.2-4, Study X2101 [ongoing since September 2011 (data cut-off August 18, 2014)])

In the dose-titration part of the global phase I study, an open-label, uncontrolled study was conducted in 54 patients with unresectable malignant melanoma with BRAF V600 mutation (54 patients included in PK analysis) to investigate PK, etc., of ENCO. In each of the 28-day treatment cycles, patients received ENCO ([redacted]) 50 or 100 mg orally QD, ENCO (capsules) 50, 100, 150, 200, 300, 450, 550, or 700 mg orally QD, or ENCO (capsules) 75, 100, or 150 mg orally BID, and plasma ENCO concentration was measured.

Table 32 shows PK parameter values of ENCO in Cycle 1. The applicant explained that analysis of PK data obtained using a power model showed that C_{max} and AUC_{inf} increased roughly in proportion to dose over the dose range tested. C_{max} and AUC of ENCO on Day 15 were lower than the values on Day 1, showing the accumulation ratio[38)] of 0.438 in the 450 mg group. In the 450 mg group, plasma trough concentration (arithmetic mean ± SD) of ENCO on Days 1 and 15 of Cycle 1 and on Day 1 of Cycle 2 was 99.9 ± 192, 5.02 ± 2.85, and 5.02 ± 2.21 ng/mL, respectively, based on which, the applicant explained that the plasma ENCO concentration reaches a steady state within 15 days after the start of administration.

38) Ratio of AUC_{tau} on Day 15 to that on Day 1

Table 32. PK parameters of ENCO in Cycle 1

Formulation	Dosage regimen	Day of measurement	n	C_{max} (ng/mL)	t_{max} [*1] (h)	AUC_{tau} (ng•h/mL)	AUC_{inf} (ng•h/mL)	$t_{1/2}$ [*1] (h)	CL (L/h)
[redacted]	50 mg QD	1	3	1,020 ± 785	0.5 (0.167, 0.5)	2,680 ± 1,850	2,710 ± 1,870	3.77 (3.57, 4.44)	23.9 ± 11.9
		15	3	370 ± 212	0.5 (0.5, 2)	1,130 ± 229	1,140 ± 236	3.71 (3.66, 5.63)	45.3 ± 8.4
	100 mg QD	1	5	1,130 ± 597	2 (0.5, 2)	5,310 ± 2,090	5,360 ± 2,130	3.7 (3.32, 3.96)	20.9 ± 7.21
		15	3	972 ± 246	0.5 (0.5, 0.533)	3,010 ± 1,050	3,030 ± 1,070	3.61 (3.26, 4.1)	36.2 ± 13.3
Capsules	50 mg QD	1	1	970	2	5,360	5,470	4.38	9.14
		15	1	465	2	2,660	2,700	4.14	18.8
	100 mg QD	1	5	1,730 ± 648	2 (0.5, 2)	9,220 ± 6,250	9,310 ± 6,330	3.47 (3.38, 3.88)	16.3 ± 13
		15	4	981 ± 243	2.99 (2, 4)	5,590 ± 2,030	5,650 ± 2,070	3.99 (3.22, 4.05)	19.4 ± 6.68
	150 mg QD	1	5	1,620 ± 456	2 (0.517, 3.95)	9,560 ± 1,960	9,670 ± 1,990	3.66 (3.09, 4.5)	16 ± 3.07
		15	5	1,340 ± 382	2 (0.5, 2.03)	4,780 ± 587	4,860 ± 540	3.65 (3.43, 7.47)	31.7 ± 3.83
	200 mg QD	1	4	1,910 ± 570	2 (2, 2)	10,100 ± 2640	10,200 ± 2630	3.3 (2.56, 3.58)	20.7 ± 5.21
		15	3	1,340 ± 396	2 (2, 2.17)	5,250 ± 1,630	5,270 ± 1,640	3.13 (2.95, 3.22)	41.2 ± 15.3
	300 mg QD	1	5	3,520 ± 1,260	2 (2, 8)	20,900 ± 5,460	20,800 ± 6,300 [*2]	3.42 [*2] (2.84, 4.77)	15.6 ± 5.32 [*2]
		15	4	3,040 ± 926	2 (2, 2.02)	11,000 ± 4230	11,100 ± 4,290	3.57 (1.61, 4.06)	32.9 ± 19.5
	450 mg QD	1	6	6,650 ± 3,220	2 (2, 2.33)	38,500 ± 24,100	39,100 ± 25,100	2.92 (2.32, 4.98)	15.9 ± 9.28
		15	6	4,330 ± 2,070	2 (0.5, 2)	13,800 ± 5,050	13,900 ± 5,050	3.19 (2.82, 3.56)	35.8 ± 11
	550 mg QD	1	5	5,650 ± 2,070	2 (2, 2.07)	34,000 ± 13,100	34,300 ± 13,200	3.32 (3.28, 3.61)	18.6 ± 8.27
		15	3	4,490 ± 2,200	2 (2, 2)	15,900 ± 5,510	16,300 ± 5,500	3.25 (2.96, 8)	37.5 ± 13.1
	700 mg QD	1	2	8,170, 9,880	2, 2.08	63,300, 64,600	63,600, 65,200	2.96, 3.53	10.7, 11
	75 mg BID	1	3	779 ± 317	2.02 (2, 4.08)	3,930 ± 2,990	1,550, 3,170	2.82 (2.02, 3.84)	23.7, 48.3
	100 mg BID	1	5	1,270 ± 478	2 (2, 2.08)	5,210 ± 2,150	4,960 ± 2,650 [*3]	2.53 [*3] (1.69, 2.68)	26 ± 17 [*3]
	150 mg BID	1	4	2,750 ± 1,160	1.25 (0.5, 2.25)	9,330 ± 3,470	9,600 ± 3,560	2.16 (2.16, 2.42)	18.4 ± 10.2

Arithmetic mean ± SD (individual values for n = 1 and 2); *[1], Median (range); *[2], n = 4; *[3], n = 3

6.2.1.2 Foreign phase I study (CTD 5.3.3.1-4, Study CLGX818A2101 [A2101] [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in 4 healthy adults (4 subjects included in PK analysis) to investigate the mass balance of ENCO. ^{14}C-ENCO 100 mg was administered orally in a single dose, and radioactivity concentrations in blood, plasma, urine, and feces were investigated.

The blood/plasma concentration ratio of radioactivity (arithmetic mean) from 1 to 24 hours after administration was 0.59, based on which the applicant explained that distribution of ENCO and its metabolites in blood cells is low. Mainly the unchanged ENCO was detected in the plasma up to 24 hours after administration (accounting for 27.5% of total radioactivity in plasma). Main metabolites detected were M12.8 (glucuronide conjugate of metabolites formed by *N*-dealkylation and hydrolysis), M42.5A (*N*-dealkylated form), M17.3 (glucuronide conjugate of M32.7 [*N*-dealkylated form]), and M44 (metabolite formed by hydrolysis, oxidative deamidation, and reduction) (accounting for 23.0%, 15.5%, 6.22%, and 5.09%, respectively, of total radioactivity in plasma).

Urinary and fecal excretion rates of radioactivity (percentage of administered radioactivity) up to 144 hours after administration were both 47.2%. Renal clearance (0.5 L/h[39)]) accounted for 1.8% of CL/F (27.9 L/h). Main metabolites detected in urine up to 48 hours after administration were M12.8 and M23.8 (*N*-dealkylated form) (accounting for 13.8% and 12.8%, respectively, of the administered radioactivity). The unchanged ENCO also was detected (accounting for 1.8% of the administered radioactivity). Main metabolites detected in feces up to 96 hours after administration were M19.6 (glucose conjugate of M32.7), M25.5 (metabolite formed by *N*-dealkylation, hydrolysis, oxidative deamination, and reduction), M32.7, M44, and M46.3 (hydroxylated form) (accounting for 5.4%, 4.3%, 10.3%, 3.0%, and 5.5%, respectively, of administered radioactivity). The unchanged ENCO also was detected (accounting for 5% of administered radioactivity). The applicant explained that the absorption rate of ENCO in humans is determined to be ≥86%, considering the radioactivity excreted in urine and the radioactivity of metabolites in feces.

6.2.2 BINI

6.2.2.1 Japanese phase I study (CTD 5.3.3.2-2, Study X1101 [ongoing since November 2011 (data cut-off February 10, 2014)])

An open-label, uncontrolled study was conducted in 21 patients with advanced solid cancer (21 patients included in PK analysis) to investigate PK, etc., of BINI. In each of the 28-day treatment cycles, BINI 30 or 45 mg was administered orally QD on Day 1, followed by oral administration of BINI 30 or 45 mg, BID from Day 2 onward, and BINI concentration in plasma was measured. Of patients assigned to the 45 mg group, 6 patients received BINI 15 mg QD on Day 1 and 45 mg BID from Day 2 in Cycle 1. Data of these patients were analyzed as those in the 15 mg group.

Table 33 shows PK parameter values of BINI in Cycle 1. The applicant explained that analysis of PK data obtained using a power model showed that C_{max} and AUC_{inf} increased roughly in proportion to dose over the dose range tested. The mean accumulation ratio[38)] in the 45 mg group was 1.80. In the 45 mg group, the trough concentration of BINI in plasma (arithmetic mean ± SD) on Days 2, 8, 15, and 16 of Cycle 1 was 16.7 ± 10.4, 145 ± 60.2, 123 ± 77.5, and 150 ± 64.4 ng/mL, respectively, based on which the applicant explained that the plasma BINI concentration reaches a steady state within 2 weeks after the start of administration.

Table 33. PK parameters of BINI in Cycle 1

Dose (mg)	Day of measurement	n	C_{max} (ng/mL)	t_{max}[*1] (h)	AUC_{tau} (ng•h/mL)	AUC_{inf} (ng•h/mL)	$t_{1/2}$ (h)	CL/F (L/h)
15	1	6	210 ± 60.9	1.5 (0.5, 2)	776 ± 159	1,010 ± 165	7.27 ± 1.76	15.1 ± 2.36
30	1	6	498 ± 226	1.5 (0.5, 4)	1,870 ± 726	2,700 ± 1,060[*3]	9.72 ± 3.63	12.7 ± 5.23[*3]
	15	5	431 ± 207	2.0 (0.5, 8)	2,550 ± 896[*2]	4,390[*4]	4.65 ± 0.482[*2]	8.20[*4]
45	1	9	559 ± 145	1.5 (0.5, 4)	2,030 ± 475	2,650 ± 698	8.24 ± 3.78	18.3 ± 6.01
	15	9	805 ± 274	1.5 (0.5, 2)	3,670 ± 1,100	3,380 ± 370[*3]	4.11 ± 1.13	14.9 ± 1.58[*3]

Arithmetic mean ± SD (individual value for n = 1); *[1], Median (range); *[2], n = 4; *[3], n = 5; *[4], n = 1

[39)] Calculated by dividing urinary excretion (1.8×10^6 ng) by AUC_{inf} (3,940 ng•h/mL).

6.2.2.2 Foreign phase I study (CTD 5.3.3.1-3, Study CMEK162A2102 [Study A2102] [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in 6 healthy adults (6 subjects included in PK analysis) to investigate the mass balance of BINI. ^{14}C-BINI 45 mg was administered orally in a single dose, and radioactivity concentrations in blood, plasma, urine, and feces were measured.

The blood/plasma concentration ratio of radioactivity (arithmetic mean) from 1 to 8 hours after administration was 0.63, based on which the applicant explained that distribution of BINI and its metabolites in blood cells is low. In plasma collected up to 24 hours after administration, mainly the unchanged BINI was detected (accounting for 60.2% of total radioactivity in plasma). Main metabolites detected were M10.2 (glucuronide conjugate), M10.5 (metabolite formed by dehydrogenation and glucuronide conjugation of M4 [amide form]), M3 (*N*-demethylated form), and M15.9 (carboxylate formed by hydrolysis of M4) (accounting for 5.5%, 6.7%, 7.3%, and 7.4%, respectively, of the total radioactivity in plasma).

The urinary and fecal excretion rate of radioactivity (percentage relative to administered radioactivity) up to 360 hours after administration was 31.4% and 62.3%, respectively. In (a) urine and (b) feces collected up to 360 hours after administration, mainly the unchanged BINI was detected (accounting for (a) 6.5% and (b) 29.8%, respectively, of administered radioactivity). Main metabolites detected were (a) M10.9 (glucuronide conjugate), M3, and M10.2; and (b) M4 and M15.9 (accounting for [a] 6.2%, 5.1%, and 4.2%, and [b] 17.2% and 6.7%, respectively, of administered radioactivity).

6.2.2.3 Foreign phase I study (CTD 5.3.3.1-2, Study ARRY-162-0602 [Study 162-0602] [[redacted] 20[redacted] to [redacted] 20[redacted]])

A double-blind, placebo-controlled, randomized study was conducted in 50 healthy adults (38 subjects included in PK analysis) to investigate PK and other endpoints of BINI. Subjects received BINI ([redacted]) 5, 10, or 20 mg or BINI ([redacted]) 40 or 60 mg orally QD, BINI ([redacted]) 80 mg orally in a single dose, or BINI ([redacted]) 20 mg orally BID, and plasma BINI concentration was measured.

Table 34 shows PK parameters of BINI. The applicant explained that analysis of PK data obtained using a power model showed that C_{max} and AUC_{tau} increased roughly in proportion to dose over the dose range tested.

Table 34. PK parameters of BINI

Formulation	Dosage regimen	Day of measurement	n	C_{max} (ng/mL)	t_{max}[*1] (h)	AUC_{tau} (ng•h/mL)	$t_{1/2}$ (h)
[redacted]	5 mg QD	1	6	46.4 ± 20.3	0.992 (0.483, 4.00)	180 ± 17.1[*2]	5.30 ± 1.46[*2]
		14	6	34.7 ± 3.99	0.750 (0.483, 1.48)	169 ± 33.7[*2]	5.26 ± 0.778[*2]
	10 mg QD	1	6	70.6 ± 15.2	0.492 (0.483, 1.00)	264 ± 36.2	6.69 ± 1.71
		14	6	84.5 ± 18.4	0.750 (0.500, 1.48)	326 ± 44.5	6.38 ± 2.31
	20 mg QD	1	4	129 ± 32.6	0.992 (0.983, 1.50)	609 ± 98.6	6.53 ± 2.21
		14	4	154 ± 69.5	1.24 (0.500, 1.50)	654 ± 141	8.01 ± 2.18
[redacted]	80 mg in single dose	1	4	702 ± 250	1.00 (0.983, 2.00)	2,750 ± 688	12.5, 14.2[*3]
	40 mg QD	1	6	395 ± 99.0	0.784 (0.483, 1.48)	1,420 ± 284	7.03 ± 0.855
		14	5	442 ± 177	1.50 (0.500, 2.00)	1,990 ± 476	10.8, 13.8[*3]
	60 mg QD	1	6	421 ± 128	1.50 (0.500, 2.00)	1,970 ± 486	7.37 ± 2.72
		14	4	454 ± 98.1	1.25 (1.00, 2.00)	2,500 ± 902	10.2[*4]
	20 mg BID	1	6	174 ± 47.1	1.50 (0.983, 2.03)	630 ± 145	—
		14	5	262 ± 77.6	1.53 (1.50, 3.98)	1,330 ± 406	7.51 ±1 .44[*2]

Arithmetic mean ± SD (individual values for n = 1 or 2); *1, Median (range); *2, n = 4; *3, n = 2; *4, n = 1; —, Not calculated.

6.2.2.4 Foreign phase II study (CTD 5.3.5.2-3, Study X2201 [ongoing since March 2011 (data cut-off January 7, 2014)])

An open-label, uncontrolled study was conducted in 183 patients with unresectable malignant melanoma with BRAF V600 mutation or *NRAS* gene mutation (165 patients included in PK analysis). In each of the 28-day treatment cycles, BINI 45 or 60 mg was administered orally BID, and plasma BINI concentration was measured.

Table 35 shows PK parameters of BINI in Cycle 1. The accumulation ratio[38)] in the 45 mg group was 1.31.

Table 35. PK parameters of BINI in Cycle 1

Dose (mg)	Day of measurement	n	C_{max} (ng/mL)	t_{max}[*1] (h)	AUC_{tau} (ng•h/mL)
45	1	23	499 ± 198	1.33 (0.50, 3.25)	1,729 ± 558[*2]
	15	22	489 ± 217	1.48 (0.42, 8.00)	2,211 ± 655[*2]
60	1	19	568 ± 168	0.75 (0.50, 7.98)	1,694 ± 720[*3]
	15	20	585 ± 258	1.42 (0.00, 5.17)	2,682 ± 591[*4]

Arithmetic mean ± SD; *1, Median (range); *2, n = 7; *3, n = 8; *4, n = 4

6.2.3 ENCO/BINI

6.2.3.1 Foreign phase Ib/II study (CTD 5.3.3.2-3, Study X2110 [ongoing since May 2012 (data cut-off [redacted])])

In the dose-titration part of the foreign phase Ib/II study, an open-label, uncontrolled study was conducted in 47 patients with advanced solid cancer with BRAF V600 mutation (47 patients included

in PK analysis) to investigate PK and other endpoints of ENCO and BINI. In each of the 28-day treatment cycles, patients received BINI 45 mg orally BID and ENCO 50, 100, 200, 400, 450, 600, or 800 mg orally QD, and plasma concentrations of ENCO and BINI were measured.

Table 36 shows PK parameters of ENCO in Cycle 1. The applicant explained that analysis of PK data obtained using a power model showed that C_{max} and AUC_{tau} increased roughly in proportion to dose over the dose range tested. C_{max} and AUC_{tau} of ENCO on Day 15 were lower than the values on Day 1, showing the accumulation ratio[38)] of 0.458 in the 450 mg group.

Table 36. PK parameters of ENCO in Cycle 1

Dose (mg)	Day of measurement	n	C_{max} (ng/mL)	AUC_{tau} (ng•h/mL)	$t_{1/2}$ (h)
50	1	6	855 ± 480	3,700 ± 2,320	3.68 ± 0.605
	15	6	587 ± 321	2,620 ± 1,260	4.74 ±1.18[*1]
100	1	5	1,930 ± 652	11,500 ± 6,070	3.65 ± 0.351
	15	5	1,190 ± 409	5,510 ± 1,280	4.47 ± 0.380[*2]
200	1	4	3,820 ± 1,550	22,000 ± 9,750	2.88 ± 0.121
	15	2	1,200, 926	5,780, 3,460	3.44, 5.21
400	1	4	6,930 ± 1,950	40,200 ± 21,700	4.19 ± 2.13
	15	3	3,760 ± 1,380	10,200 ± 2,280	4.21 ± 0.724
450	1	13	7,620 ± 3,350	36,300 ± 19,000	3.47 ± 0.402
	15	11	4,320 ± 2,260	15,900 ± 8,730	3.57 ± 0.688
600	1	7	10,300 ± 3,170	57,000 ± 26,800	3.21 ± 0.550
	15	6	11,100 ± 14,100	27,300 ± 17,900	3.40 ± 0.223
800	1	6	6,560 ± 3,430	36,500 ± 13,400[*1]	3.04 ± 0.0935
	15	6	6,650 ± 3,110	24,500 ± 7,030[*1]	3.27 ± 0.511[*1]

Arithmetic mean ± SD (individual values for n = 2); *1, n = 5; *2, n = 4

In the global phase I study (Study X2101) [see Section 6.2.1.1] and in the foreign phase Ib/II study (Study X2110), C_{max} and AUC_{tau} of ENCO following multiple administration were low. The applicant explained that the decreases attributed to the self-induction of CYP3A by ENCO, considering the observations that ENCO is metabolized mainly by CYP3A4 [see Section 4.1.3.1] and that ENCO induces CYP3A [see Section 4.1.5.2].

Table 37 shows PK parameters of BINI in Cycle 1. The dose of ENCO did not have any clear effect on C_{max} or AUC of BINI.

Table 37. PK parameters of BINI in Cycle 1

Dose of ENCO (mg)	Day of measurement	n	C_{max} (ng/mL)	AUC_{tau} (ng•h/mL)	AUC_{inf} (ng•h/mL)	$t_{1/2}$ (h)
50	1	6	635 ± 402	2,130 ± 1,330[*1]	2,190 ± 1,350[*1]	2.36 ± 0.427[*1]
	15	6	693 ± 283	2,950 ± 1,380	—	5.75, 3.73[*2]
100	1	5	587 ± 147	1,860 ± 532[*3]	1,930 ± 529[*3]	2.37 ± 0.704[*3]
	15	5	568 ± 233	2,610 ± 873	—	4.80 ± 1.40[*3]
200	1	3	986 ± 771	3,600 ± 2,160	3,730 ± 2,250	2.10 ± 0.522
	15	2	926, 306	4,000, 1,320	—	3.28[*4]
400	1	4	532 ± 227	1,890 ± 1,110[*5]	1,960 ± 1,140[*5]	2.51 ± 0.472[*5]
	15	4	553 ± 336	2,110 ± 1,220	—	4.20 ± 1.36
450	1	13	807 ± 398	2,650 ± 1,410[*6]	2,750 ± 1,490[*6]	2.22 ± 0.439[*6]
	15	11	638 ± 283	2,550 ± 901	—	3.61 ± 1.14[*7]
600	1	7	901 ± 480	3,010 ± 1,560	3,090 ± 1,600	2.12 ± 0.314
	15	6	716 ± 321	2,590 ± 1,640	—	—
800	1	4	621 ± 160	2,280 ± 477	2,340 ± 462	1.99 ± 0.601
	15	5	726 ± 206	2,540 ± 529	—	2.91 ± 0.157[*5]

Arithmetic mean ± SD (individual value for n = 1 or 2); *[1], n = 5; *[2], n = 2; *[3], n = 4; *[4], n=1; *[5], n = 3; *[6], n = 11; *[7], n = 9; —, Not calculated.

The applicant explained that pharmacokinetic interactions are unlikely to occur between ENCO and BINI, taking account of the following findings:

- In the global phase I study (Study X2101, [see Section 6.2.1.1]) and the foreign phase Ib/II study (Study X2110), no clear difference was observed in PK of ENCO between ENCO monotherapy and ENCO/BINI therapy.

- In the foreign phase II study (Study X2201, [see Section 6.2.2.4]) and the foreign phase Ib/II study (Study X2110), no clear difference was observed in PK of BINI between BINI monotherapy and ENCO/BINI therapy.

6.2.4 Drug-drug interactions

6.2.4.1 Drug-drug interaction between ENCO and posaconazole or diltiazem (CTD 5.3.3.4-5, Study ARRAY-818-105 [Study 818-105] [[redacted] to [redacted] 20[redacted]])

A 2-part, open-label, uncontrolled study was conducted in 32 healthy adults (16 subjects included in PK analysis for each part) to investigate the effect of posaconazole and diltiazem (both are CYP3A inhibitors) on PK of ENCO. A washout period of ≥7 days was allowed between each treatment period.

Part 1: In Period 1, ENCO 50 mg was administered orally in a single dose on Day 1. In Period 2, posaconazole 400 mg was administered orally BID on Days 1 to 9, and ENCO 50 mg was administered orally in a single dose on Day 7.

Part 2: In Period 1, ENCO 50 mg was administered orally in a single dose on Day 1. In Period 2, diltiazem 240 mg was administered orally QD on Days 1 to 4, and ENCO 50 mg was administered orally in a single dose on Day 2.

The geometric mean ratio [90% CI] of C_{max} and AUC_{inf} of ENCO following the concomitant use with (a) posaconazole or (b) diltiazem to those following the administration of ENCO alone was (a) 1.68 [1.54, 1.85] and 2.83 [2.54, 3.16], and (b) 1.45 [1.24, 1.69] and 1.83 [1.65, 2.03], respectively.

6.2.4.2 Drug-drug interaction between BINI and midazolam (CTD 5.3.3.4-4, Study CMEK162A2105 [Study A2105] [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted in 15 healthy adults (11 subjects included in PK analysis) to investigate the effect of BINI on PK of midazolam (a substrate of CYP3A). BINI (30 mg) was administered orally BID from Day 3 to 16 and QD on Day 17. Midazolam 4 mg was administered orally in a single dose on Days 1, 10, and 17.

The geometric mean ratio [90% CI] of C_{max} and AUC_{inf} of midazolam following the concomitant use with BINI to those following the administration of midazolam alone was 0.925 [0.752, 1.14] and 1.10 [0.979, 1.24], respectively. The applicant explained that pharmacokinetic interactions are unlikely to occur between BINI and substrates of CYP3A, based on the above.

6.2.5 Administration of ENCO to patients with renal impairment

The applicant explained that it is unnecessary to adjust the dose of ENCO in patients with renal impairment, given the following observations:

- Results of the foreign phase I study (Study A2101, [see Section 6.2.1.2]) suggest that the contribution of renal excretion to ENCO elimination is minimal.
- In the pooled analysis of the data of part 1 of the global phase III study (Study B2301), the foreign phase II study (Study X2109), and the foreign phase Ib/II study (Study X2110), the incidences of (a) all adverse events and (b) Grade ≥3 adverse events in patients with normal renal function (n = 158) and patients with mild or moderate renal impairment[40] (n = 78 and 13, respectively) who received ENCO at the proposed dosage regimen were (a) 99.4%, 97.4%, and 100%, and (b) 54.4%, 61.5%, and 61.5%, respectively, showing no clear relationship between renal impairment and the incidence of adverse events.

6.2.6 Foreign phase I study to investigate the effect of renal impairment on PK of BINI (CTD 5.3.3.3-1, Study ARRAY-162-106 [Study 162-106] [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted in 6 each of healthy adults and patients with severe renal impairment (6 each of subjects included in PK analysis) to investigate the effect of renal impairment on PK of BINI. BINI 45 mg was administered orally in a single dose, and plasma BINI concentration, etc., were measured.

Table 38 shows PK parameters of BINI. The geometric mean ratio [90% CI] of C_{max} and AUC_{inf} of BINI unbound to plasma protein in patients with severe renal impairment to those in healthy adults was 1.43 [0.882, 2.33] and 1.53 [1.03, 2.28], respectively. However, the applicant explained that it is unnecessary to adjust the dose of BINI in patients with renal impairment, considering the geometric variation coefficient of (a) C_{max} and (b) AUC_{inf} ([a] 68.5% and 21.4%, and [b] 53.2% and 20.4% in healthy adults and patients with renal impairment, respectively).

[40] Severity of renal impairment was classified according to eGFR: ≥90 mL/min/1.73 m^2, normal; ≥60 mL/min/1.73 m^2 and ≤89 mL/min/1.73 m^2, mild; ≥30 mL/min/1.73 m^2 and ≤59 mL/min/1.73 m^2, moderate.

Table 38. PK parameters of BINI, classified by severity of renal impairment

Severity of renal impairment[*1]	Analyte	n	C_{max} (ng/mL)	t_{max}[*2] (h)	AUC_{inf} (ng•h/mL)	$t_{1/2}$ (h)	CL/F (L/h)
Normal	Bound form + unbound form	6	248 ± 121	3.00 (0.500, 8.00)	2,220 ± 847	9.16 ± 2.98	23.3 ± 9.89
	Unbound form	6	10.8 ± 6.80	—	95.4 ± 46.3	—	578 ± 275
Severe	Bound form + unbound form	6	286 ± 122	2.00 (1.00, 5.00)	2,740 ± 701	11.2 ± 3.00	17.3 ± 4.32
	Unbound form	6	13.5 ± 3.04	—	134 ± 28.6	—	347 ± 66.3

Arithmetic mean ± SD; *[1], Classified as normal if estimated glomerular filtration rate (eGFR) was ≥80 mL/min/1.73 m^2 and as severe if eGFR was ≤29 mL/min/1.73 m^2; *[2], Median (range); Bound form, BINI bound to plasma protein; Unbound form, BINI not bound to plasma protein; —, Not calculated.

6.2.7 Clinical studies to investigate the effect of hepatic impairment on PK

6.2.7.1 Foreign phase I study to investigate the effect of hepatic impairment on PK of ENCO (CTD 5.3.3.3-3, Study ARRAY-818-101 [Study 818-101] [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in 6 healthy adults and 7 patients with mild hepatic impairment (Child-Pugh class A) (6 each of subjects included in PK analysis) to investigate the effect of hepatic impairment on PK of ENCO. ENCO 50 mg was administered orally in a single dose, and plasma ENCO concentration was measured.

Table 39 shows PK parameters of ENCO. The geometric mean ratio [90% CI] of C_{max} and AUC_{inf} of ENCO unbound to plasma protein in patients with mild hepatic impairment to those in healthy adults was 1.21 [0.901, 1.64] and 1.55 [1.05, 2.30], respectively.

Table 39. PK parameters of ENCO, classified by severity of hepatic impairment

Severity of hepatic impairment	Analyte	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_{inf} (ng•h/mL)	$t_{1/2}$ (h)	CL/F (L/h)
Normal	Bound form + Unbound form	6	517 ± 192	1.50 (1.00, 3.00)	2,060 ± 652	5.62 ± 4.47	26.0 ± 6.82
	Unbound form	6	35.1 ± 13.2	—	139 ± 36.7	—	382 ± 97.7
Mild	Bound form + Unbound form	6	498 ± 132	1.50 (1.00, 2.00)	2,730 ± 1,410	5.72 ± 2.29	21.6 ± 7.95
	Unbound form	6	41.7 ± 10.6	—	231 ± 121	—	258 ± 96.5

Arithmetic mean ± SD; *, Median (range); Bound form, ENCO bound to plasma protein; Unbound form, ENCO not bound to plasma protein; —, Not calculated.

6.2.7.2 Foreign phase I study to investigate the effect of hepatic impairment on PK of BINI (CTD 5.3.3.3-2, Study CMEK162A2104 [Study A2104] [March 2014 to August 2016])

An open-label, uncontrolled study was conducted in healthy adults and patients with mild, moderate, and severe hepatic impairment[41)] (10, 6, 6, and 5 subjects each; 10, 6, 6, and 5 subjects included in PK analysis, respectively) to investigate the effect of hepatic impairment on PK of BINI. BINI was administered orally at a single dose of 45 mg to healthy adults and to patients with mild or moderate hepatic impairment and at a single dose of 15 mg to patients with severe hepatic impairment, and plasma BINI concentration was measured.

Table 40 shows PK parameters of BINI. The geometric mean ratio [90% CI] of DN C_{max} and DN AUC_{last} of BINI unbound to plasma protein in patients with (a) mild, (b) moderate, and (c) severe hepatic impairment to those in healthy adults was (a) 1.28 [0.838, 1.95] and 1.22 [0.834, 1.79], (b) 2.63 [1.62, 4.26] and 3.80 [2.46, 5.88], and (c) 2.68 [1.66, 4.35] and 3.48 [2.25, 5.39], respectively.

41) Classified according to the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria.

Table 40. PK parameters of BINI, classified by severity of hepatic impairment

Severity of hepatic impairment	Dose (mg)	Analyte	n	C_{max} (ng/mL)	DN C_{max} (ng/mL/mg)	t_{max}* (h)	AUC_{last} (ng•h/mL)	DN AUC_{last} (ng•h/mL/mg)	$t_{1/2}$ (h)	CL/F (L/h)
Normal	45	Bound form + unbound form	10	370 ± 142	8.22 ± 3.16	1.00 (0.500, 3.00)	1960 ± 495	43.5 ± 11.0	12.9 ± 2.66	23.9 ± 6.32
		Unbound form	10	14.4 ± 5.01	0.319 ± 0.111	1.00 (0.500, 3.00)	76 ± 18.2	1.69 ± 0.404	—	610 ± 148
Mild	45	Bound form + unbound form	6	387 ± 140	8.59 ± 3.12	0.500 (0.500, 1.00)	1970 ± 419	43.7 ± 9.32	12.4 ± 2.26	23.0 ± 4.29
		Unbound form	6	20.3 ± 13.6	0.451 ± 0.302	0.500 (0.500, 1.00)	102 ± 61.5	2.26 ± 1.37	—	528 ± 207
Moderate	45	Bound form + unbound form	6	463 ± 86	10.3 ± 1.91	1.25 (0.500, 3.00)	3590 ± 979	79.7 ± 21.7	10.8 ± 3.80	13.2 ± 3.39
		Unbound form	4	39.1 ± 19.3	0.869 ± 0.430	1.25 (0.500, 3.00)	340 ± 272	7.55 ± 6.04	—	180 ± 83.7
Severe	15	Bound form + unbound form	5	183 ± 35.3	12.2 ± 2.35	1.50 (1.00, 3.00)	1380 ± 386	92.0 ± 25.7	12.1 ± 5.55	11.4 ± 3.57
		Unbound form	4	12.6 ± 4.18	0.838 ± 0.279	1.25 (1.00, 2.00)	91.5 ± 34.7	6.10 ± 2.31	—	184 ± 87.3

Arithmetic mean ± SD; *, Median (range); Bound form, BINI bound to plasma protein; Unbound form, BINI not bound to plasma protein; —, Not calculated.

6.2.8 Relationship between exposure and variation in QT/QTc

The applicant explained that, in clinical use, ENCO may cause QT/QT interval corrected (QTc) prolongation, whereas BINI is unlikely to cause QT/QTc interval prolongation, given the following results:

- On the basis of the results from the global phase I study (Study X2101), the relationship between plasma ENCO concentration and change in QTcF from baseline (ΔQTcF) was investigated. From the analysis using the linear mixed-effects model, the upper limit of 90% CI of ΔQTcF at the mean C_{max} under the steady state was estimated to be 17.2 and 18.8 ms, respectively, following administration of ENCO 300 and 450 mg QD. The upper limit of 90% CI of ΔQTcF (measured value) following administration of ENCO 450 mg QD was 16.2 and 26.5 ms, respectively, at 2 hours after administration on Days 1 and 15 in Cycle 1.
- On the basis of the results from the global phase III study (Study B2301), the foreign phase Ib/II study (Study X2110), and the foreign phase II study (Study X2109), the relationship between plasma ENCO or BINI concentrations and ΔQTcF was investigated. From the analysis using the linear mixed-effects model, the upper limit of 90% CI of ΔQTcF at 1.5 hours after administration under the steady state was estimated to be 6.82 and 6.58 ms, respectively, following the concomitant use of ENCO 450 mg QD and BINI 45 mg BID. The measured upper limit of 90% CI of ΔQTcF at 1.5 hours after administration under steady state was 16.6 ms.
- On the basis of the results from the Japanese phase I study (Study X1101), the global phase III study (Study A2301), the foreign phase I studies (Study CMEK162A2101J [Study A2101J], Study ARRAY-162-111 [Study 162-111], Study 162-0601, and Study 162-0602), and the foreign phase II study (Study X2201), the relationship between plasma BINI concentration and ΔQTcF was investigated using the linear mixed-effects model. The results showed that the upper limit of 90% CI of ΔQTcF at the mean C_{max} following oral administration of BINI 45 mg BID was estimated to be 4.10 ms.

6.2.9 PPK analysis

6.2.9.1 ENCO

Population pharmacokinetic (PPK) analysis was conducted on the PK data of ENCO (5,326 measuring time points in 701 subjects) obtained from the global phase I study (Study X2101), the global phase III study (Study B2301), the foreign phase I study (Study 162-105), the foreign phase Ib/II study (Study X2110), and the foreign phase II study (Study X2109), using a non-linear mixed effects model (software, Phoenix NLME Version 6). PK of ENCO was described by a 2-compartment model with first order absorption process.

Table 41 shows PK parameters and covariates investigated in the analysis.

Table 41. Covariates investigated

PK parameter	Covariates
CL/F	Body weight, age, eGFR, AST, ALT, bilirubin, albumin, total protein, sex, race, ethnicity, renal impairment,[*1] hepatic impairment,[*2] disease (healthy adult or patient with cancer), ECOG PS, LDH, dose, CYP3A inhibitor (no or weak inhibitor, moderate or potent inhibitor), and use/non-use of BINI
V/F	Body weight, age, eGFR, AST, ALT, bilirubin, albumin, total protein, sex, race, ethnicity, renal impairment,[*1] hepatic impairment,[*2] disease (healthy adult or patient with cancer), ECOG PS, LDH, dose, and use/non-use of BINI
ka, CL2/F, and V2/F	Sex, race, ethnicity, renal impairment,[*1] hepatic impairment,[*2] disease (healthy adult or patient with cancer), ECOG PS, and use/non-use of BINI

*[1], Severity of renal impairment was classified by eGFR according to the following criteria: ≥90 mL/min/1.73 m^2, normal; ≥60 mL/min/1.73 m^2 and ≤89 mL/min/1.73 m^2, mild; ≥30 mL/min/1.73 m^2 and ≤59 mL/min/1.73 m^2, moderate; ≥15 mL/min/1.73 m^2 and ≤29 mL/min/1.73 m^2, severe. *[2], Classified according to NCI-ODWG criteria.

As significant covariates for (a) CL/F and (b) V/F, the following parameters were identified: (a) Disease (healthy adult or patient with cancer), Eastern Cooperative Oncology Group (ECOG) performance status (PS), concomitant use with potent to moderate CYP3A inhibitor, estimated glomerular filtration rate (eGFR), total protein, bilirubin, lactate dehydrogenase (LDH), and body weight, and (b) age and body weight. The effect of each covariate on CL/F and V/F of ENCO was within the range of inter-individual variability of CL/F and V/F (32.1% and 128.3%, respectively).Therefore, the applicant explained that the effect of these covariates on PK of ENCO is limited.

6.2.9.2 BINI

PPK analysis was conducted on PK data of BINI (5,565 measuring time points in 601 subjects) obtained from the Japanese phase I study (Study X1101), the global phase III study (Study A2301), the foreign phase I studies (Studies A2101J, 162-0602, and 162-111), and the foreign phase II study (Study X2201), using a non-linear mixed effects model (software, Phoenix NLME Version 6). PK of BINI was described by a 2-compartment model with first order absorption process.

In this analysis, the following parameters were investigated as possible covariates for (a) CL/F and (b) V/F: (a) Body weight, age, sex, hepatic impairment,[41)] renal impairment,[42)] total bilirubin, total protein, and disease (healthy adult or patient with cancer), and (b) body weight, age, sex, and albumin. The results showed that the following parameters were identified as significant covariates of (a) CL/F and (b) V/F, respectively: (a) Age, sex, renal impairment, total bilirubin, and disease (healthy adult or patient with cancer), and (b) body weight, age, sex, and albumin. The effect of each covariate on CL/F

[42)] Classified according to CrCL level.

and V/F of BINI was within the range of inter-individual variability of CL/F and V/F (33% and 24%, respectively). Therefore, the applicant explained that the effect of these covariates on PK of BINI is limited.

6.2.9.3 ENCO/BINI

PPK analysis was conducted on the PK data of BINI (3,130 measuring time points in 428 patients) obtained from the global phase III study (Study B2301), the foreign phase I study (Study 162-105), the foreign phase Ib/II study (Study X2110), and the foreign phase II study (Study X2109), using a non-linear mixed effects model (software, Phoenix NLME Version 6). PK of BINI was described by a 2-compartment model with zero order absorption process.

In this analysis, the model constructed in the PPK analysis of BINI [see Section 6.2.9.2] was used, and (a) body weight, concomitant use with ENCO, and albumin, and (b) disease (healthy adult or patient with cancer) were investigated as possible covariates for (a) CL/F and (b) V/F, respectively. The results showed that the effect of (a) body weight, concomitant use with ENCO, and albumin, and (b) disease (healthy adult or patient with cancer) was included in the final model, in addition to the covariates identified in PPK analysis of BINI [see Section 6.2.9.2].

The applicant's explanation about the effect of covariates on CL/F and V/F of BINI, based on the above results:

- Effects of (a) concomitant use with ENCO, sex, renal impairment, age, total bilirubin, albumin, and body weight, and (b) sex and age on (a) CL/F and (b) V/F, respectively, were generally within the range of inter-individual variability of CL/F and V/F (22.8% and 21.4%, respectively). The above results show that the effects of these covariates on PK of BINI are limited.
- V/F of patients with body weight at 5 percentile (54 kg) or 95 percentile (111.85 kg) of the analysis population was estimated to be lower by 26% and higher by 34.4%, respectively, than patients with the reference value (78 kg). This result was considered to be caused by the following facts: (1) The distribution volume of BINI (V/F and V2/F were 107 and 185 L, respectively) is estimated to be greater than the total body fluid volume of a human, and (2) the total amount of body fluid and of tissue depends on body weight.
- V/F of patients with albumin content of 5 percentile (49 g/L) or 95 percentile (33 g/L) of the analysis population was estimated to be lower by 15% and higher by 39.1%, respectively, than the patients with the reference value (43 g/L). In light of the observations that, in healthy adults and patients with mild, moderate, and severe hepatic impairment in the foreign phase I study (Study A2104), the baseline albumin concentration was 43.6, 41.8, 27.5, and 29.4 g/L, respectively, and the percentage of BINI not bound to plasma protein was 3.93%, 4.88%, 8.63%, and 6.65%, respectively, the above results were considered to be caused by the increase in the percentage of plasma protein-unbound BINI with the decrease in baseline albumin concentration.
- Although estimated CL/F and V/F in healthy adults were higher by 37.2% and 189%, respectively, than patients with cancer, these effects are unlikely to have any clinical significance because BINI is administered only to patients with cancer.

6.2.10 Relationship between exposure and efficacy or safety

6.2.10.1 ENCO

6.2.10.1.1 Relationship between exposure and efficacy

On the basis of the data obtained from the global phase III study (Study B2301), patients in the ENCO group were divided into 2 groups according to the steady state exposure (C_{max}, AUC, and trough concentration) to ENCO, i.e., patients with higher than median exposure[43)] and patients with lower than median exposure, and progression-free survival (PFS) in the VEM group and each ENCO group was estimated by Kaplan-Meier method. Results showed no clear relationship between exposure to ENCO and PFS.

6.2.10.1.2 Relationship between exposure and safety

On the basis of the data obtained from the global phase I study (Study X2101), the global phase III study (Study B2301), the foreign phase Ib/II study (Study X2110), and the foreign phase II study (Study X2109), the relationship between exposure[44)] (C_{max}, AUC, and trough concentration) to ENCO and the incidence of increased alanine aminotransferase (ALT) or Grade ≥2 palmar-plantar erythrodysaesthesia syndrome, pyrexia, or diarrhoea[45)] was investigated by logistic regression analysis. Results showed no clear relationship between exposure to ENCO and the incidence of any of the above adverse events.

6.2.10.2 BINI

6.2.10.2.1 Relationship between exposure and efficacy

On the basis of the data obtained from the global phase III study (Study A2301), patients in BINI group were divided into 4 quartile groups according to exposure[44)] (C_{max} and AUC) to BINI, and PFS in each BINI group was estimated by Kaplan-Meier method. Results showed a tendency of PFS prolongation with increase in C_{max} and AUC.

6.2.10.2.2 Relationship between exposure and safety

On the basis of the data obtained from the Japanese phase I study (Study X1101), the global phase III study (Study A2301), the foreign phase I study (Study 162-111), and the foreign phase II study (Study X2201), the relationship between the steady state exposure[44)] (C_{max}, AUC, and trough concentration) to BINI and the incidence of retinal disorder, Grade 3 or 4 increased creatine phosphokinase (CK), or Grade ≥2 left ventricular ejection fraction[46)] was investigated by logistic regression analysis. Results showed the following significant correlations between exposure to BINI and the incidences of above adverse events:

- An increase in the incidence of retinal disorder with the increase in C_{max} was suggested.
- An increase in the incidence of Grade 3 or 4 CK increased with the increase in C_{max}, AUC, and trough concentration was suggested.

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43) C_{max}, AUC, and trough concentration under the steady state were estimated to be 1,960 ng/mL, 8.19 μg▪h/mL, and 4.69 ng/mL, respectively, by PPK analysis [see Section 6.2.9].

44) Estimated by PPK analysis [see Section 6.2.9].

45) Adverse events to be analyzed were selected by referring to the data of the repeated-dose toxicity studies in male and female monkeys and clinical studies on ENCO.

46) The adverse events to be analyzed were selected by referring to the data of clinical studies, etc.

6.2.10.3 ENCO/BINI

On the basis of the data obtained from the ENCO/BINI group in the global phase III study (Study B2301), the relationship between exposure to ENCO or BINI and efficacy or safety was investigated.

6.2.10.3.1 Relationship between exposure and efficacy

The following investigations were conducted on the relationship between exposure and efficacy:

- Patients in the ENCO/BINI group were divided into 2 groups according to the steady state exposure (C_{max}, AUC, and trough concentration) to ENCO, i.e., patients with higher than median exposure[47] and patients with lower than median exposure, and PFS in the VEM group and each ENCO group was estimated by Kaplan-Meier method. Results showed no clear relationship between exposure to ENCO and PFS.
- Patients in the ENCO/BINI group were divided into 2 groups according to the steady state exposure (C_{max}, AUC, and trough concentration) to BINI, i.e., patients with higher than median exposure[48] and patients with lower than median exposure, and PFS in the VEM group and each BINI group was estimated by Kaplan-Meier method. Results showed a tendency of PFS prolongation with increase in C_{max}, AUC, and trough concentration under the steady state.

6.2.10.3.2 Relationship between exposure and safety

The following investigations were conducted on the relationship between exposure and safety:

- The relationship between the steady state exposure[44] (C_{max}, AUC, and trough concentration) to ENCO and the incidence of increased ALT, Grade ≥2 palmar-plantar erythrodysaesthesia syndrome, pyrexia, or diarrhoea was investigated by logistic regression analysis. Results showed no clear relationship between exposure to ENCO and the incidence of any of the above adverse events.
- The relationship between the steady state exposure[44] (C_{max}, AUC, and trough concentration) to BINI and the incidence of increased ALT, Grade ≥2 palmar-plantar erythrodysaesthesia syndrome, pyrexia, or diarrhoea was investigated by logistic regression analysis. Results suggested that the incidence of Grade ≥2 palmar-plantar erythrodysaesthesia syndrome decreases with the increase in C_{max}, AUC, and trough concentration under the steady state.

6.2.11 Difference in PK between Japanese and non-Japanese patients

6.2.11.1 ENCO

The applicant explained that there is no clear difference in PK of ENCO between Japanese and non-Japanese patients, either following the administration of ENCO alone or following the administration of ENCO/BINI, taking account of the following observations:

- There was no clear difference in PK parameters of ENCO between Japanese and non-Japanese patients following the administration of ENCO 300 mg alone in the global phase I study (Study X2101) (Table 42).
- There was no clear difference in PK parameters of ENCO between Japanese and non-Japanese patients following the administration of BINI 45 mg and ENCO 450 mg in combination in the global phase III study (Study B2301) and the foreign phase Ib/II study (Study X2110) (Table 42).

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47) The steady state C_{max}, AUC, and trough concentration were estimated to be 2,550 ng/mL, 10.7 μg•h/mL, and 6.32 ng/mL, respectively, from PPK analysis [see Section 6.2.9].

48) The steady state C_{max}, AUC, and trough concentration were estimated to be 601 ng/mL, 2.21 μg•h/mL, and 34.9 ng/mL, respectively, from PPK analysis [see Section 6.2.9].

Table 42. PK parameters of ENCO in Cycle 1

		Study	Date of measurement (Day)	n	C_{max} (ng/mL)	AUC_{24h} (ng•h/mL)
ENCO alone	Japanese	X2101	1	4	5,290 ± 2,030	31,300 ± 25,800
			15	3	2,180 ± 936	8,210 ± 4,760
	Non-Japanese	X2101	1	5	3,520 ± 1,260	20,900 ± 5,460
			15	4	3,040 ± 926	11,000 ± 4,230
ENCO/BINI	Japanese	B2301	1	3	9,670 ± 5,370	47,700 ± 19,700
			15	2	3,610, 4,320	12,500, 13,700
	Non-Japanese	X2110*	1	12	6,850 ± 2,520	30,900 ± 13,800
			15	10	3,910 ± 2,040	13,600 ± 6,370

Arithmetic mean ± SD (individual values for n = 2); *, Combined results of phase Ib part and phase II part.

6.2.11.2 BINI

The applicant explained that there is no clear difference in PK of BINI between Japanese and non-Japanese patients, either following the administration of BINI alone or following the administration of ENCO/BINI, taking account of the following observations:

- There was no clear difference between Japanese and non-Japanese patients in PK parameters on Day 1 following the administration of BINI 45 mg alone in the Japanese phase I study (Study X1101) and the foreign phase II study (Study X2201) [see Sections 6.2.2.1 and 6.2.2.4]. Although C_{max} and AUC_{tau} on Day 15 tended to be higher in Japanese patients than in non-Japanese patients, it is considered that there was no clear difference in PK of BINI on Day 15 between Japanese and non-Japanese patients, taking account of the observation that the ranges of C_{max} and AUC_{tau} overlapped between Japanese and non-Japanese patients (538-1,350 ng/mL and 2,570-5,510 ng•h/mL, respectively, in Japanese patients, 132.0-860.0 ng/mL and 972-2,943 ng•h/mL, respectively, in non-Japanese patients).
- There was no clear difference between Japanese and non-Japanese patients in PK parameters of BINI following the concomitant use of BINI 45 mg and ENCO 450 mg in the global phase III study (Study B2301) and the foreign phase Ib/II study (Study X2110) (Table 43).

Table 43. PK parameters of BINI in Cycle 1

	Study	Day of measurement	n	C_{max} (ng/mL)	AUC_{12h} (ng•h/mL)
Japanese	B2301	1	3	1,440 ± 1,060	5,110 ± 2,660
		15	2	736, 1190	2,250, 4,170
Non-Japanese	X2110*1	1	12	852 ± 416	2,760 ± 1,590*2
		15	11	669 ± 291	2,430 ± 875

Arithmetic mean ± SD (individual values for n = 2); *1, Combined results of phase Ib part and phase II part; *2, n = 10

6.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA concluded that the applicant's discussions on the clinical pharmacology, etc., of ENCO and BINI are acceptable, except for those discussed in the following sections.

6.R.1 Administration of ENCO to patients with hepatic impairment

The applicant's explanation about administration of ENCO to patients with (a) mild and (b) moderate to severe hepatic impairment:

(a) In the foreign phase I study (Study 818-101), the exposure to plasma protein-unbound ENCO (C_{max} and AUC_{inf}) increased in patients with mild hepatic impairment compared with healthy adults [see Section 6.2.7.1]. However, the pooled analysis of part 1 of the global phase III study (Study B2301), the foreign phase II study (Study X2109), and the foreign phase Ib/II study (Study X2110) showed

that the incidence of (i) all adverse events and (ii) Grade ≥3 adverse events following the administration of ENCO according to the proposed dosage regimen in patients with normal hepatic function (n = 250) and in patients with mild hepatic impairment[41)] (n = 22) was (i) 98.8% and 100%, and (ii) 57.6% and 63.6%, respectively. These results suggest that it is unnecessary to adjust the dose of ENCO in patients with mild hepatic impairment.

(b) It is considered necessary to carefully administer ENCO in patients with moderate or severe hepatic impairment, taking account of the following:
- Because ENCO is eliminated mainly by hepatic metabolism [see Section 6.2.1.2], exposure to ENCO may be greater in patients with moderate or severe hepatic impairment than patients with mild hepatic impairment.
- There is limited experience of administration of ENCO to patients with moderate or severe hepatic impairment according to the proposed dosage regimen.

PMDA's view:
Given that exposure to plasma protein-unbound ENCO increases in patients with mild hepatic impairment [see Section 6.2.7.1], it may be necessary to reduce the dose of ENCO in patients with hepatic impairment. Therefore, information on the effect of hepatic impairment on PK of ENCO obtained in the foreign phase I study (Study 818-101) should be provided to healthcare professionals appropriately using the package insert, etc., and that the following precautions should be provided in the "Precautions for Dosage and Administration" section [see Section 7.R.5].

- Increased blood ENCO concentration has been reported in patients with hepatic impairment. The dose reduction of ENCO should be considered in these patients, and patients should be monitored more carefully for occurrence of adverse events

6.R.2 Concomitant use of ENCO with a CYP3A inhibitor

The applicant's explanation about concomitant use of ENCO with (a) a potent or moderate CYP3A inhibitor or with (b) a weak CYP3A inhibitor:

(a) In light of the ratio of AUC_{inf} of ENCO in concomitant use with a potent or moderate CYP3A inhibitor to that in administration of ENCO alone [see Section 6.2.4.1], it is considered appropriate to advise physicians in the "Precautions for Dosage and Administration" to reduce the dose of ENCO to 150 mg and 250 mg, respectively, when ENCO is concomitantly administered with a potent or moderate CYP3A inhibitor.

(b) In the pooled analysis of the data obtained from part 1 of the global phase III study (Study B2301), the foreign phase II study (Study X2109), and the foreign phase Ib/II study (Study X2110), the incidence of (i) all adverse events and (ii) Grade ≥3 adverse events in patients receiving ENCO according to the proposed dosage regimen in combination with a weak CYP3A inhibitor (n = 48) and in patients not receiving the inhibitor (n = 197) was (i) 97.9% and 99.0%, and (ii) 66.7% and 52.3%, respectively. These results suggest that it is unnecessary to provide any precaution in concomitant use with a weak CYP3A inhibitor.

PMDA's view:

Since exposure to ENCO increased when ENCO was concomitantly administered with a CYP3A inhibitor [see Section 6.2.4.1], it may be necessary to reduce the dose of ENCO in concomitant use with a CYP3A inhibitor regardless of the potency of the inhibitor. However, because there are no clinical data available on the efficacy or safety of ENCO at an adjusted dose, the optimal dose of ENCO in concomitant use with a CYP3A inhibitor is unknown currently. Therefore, information on the effect of CYP3A inhibitors on PK of ENCO, obtained in the foreign phase I study (Study 818-105), should be provided appropriately to healthcare professionals using the package insert, etc., and concomitant use with a CYP3A inhibitor should be avoided whenever possible. In case the concomitant use is necessitated, the dose reduction of ENCO should be considered and, during treatment with ENCO, patient should be carefully monitored for occurrence of adverse events.

6.R.3 Administration of BINI in patients with hepatic impairment

The applicant's explanation about administration of BINI to patients with (a) mild or (b) moderate or severe hepatic impairment:

(a) In the pooled analysis of the data of part 1 of the global phase III study (Study B2301), the foreign phase II study (Study X2109), and the foreign phase Ib/II study (Study X2110), the incidence of (i) all adverse events and (ii) Grade ≥3 adverse events in patients with normal hepatic function (n = 250) and in patients with mild hepatic impairment (n = 22) receiving BINI at the proposed dosage regimen was (i) 98.8% and 100%, and (ii) 57.6% and 63.6%, respectively. These results suggest that it is unnecessary to adjust the dose of BINI in patients with mild hepatic impairment.

(b) Using the final model of PPK analysis [see Section 6.2.9.3], the effect of hepatic impairment on PK of BINI was investigated based on the results of the foreign phase I study (Study A2104). The results showed that AUC of plasma protein-unbound BINI (182 and 176 ng•h/mL, respectively) in patients with moderate and severe hepatic impairment receiving BINI 15 mg was estimated to correspond to AUC of plasma protein-unbound BINI (154 ng•h/mL) in healthy adults receiving BINI 45 mg. It is therefore considered necessary to select the dosage regimen of BINI 15 mg BID in patients with moderate or severe hepatic impairment in the "Precautions for Dosage and Administration" section.

PMDA's view:

PMDA accepted the applicant's above explanation regarding patients with mild hepatic impairment.

Since exposure to plasma protein-unbound BINI was shown to increase in patients with moderate or severe hepatic impairment [see Section 6.2.7.2], it may be necessary to administer BINI at a reduced dose in these patients. However, because there are no clinical data available on the efficacy and safety of BINI given at an adjusted dose to patients with hepatic impairment, the optimal dose of BINI in patients with hepatic impairment is unknown currently. Therefore, information on the effect of hepatic impairment on PK of BINI, obtained in the foreign phase I study (Study A2104), should be provided appropriately to healthcare professionals using the package insert, etc., and the following precautionary description should be included in the "Precautions for Dosage and Administration" section [see Section 7.R.5].

- Increased blood BINI concentration has been reported in patients with moderate or severe hepatic impairment. The dose reduction of BINI should be considered in these patients, and patients should be monitored more carefully for occurrence of adverse events.

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

The applicant submitted efficacy and safety evaluation data, in the form of results from a total of 23 studies consisting of 1 Japanese phase I study, 1 global phase I study, 2 global phase III studies, 15 foreign phase I studies, 1 foreign phase Ib/II study, and 3 foreign phase II studies, as shown in Table 44.

Table 44. List of clinical studies on efficacy and safety

Data category	Region	Study	Phase	Study population	Number of enrollments	Dosage regimen[*1]	Main endpoints
Evaluation	Japan	X1101	I	Patients with advanced solid cancer	21 (a) 14 (b) 7	(a) BINI 15 mg orally QD on Day 1, followed by BINI 30 or 45 mg orally BID from Day 2 (b) BINI 45 mg orally BID	PK Tolerability Safety
	Global	X2101	I	Patients with advanced solid cancer with BRAF V600 mutation	107 (a) 54 (b) 53	(a) ENCO 50, 100, 150, 200, 300, 450, 550, or 700 mg orally QD, or ENCO 75, 100, or 150 mg orally BID (b) ENCO 300 mg orally QD from Day 1 to 14, followed by ENCO 450 mg orally QD from Day 15	PK Tolerability Safety
		B2301	III	Patients with unresectable malignant melanoma with BRAF V600 mutation	Part 1 577 (a) 192 (b) 194 (c) 191 Part 2 344 (a) 258 (b) 86	Part 1: (a) ENCO 450 mg orally QD and BINI 45 mg orally BID (b) ENCO 300 mg orally QD (c) VEM 960 mg orally BID Part 2: (a) ENCO 300 mg orally QD and BINI 45 mg orally BID (b) ENCO 300 mg orally QD	Efficacy Safety
		A2301	III	Patients with unresectable malignant melanoma with NRAS Q61 mutation	402 (a) 269 (b) 133	(a) BINI 45 mg orally BID (b) DTIC 1,000 mg/m^2 intravenously Q3W	Efficacy Safety
	Foreign	A2101	I	Healthy adults	4	^{14}C-ENCO 100 mg in a single oral dose	PK
		A2101J	I	Healthy adults	37	Cross-over single oral administration of 2 types of BINI*[2] 45 mg	PK Safety
		A2102	I	Healthy adults	6	^{14}C-BINI 45 mg in a single oral dose	PK
		A2103	I	Healthy adults	12	Cross-over single oral administration of BINI 45 mg after fasting, low-fat diet, or high-fat diet	PK
		A2104	I	Healthy adults and patients with hepatic impairment	27	BINI 15 mg or 45 mg in a single oral dose	PK Safety Tolerability
		A2105	I	Healthy adults	15	BINI 30 mg orally BID in combination with midazolam	PK
		162-0601	I	Healthy adults	25 (a) 20 (b) 5	(a) BINI 5, 10, 20, 30, or 40 mg in a single oral dose (b) Placebo in a single oral dose	PK Safety Tolerability
		162-0602	I	Healthy adults	50 (a) 38 (b) 12	(a) BINI 5, 10, 20, 40, or 60 mg orally QD, BINI 40 mg orally BID, or BINI 80 mg in a single oral dose (b) Placebo orally QD, BID, or in a single dose	PK Safety Tolerability
		162-104	I	Healthy adults	12	Cross-over single oral administration of BINI 40 mg (tablets and [redacted])*[3]	PK

Data category	Region	Study	Phase	Study population	Number of enrollments	Dosage regimen[*1]	Main endpoints
		162-105	I	Healthy adults	30 (a) 15 (b) 15	(a) ENCO 300 mg in a single dose, followed by ENCO 100 mg in a single oral dose in combination with rabeprazole (b) BINI 45 mg in a single oral dose in combination with rabeprazole	PK
		162-106	I	Healthy adults and patients with renal impairment	12	BINI 45 mg in a single oral dose	PK
		818-101	I	Healthy adults and patients with hepatic impairment	13	ENCO 50 mg in a single oral dose	PK
		818-102	I	Healthy adults	40	Cross-over single oral administration of ENCO 100 mg after fasting or high-fat diet	PK Safety Tolerability
		818-105	I	Healthy adults	32 (a) 16 (b) 16	(a) Cross-over single oral administration of ENCO 50 mg in combination with or without posaconazole (unapproved in Japan) (b) Cross-over single oral administration of ENCO 50 mg in combination with or without diltiazem	PK
		162-111	I	Patients with advanced solid cancer	93 (a) 19 (b) 74	(a) BINI 30, 45, 60, or 80 mg orally QD on Day 1 and BID from Day 2 (b) BINI 45 or 60 mg orally BID	PK Tolerability Safety
		X2110	Ib/II	Phase Ib part: Patients with advanced solid cancer with BRAF V600 mutation Phase II part: Patients with unresectable malignant melanoma with BRAF V600 mutation or patients with unresectable advanced/recurrent CRC	Phase Ib part 47 Phase II part 79	Phase Ib part: ENCO 50, 100, 200, 400, 450, 600, or 800 mg orally QD and BINI 45 mg orally BID Phase II part: ENCO 450 or 600 mg orally QD and BINI 45 mg orally BID	PK Tolerability Safety Efficacy
		X2102	II	BRAF inhibitor treatment naïve patients with unresectable malignant melanoma with BRAF V600 mutation	15 (a) 15 (b) 1	(a) ENCO 300 mg orally QD (b) ENCO 450 mg orally QD and BINI 45 mg orally BID	Efficacy Safety
		X2109	II	Patients with unresectable malignant melanoma with BRAF V600 mutation	158	ENCO 450 mg orally QD and BINI 45 mg orally BID	Efficacy Safety
		X2201	II	Patients with unresectable malignant melanoma with BRAF V600 mutation or *NRAS* gene mutation	183	BINI 45 or 60 mg orally BID	Efficacy Safety

*[1] The study drug was administered in a cross-over design in Studies A2101J, 162-104, 818-102, and 818-105 with a washout period of ≥7 days, and in Study A2103 with a washout period of ≥8 days.
*[2] Tablets supplied by Array and Novartis were used.
*[3] BINI was administered after ≥8 hour fasting or a high-fat diet, and placebo was administered after ≥8 hour fasting.

The outline of each clinical study is as described below.

Main adverse events other than death observed in each clinical study are summarized in Section "7.2 Adverse events etc. observed in clinical studies," and PK-related data in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Clinical pharmacology studies

The applicant submitted the following 14 clinical pharmacology studies in healthy adults and patients with renal or hepatic impairment [see Sections 6.1 and 6.2]. No death occurred during the period of administration of study drug in these studies.

7.1.1.1 Foreign phase I study (CTD 5.3.3.1-4, Study A2101 [[redacted] to [redacted] 20[redacted]])

7.1.1.2 Foreign phase I study (CTD 5.3.1.2-1, Study A2101J [[redacted] to [redacted] 20[redacted]])

7.1.1.3 Foreign phase I study (CTD 5.3.3.1-3, Study A2102 [[redacted] to [redacted] 20[redacted]])

7.1.1.4 Foreign phase I study (CTD 5.3.3.4-3, Study A2103 [[redacted] to [redacted] 20[redacted]])

7.1.1.5 Foreign phase I study (CTD 5.3.3.3-2, Study A2104 [March 2014 to August 2016])

7.1.1.6 Foreign phase I study (CTD 5.3.3.4-4, Study A2105 [[redacted] 20[redacted] to [redacted] 20[redacted]])

7.1.1.7 Foreign phase I study (CTD 5.3.3.1-1, Study 162-0601 [[redacted] to [redacted] 20[redacted]])

7.1.1.8 Foreign phase I study (CTD 5.3.3.1-2, Study 162-0602 [[redacted] 20[redacted] to [redacted] 20[redacted]])

7.1.1.9 Foreign phase I study (CTD 5.3.3.4-1, Study ARRAY-162-104 [Study 162-104] [[redacted] to [redacted] 20[redacted]])

7.1.1.10 Foreign phase I study (CTD 5.3.3.4-2, Study 162-105 [[redacted] 20[redacted] to [redacted] 20[redacted]])

7.1.1.11 Foreign phase I study (CTD 5.3.3.3-1, Study 162-106 [[redacted] to [redacted] 20[redacted]])

7.1.1.12 Foreign phase I study (CTD 5.3.3.3-3, Study 818-101 [[redacted] 20[redacted] to [redacted] 20[redacted]])

7.1.1.13 Foreign phase I study (CTD 5.3.1.1-1, Study 818-102 [[redacted] to [redacted] 20[redacted]])

7.1.1.14 Foreign phase I study (CTD 5.3.3.4-5, Study 818-105 [[redacted] to [redacted] 20[redacted]])

7.1.2 Japanese clinical study

7.1.2.1 Japanese phase I study (CTD 5.3.3.2-2, Study X1101 [ongoing since November 2011 (data cut-off February 10, 2014)])

An open-label, uncontrolled study in patients with advanced solid cancer[49)] (target sample size; ≥6 patients in dose-titration part, ≥6 patients in the expanded part) was conducted at 2 study sites in Japan to investigate the tolerability and other endpoints of BINI.

In each of the 28-day treatment cycles, BINI 30 or 45 mg was administered orally BID[50)] in the dose-titration part, and BINI 45 mg was administered orally BID[50)] in the expanded part. The treatment was continued until disease progression or the patient met the criteria for study discontinuation.

All of the 21 patients enrolled in the study (14 in dose-titration part, 7 in expanded part) received BINI, and were included in the safety analysis population.

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49) In the expanded part, patients with advanced solid cancer (except pancreatic cancer) with wild-type *KRAS* gene, *NRAS* gene mutation, or *BRAF* gene mutation were enrolled. Patients with pancreatic cancer were enrolled in the study regardless of the presence or absence of such mutations.

50) In Cycle 1, a single dose of BINI (15 mg) was administered orally on Day 1 of the cycle.

In the dose-titration part, dose-limiting toxicity (DLT) was evaluated in each cohort during 28 days of Cycle 1. DLT was observed in 2 of 8 patients in the BINI 45 mg group (Grade 2 detachment of retinal pigment epithelium in 2 patients[51]) in the dose-titration part. Taking account of Bayesian model-based estimation, safety, and PK parameters, 45 mg BID was determined to be the maximum tolerated dose (MTD).

No death occurred during the period of administration of BINI or within 28 days after the end of administration.

7.1.3 Global clinical studies

7.1.3.1 Global phase I study (CTD 5.3.3.2-4, Study X2101 [ongoing since September 2011 (data cut-off August 18, 2014)])

An open-label, uncontrolled study in patients[52] with malignant melanoma or colorectal cancer (CRC) with BRAF V600 mutation (target sample size; 72 patients in dose-titration part, 21 patients in expanded part) was conducted at 13 study sites in 7 countries including Japan to investigate the tolerability and other endpoints of ENCO.

Each treatment cycle consisted of 28 days. In the dose-titration part, ENCO 50, 100, 150, 200, 300, 450, 550, or 700 mg was administered orally QD, or ENCO 75, 100, or 150 mg was administered orally BID. In the expanded part, ENCO 300 mg was administered QD or, in the stepwise dose-increase group,[53] the treatment was started with ENCO 300 mg QD and, if tolerated, the dose was increased to 450 mg orally QD.[54] Treatment with ENCO was continued until disease progression or the patient met the criteria for study discontinuation.

All of the 107 patients enrolled in the study (54 in dose titration part, 53 in expanded part) received ENCO (Japanese patients, 0 in dose-titration part, 4 in expanded part) and were included in the safety analysis population.

In both dose-titration part and expanded part, 28 days in Cycle 1 in each cohort were handled as DLT evaluation period. In the dose-titration part, DLT was observed in 1 of 9 patients in the 100 mg QD group (Grade 3 palmar-plantar erythrodysaesthesia syndrome), 1 of 5 patients in the 300 mg QD group (Grade 3 neuralgia), 1 of 4 patients in the 550 mg QD group (Grade 3 fatigue), 2 of 2 patients in the 700 mg QD group (Grade 3 diarrhoea, asthenia, headache, insomnia, and rash in 1 patient each [including duplicate counting]), 1 of 4 patients in the 100 mg BID group (Grade 3 facial paresis and confusional state), and 1 of 3 patients in the 150 mg BID group (Grade 3 musculoskeletal pain, neck pain, and neuralgia), and 450 mg QD was determined to be MTD. In the expanded part, DLT was observed in 10 of the first 34 patients assigned to the group receiving MTD of 450 mg QD (7 patients with malignant melanoma, 3 patients with CRC), from which 300 mg QD was identified as the recommended Phase 2 dose (RP2D). In the entire expanded part, 12 (9 patients with malignant melanoma, 3 patients with CRC)

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51) In both patients, the event occurred during Cycle 1. Administration was resumed at a reduced dose of 30 mg BID, but Grade 2 detachment of retinal pigment epithelium occurred again. The event was therefore handled as DLT.

52) Patients with unresectable malignant melanoma were enrolled in the dose-titration part, and patients with unresectable malignant melanoma and patients with unresectable advanced/recurrent CRC were enrolled in the expanded part.

53) Only patients with previously treated malignant melanoma were enrolled.

54) If a clinically significant Grade 3 or 4 adverse event for which a causal relationship to ENCO could not be ruled out was not observed until Day 14 of Cycle 1, the dose of ENCO was increased to 450 mg from Day 15.

of 53 patients experienced DLT (myalgia in 7 patients, arthralgia in 6 patients, fatigue and insomnia in 3 patients each, asthenia in 2 patients, pancreatitis acute, vomiting, bone pain, and VIIth cranial nerve paralysis in 1 patient each [including duplicate counting]).

The safety analysis revealed death during, or within 30 days after, administration of ENCO as follows: 1 of 4 patients (25.0%) in the 50 mg QD group, 3 of 10 patients (30.0%) in the 100 mg QD group, 1 of 6 patients (16.7%) in the 150 mg QD group, 1 of 4 patients (25.0%) in the 200 mg QD group, 1 of 5 patients (20.0%) in the 100 mg BID group, 2 of 5 patients (40.0%) in the 300 mg QD group, 1 of 4 patients (25.0%) in the 150 mg BID group, and 1 of 6 patients (16.7%) in the 450 mg QD group in the dose-titration part; and in 2 of 16 patients (12.5%) in the 450 mg QD group for malignant melanoma, 2 of 6 patients (33.3%) in the 300 mg QD group for CRC, and 2 of 12 patients (16.7%) in the 450 mg QD group for CRC in the expanded part. Except for death due to disease progression (1 patient in the 50 mg QD group, 3 patients in the 100 mg QD group, 1 patient in the 150 mg QD group, 1 patient in the 200 mg QD group, 1 patient in the 100 mg BID group, 1 patient in the 300 mg QD group, 1 patient in the 150 mg BID group, and 1 patient in the 450 mg QD group in the dose-titration part; and 2 patients in the 450 mg QD group for malignant melanoma, 2 patients in the 300 mg QD group for CRC, and 2 patients in the 450 mg QD group for CRC in the expanded part), the cause of death was general physical condition decreased in 1 patient in the 300 mg QD group in the dose-titration part, and its causal relationship to ENCO could not be ruled out (no Japanese patient died of adverse event).

7.1.3.2 Global phase III study (CTD 5.3.5.1-1, Study B2301 [ongoing since [redacted] 2013 (data cut-off May 19, 2016, November 9, 2016)])

An open-label, randomized controlled study in patients with unresectable malignant melanoma[55] with BRAF V600E or V600K mutation[56] (target sample size,[57] 896 patients [576 in part 1, 320[58] in part 2]) was conducted at 162 study sites in 28 countries including Japan to compare the efficacy and safety among the Combo 450 group, the Combo 300 group, the ENCO group, and the VEM group.

The study drugs were administered according to the following dosage regimens, and the treatment was continued until disease progression or the patient met the criteria for study discontinuation;

Part 1
- Combo 450 group: Oral administration of ENCO 450 mg QD and BINI 45 mg BID
- ENCO group: Oral administration of ENCO 300 mg QD
- VEM group: Oral administration of VEM 960 mg BID

Part 2
- Combo 300 group: Oral administration of ENCO 300 mg QD and BINI 45 mg BID

55) Patients with a prior treatment with BRAF or MEK inhibitor were excluded.
56) Patients were confirmed to have BRAF V600E or V600K mutation by THxID BRAF kit of BioMérieux at the central laboratory.
57) At the start of the study, the target sample size had been 900 but was changed to 896 (clinical study protocol, ver. 3, dated November 4, 2014) as a result of the foreign phase III study (Combi-V study) conducted to compare the efficacy and safety between combination of DAB and TRA (DAB/TRA) and VEM in patients with unresectable malignant melanoma with BRAF V600 mutation (*N Engl J Med*. 2015;372:30-9) and the foreign phase III study (co-BRIM study) conducted to compare the efficacy and safety between combination of cobimetinib fumarate (cobimetinib) and VEM (Cobimetinib/VEM) and VEM in patients with unresectable malignant melanoma with BRAF V600 mutation (*N Engl J Med*. 2014;371:1867-76).
58) After the completion of assignment of patients to the Combo 450, ENCO, and VEM groups at 1:1:1 ratio in part 1, assignment to the Combo 300 and ENCO groups was started at 3:1 ratio.

- ENCO group: Oral administration of ENCO 300 mg QD

In part 1, a total of 577 enrolled and randomized patients (192 in the Combo 450 group, 194 in the ENCO group, 191 in the VEM group; the number of Japanese patients among them was 3 in the Combo 450 group, 3 in the ENCO group, and 5 in the VEM group) were included in the full analysis set (FAS) and subjected to efficacy analysis. Of the patients in FAS, a total of 570 patients (192 in the Combo 450 group, 192 in the ENCO group, 186 in the VEM group; the number of Japanese patients among them was 3 in the Combo 450 group, 3 in the ENCO group, and 5 in the VEM group), excluding 7 patients (0 in the Combo 450 group, 2 in the ENCO group, 5 in the VEM group) who did not receive the study drug, were subjected to safety analysis.

In part 2, a total of 344 enrolled and randomized patients (258 in the Combo 300 group, 86 in the ENCO group; the number of Japanese patients among them was 7 in the Combo 300 group and 3 in the ENCO group) were included in FAS and subjected to efficacy analysis. Of the patients in FAS, a total of 341 patients (257 in the Combo 300 group, 84 in the ENCO group; the number of Japanese patients among them was 7 in the Combo 300 group and 3 in the ENCO group), excluding 3 patients (1 in the Combo 300 group, 2 in the ENCO group) who did not receive the study drug, were subjected to safety analysis.

The primary endpoint in this study was PFS by central assessment based on RECIST v1.1. At the start, the study had not been divided into part 1 and part 2. Instead, it had been planned to conduct primary analysis on (a) the Combo 450 group versus the VEM group and on (b) the ENCO group versus the VEM group at the time point when (a) a total of 103 PFS events were observed in the Combo 450 group and the VEM group combined, and (b) a total of 302 PFS events were observed in the ENCO group and the VEM group combined. However, as a result of the discussion with FDA, the following changes were made to the protocol: (1) the Combo 300 group was added, and the entire study was divided into part 1 and part 2, and (2) patient enrollment in part 2 was to be started after the completion of patient assignment to the ENCO group in part 1 (clinical study protocol, ver. 3, dated November 4, 2014). Also, the primary analysis was changed to comparison between the Combo 450 group and the VEM group in part 1 only, because Combi-V and co-BRIM studies demonstrated the clinical usefulness of concomitant use of a BRAF inhibitor and a MEK inhibitor compared with monotherapy with a BRAF inhibitor in patients with malignant melanoma with BRAF V600 mutation. Consequently, the timing of the primary analysis was changed to (a) when a total of 145 PFS events were observed in the Combo 450 and the VEM groups combined and (b) when a total of 191 PFS events were observed in the Combo 450 and the ENCO groups combined (clinical study protocol, ver. 3, dated November 4, 2014).

Table 45 shows the results of the primary analysis of PFS (data cut-off May 19, 2016) and Figure 2 shows Kaplan-Meier curves. Superiority of the Combo 450 group to the VEM group in PFS was demonstrated by the central assessment.

Table 45. Primary analysis of PFS (central assessment, FAS, data cut-off May 19, 2016)

	Combo 450	VEM
Number of patients	192	191
Number of events (%)	98 (51.0)	106 (55.5)
Median [95% CI] (months)	14.9 [11.0, 18.5]	7.3 [5.6, 8.2]
Hazard ratio [95% CI][*1]	0.54 [0.41, 0.71]	
P value (one-sided)[*2]	<0.001	

[*1] Stratified Cox regression analysis with disease stage (IIIB/C and IV [M1a/M1b], IV [M1c]) and ECOG PS (0, 1) as the stratification factors.
[*2] Stratified log-rank test with disease stage (IIIB/C and IV [M1a/M1b], IV [M1c]) and ECOG PS (0, 1) as the stratification factors, significance level of 0.025 (one-sided).

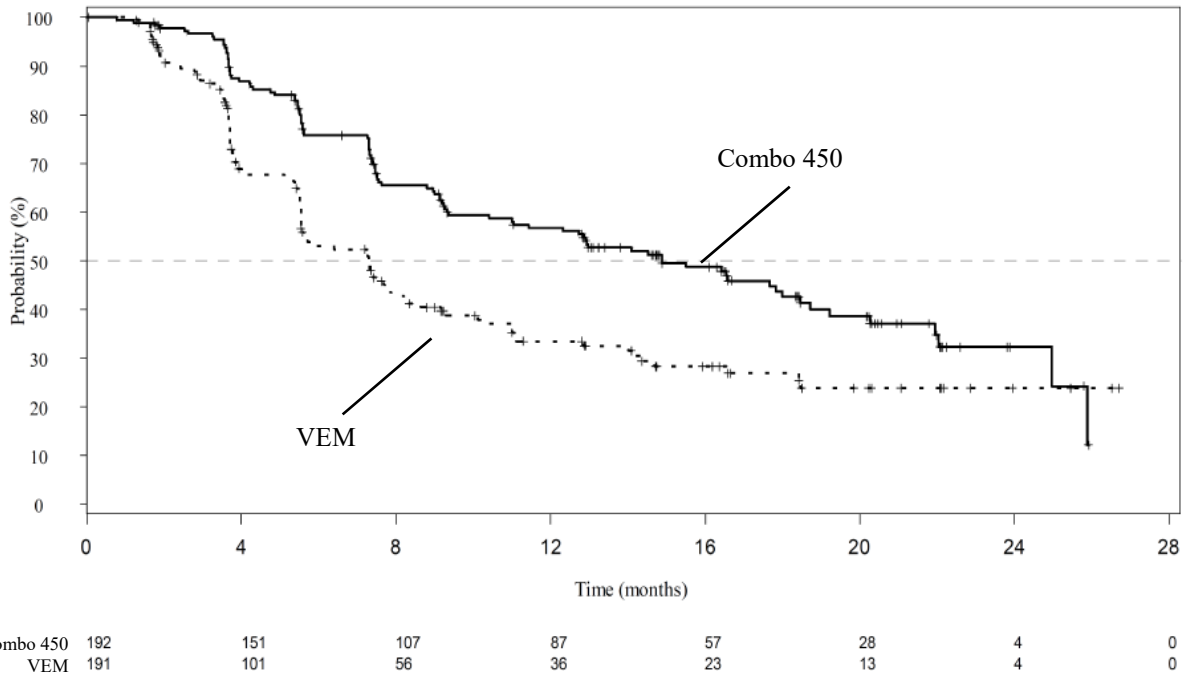

Figure 2. Kaplan-Meier curves of PFS at the primary analysis (central assessment, FAS, data cut-off May 19, 2016)

The safety analysis revealed deaths of 17 of 192 patients (8.9%) in the Combo 450 group, 25 of 257 patients (9.7%) in the Combo 300 group, 21 of 276 patients (7.6%) in the ENCO group, and 19 of 186 patients (10.2%) in the VEM group during, or within 30 days after the end of, the administration of study drug. Except for death due to disease progression (11 patients in the Combo 450 group, 21 patients in the Combo 300 group, 19 patients in the ENCO group, 17 patients in the VEM group), the causes of death were death in 2 patients, euthanasia, multiple organ dysfunction syndrome, cerebral haemorrhage, and completed suicide in 1 patient each in the Combo 450 group; pericarditis, intracranial tumour haemorrhage, renal impairment, and myocardial infarction in 1 patient each in the Combo 300 group; acute myocardial infarction and death in 1 patient each in the ENCO group; and intestinal sepsis and lung infection in 1 patient each in the VEM group. A causal relationship to the study drug could not be ruled out for death and completed suicide in 1 patient each in the Combo 450 group (no Japanese patient died of adverse event).

7.1.3.3 Global phase III study (CTD 5.3.5.1-3, Study A2301 [ongoing since July 2013 (data cut-off August 24, 2015)])

An open-label, randomized study in patients with unresectable malignant melanoma with NRAS mutation involving amino acid substitution of glutamine to other amino acid at codon 61 (NRAS Q61

mutation) (target sample size, 393 patients) was conducted at 169 study sites in 27 countries including Japan to compare the efficacy and safety between BINI and dacarbazine (DTIC).

In the BINI group, BINI 45 mg was administered orally BID and, in the DTIC group, DTIC 1,000 mg/m^2 was administered intravenously Q3W. The treatment was continued until disease progression or the patient met the criteria for study discontinuation.

All of the 402 patients enrolled and randomized in the study (269 in the BINI group, 133 in the DTIC group; the number of Japanese patients among them was 6 in the BINI group and 1 in the DTIC group) were included in FAS and subjected to efficacy analysis. A total of 383 patients (269 in the BINI group, 114 in the DTIC group; the number of Japanese patients among them was 6 in the BINI group and 1 in the DTIC group), excluding 19 patients (0 in the BINI group, 19 in the DTIC group) in the FAS who did not receive the study drug, were subjected to safety analysis.

The primary endpoint in this study was PFS by central assessment based on RECIST v1.1.

Table 46 shows the results of the final analysis of PFS (data cut-off August 24, 2015), and Figure 3 shows Kaplan-Meier curves. Superiority of the BINI group to the DTIC group in PFS was demonstrated by the central assessment.

Table 46. Final analysis of PFS (central assessment, FAS, data cut-off August 24, 2015)

	BINI	DTIC
Number of patients	269	133
Number of events (%)	179 (66.5)	88 (66.2)
Median [95% CI] (months)	2.83 [2.76, 3.55]	1.51 [1.48, 1.71]
Hazard ratio [95% CI][*1]	0.62 [0.47, 0.80]	
P value (one-sided)[*2]	<0.001	

[*1] Stratified Cox regression analysis with disease stage (IIIC and IV [M1a/M1b], IV [M1c]), prior treatment with immunotherapy for unresectable or metastatic disease (yes, no), and ECOG PS (0, 1) as the stratification factors

[*2] Stratified log-rank test with disease stage (IIIC and IV [M1a/M1b], IV [M1c]), prior treatment with immunotherapy for unresectable or metastatic disease (yes, no), and ECOG PS (0, 1) as the stratification factors, significance level of 0.0242 (one-sided)[59)]

[59)] No interim analysis for efficacy evaluation had been planned in this study. However, in the final analysis of PFS, the significance level was calculated using alpha-spending function of O'Brien-Fleming type based on Lan-DeMets method, taking account of the interim analysis conducted to assess the futility at the time point when 130 PFS events (target number of event, 260) were observed.

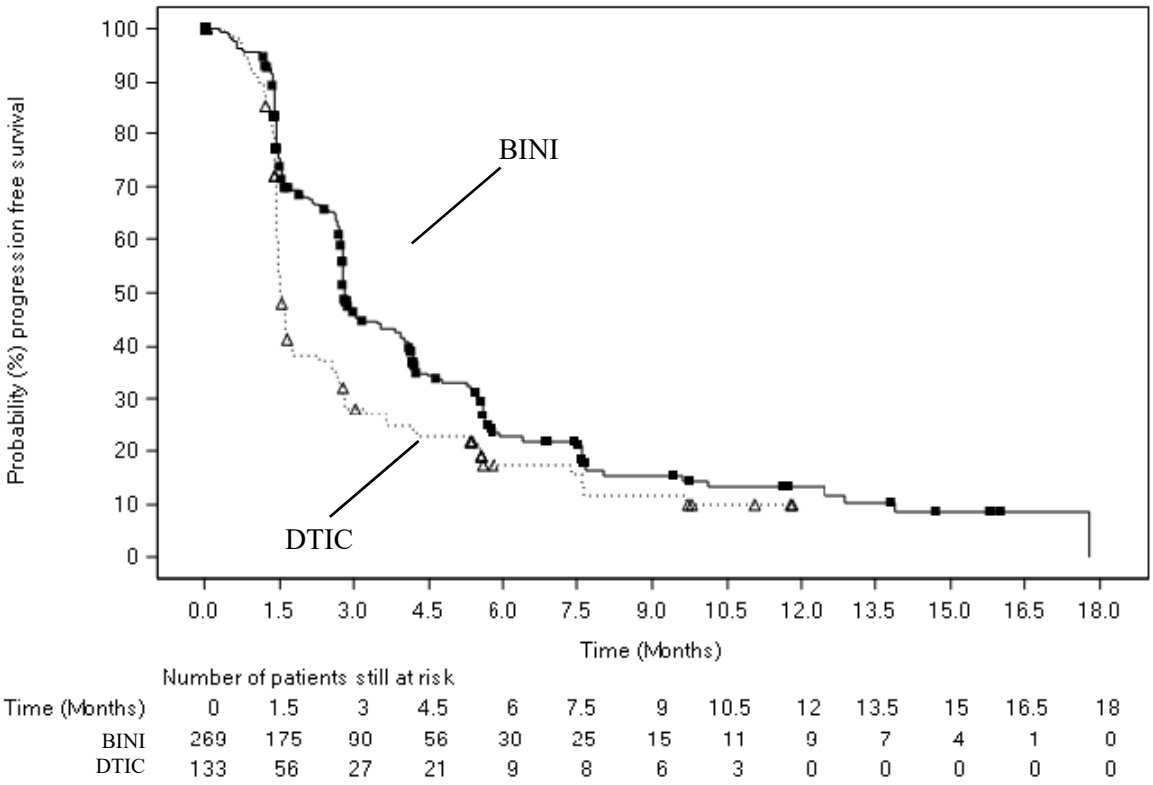

Figure 3. Kaplan-Meier curves of PFS at the final analysis (central assessment, FAS, data cut-off August 24, 2015)

The safety analysis revealed deaths of 23 of 269 patients (8.6%) in the BINI group and 3 of 114 patients (2.6%) in the DTIC group during, or within 30 days after the end of, administration of the study drug. Except for death due to disease progression (19 patients in the BINI group, 3 patients in the DTIC group), the causes of death were sepsis in 2 patients, and multi-organ failure and embolism in 1 patient each in the BINI group. A causal relationship to the study drug could not be ruled out for multi-organ failure in 1 patient in the BINI group (no Japanese patient died of adverse event).

7.1.4 Foreign clinical studies

7.1.4.1 Foreign phase I study (CTD 5.3.3.2-1, Study 162-111 [ongoing since August 2009 (data cut-off January ■, 2013])

An open-label, uncontrolled study in patients with advanced solid cancer[60)] (target sample size; 30 patients in the dose-titration part, up to 65 patients in the expanded part) was conducted at 9 study sites in the US to investigate the tolerability and other endpoints of BINI.

In each of the 21-day treatment cycles, BINI 30, 45, 60, or 80 mg was administered orally BID in the dose-titration part and, in the expanded part, BINI was administered orally BID at MTD determined at the dose-titration part. The treatment was continued until the patient met the criteria for study discontinuation.

All of the 93 patients enrolled in the study (19 in the dose-titration part, 74 in the expanded part) received BINI and were subjected to safety analysis. Patients in the expanded part were 28 patients in the 60 mg

60) In the expanded part, patients with biliary carcinoma and patients with CRC with *KRAS* or *BRAF* gene mutation were included.

BID cohort for biliary carcinoma, 31 patients in the cohort for CRC with KRAS proto-oncogene, GTPase (*KRAS)* gene mutation (6 receiving 60 mg BID, 25 receiving 45 mg BID), and 15 patients in the 45 mg BID cohort for CRC with *BRAF* gene mutation.

DLT was evaluated during the 21 days in Cycle 1 in each cohort. DLT was observed in 2 of 4 patients in the 80 mg BID group in the dose-titration part (Grade 3 chorioretinopathy and dermatitis acneiform in 1 patient each), from which MTD was determined to be 60 mg BID. However, since eye disorder was observed frequently[61)] in the expanded part, the dosage regimen in this part was changed to 45 mg BID.

The safety analysis revealed deaths during, or within 30 days after the end of, administration of the study drug, as follows: 1 of 4 patients (25.0%) in the 30 mg BID group and 2 of 4 patients (50.0%) in the 45 mg BID group in the dose-titration part; and 10 of 28 patients (35.7%) in the 60 mg BID group for biliary carcinoma, 1 of 6 patients (16.7%) in the 60 mg BID group for CRC with *KRAS* gene mutation, 4 of 25 patients (16.0%) in the 45 mg BID group for CRC with *KRAS* gene mutation, and 2 of 15 patients (13.3%) in the 45 mg BID group for CRC with *BRAF* gene mutation in the expanded part. Except for deaths due to disease progression (1 patient in the 30 mg BID group in the dose-titration part; 9 patients in the 60 mg BID group for biliary carcinoma, 1 patient in the 60 mg BID group for CRC with *KRAS* gene mutation, 4 patients in the 45 mg BID group for CRC with *KRAS* gene mutation, and 2 patients in the 45 mg BID group for CRC with *BRAF* gene mutation in the expanded part), the causes of death were colonic haemorrhage and cancer in 1 patient each in the 45 mg BID group in the dose-titration part and disease-related death in 1 patient in the 60 mg BID group for biliary carcinoma in the expanded part. A causal relationship to the study drug was denied for both of them.

7.1.4.2 Foreign phase Ib/II study (CTD 5.3.3.2-3, Study X2110 [ongoing since May 2012 (data cut-off [redacted], 20[redacted])])

In the phase Ib part, an open-label, uncontrolled study in patients with advanced solid cancer with BRAF V600 mutation (target sample size, 18 patients) was conducted at 17 study sites in 5 foreign countries to evaluate the safety, etc., of ENCO/BINI. In the phase II part, an open-label, uncontrolled study in patients with unresectable malignant melanoma with BRAF V600 mutation and patients with metastatic CRC (target sample size, 109 patients) was conducted at 17 study sites in 5 foreign countries to evaluate the efficacy, etc. of ENCO/BINI.

In the phase Ib part, ENCO 50, 100, 200, 400, 450, 600, or 800 mg QD and BINI 45 mg BID were administered orally. In the phase II part, ENCO 450 or 600 mg QD and BINI 45 mg BID were administered orally. The treatment with the study drugs was continued until disease progression or the patient met the criteria for study discontinuation.

All of the 126 patients enrolled in the study (47 in phase Ib part, 79 in phase II part [26 patients with malignant melanoma treated with a BRAF inhibitor, 42 patients with malignant melanoma previously untreated (treatment naïve) with a BRAF inhibitor, and 11 patients with CRC]) were subjected to safety analysis.

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61) Eye disorders for which a causal relationship to the study drug could not be ruled out occurred in 7 of 28 patients (25.0%) in the 60 mg BID cohort for biliary carcinoma and 4 of 6 patients (66.7%) in the 60 mg BID cohort for CRC with *KRAS* gene mutation.

DLT was evaluated during the 28-day period in Cycle 1 of phase Ib part. DLT was observed in 1 of 6 patients in the ENCO 800 mg QD group in the phase Ib part (Grade 3 arthritis), and RP2D was determined to be ENCO 600 mg QD and 450 mg QD. In the phase II part, Grade 3 serum creatinine increased was observed in 3 of 68 patients (4.4%), from which RP2D in administration of ENCO/BINI was determined to be ENCO 450 mg QD and BINI 45 mg BID.

The safety analysis revealed deaths during, or within 30 days after the end of, administration of the study drug, as follows: 1 of 6 patients (16.7%) in the ENCO 50 mg group, 1 of 4 patients (25.0%) in the ENCO 200 mg group, 2 of 5 patients (40.0%) in the ENCO 400 mg group, 2 of 13 patients (15.4%) in the ENCO 450 mg group, and 1 of 6 patients (16.7%) in the ENCO 800 mg group in phase Ib part; and in 5 of 26 patients (19.2%) with a prior treatment with a BRAF inhibitor and in 3 of 42 patients (7.1%) without a prior treatment with a BRAF inhibitor in the phase II part. Except for deaths due to disease progression (1 patient in the ENCO 200 mg group, 2 patients in the ENCO 400 mg group, 2 patients in the ENCO 450 mg group, 1 patient in the ENCO 800 mg group in the phase Ib part; 4 malignant melanoma patients with a prior treatment with a BRAF inhibitor, and 2 malignant melanoma patients without a prior treatment with a BRAF inhibitor in the phase II part), the causes of death were papillary thyroid cancer in 1 patient in the ENCO 50 mg group in the phase I part; and death in 1 malignant melanoma patient with a prior treatment with a BRAF inhibitor, and myocardial infarction in 1 malignant melanoma patient without a prior treatment with a BRAF inhibitor. A causal relationship to the study drug was denied for all of them.

7.1.4.3 Foreign phase II study (CTD 5.3.5.2-1, Study CLGX818X2102 [Study X2102] [November 2013 to March 2015])

An open-label, uncontrolled study in patients with unresectable malignant melanoma with BRAF V600 mutation without a prior treatment with a BRAF inhibitor (target sample size; not planned in part 1, 100 patients in part 2) was conducted at 6 study sites in 6 foreign countries to investigate the efficacy and safety of concomitant use of ENCO with other molecular target therapeutics after disease progression with ENCO monotherapy.

In part 1, ENCO (300 mg) was administered orally QD and, in part 2, ENCO 450 mg QD and BINI 45 mg BID were administered orally. The treatment was continued until disease progression or the patient met the criteria for study discontinuation.

All of the 15 patients enrolled in the study (15 in part 1, 1 in part 2[62]) received the study drug and were subjected to safety analysis. At the start of the study, it had been planned to concomitantly administer a molecular target therapeutic other than BINI in part 2. However, at the time point when 15 patients were enrolled in part 1 ([redacted], 20[redacted]), it became clear that patient enrollment in the study was behind schedule. Further enrollment in the study was therefore cancelled.

The safety analysis revealed death in 1 of 15 patients (6.7%) in part 1 during, or within 30 days after the end of, administration of the study drug. The cause of death was pneumonia, and its causal relationship to ENCO was denied.

[62] Of 15 patients enrolled in part 1, 1 patient was enrolled also in part 2.

7.1.4.4 Foreign phase II study (CTD 5.3.5.2-2, Study X2109 [ongoing since July 2014 (data cut-off [redacted], 20[redacted])])

An open-label, uncontrolled study in patients with unresectable malignant melanoma with BRAF V600 mutation (target sample size, 140 patients) was conducted at 16 study sites in 9 foreign countries to investigate the efficacy and safety of ENCO/BINI.

ENCO 450 mg QD and BINI 45 mg BID were administered orally, and the treatment was continued until disease progression or the patient met the criteria for study discontinuation.

All of the 158 patients enrolled in the study (83 patients with a prior treatment with BRAF or MEK inhibitor, 75 patients without the prior treatment) received the study drugs, and were subjected to safety analysis.

The safety analysis revealed death in 10 of 83 patients (12.0%) with the prior treatment and 6 of 75 patients (8.0%) without the prior treatment during, or within 30 days after the end of, administration of the study drug. The death was due to disease progression in both patients, and its causal relationship to the study drug was denied.

7.1.4.5 Foreign phase II study (CTD 5.3.5.2-3, Study X2201 [ongoing since March 2011 (data cut-off January 7, 2014)])

An open-label study in patients with unresectable malignant melanoma with BRAF V600 mutation or *NRAS* gene mutation (target sample size, 183 patients) was conducted at 13 study sites in 5 foreign countries to investigate the efficacy and safety of BINI.

BINI 45 or 60 mg was administered orally BID, and the treatment was continued until disease progression or the patient met the criteria for study discontinuation.

All of the 183 patients enrolled in the study (66 patients with malignant melanoma with BRAF V600 mutation [41 in the 45 mg BID group, 25 in the 60 mg BID group], 117 patients with malignant melanoma with *NRAS* gene mutation) received BINI, and were subjected to safety analysis.

The primary endpoint in the study was response rate assessed by the investigator according to RECIST v1.0.

Table 47 shows the response rate assessed by the investigator as the primary endpoint.

Table 47. Best overall response and response rate
(RECIST v1.0, FAS, investigator's assessment, data cut-off January 7, 2014)

Best overall response	Number of patients (%)		
	Patients with malignant melanoma with BRAF V600 mutation		Patients with malignant melanoma with *NRAS* gene mutation
	BINI 45 mg BID (n = 41)	BINI 60 mg BID (n = 25)	BINI 45 mg BID (n = 117)
CR	0	0	1 (0.9)
PR	2 (4.9)	3 (12.0)	16 (13.7)
SD	19 (46.3)	7 (28.0)	49 (41.9)
PD	14 (34.1)	13 (52.0)	39 (33.3)
NE	6 (14.6)	2 (8.0)	12 (10.3)
Response (CR + PR) (response rate [95% CI*] [%])	2 (4.9 [0.6, 16.5])	3 (12.0 [2.5, 31.2])	17 (14.5 [8.7, 22.2])

* Exact method

The safety analysis revealed deaths during, or within 30 days after the end of, administration of the study drug, as follows: 12.2% (5 of 41) of patients with malignant melanoma with BRAF V600 mutation in the 45 mg BID group, 12.0% (3 of 25) of patients with malignant melanoma with BRAF V600 mutation in the 60 mg BID group, and 15.4% (18 of 117) of patients with malignant melanoma with *NRAS* gene mutation in the 45 mg BID group. Except for deaths due to disease progression (4 patients with malignant melanoma with BRAF V600 mutation in the 45 mg BID group, 2 patients with malignant melanoma with BRAF V600 mutation in the 60 mg BID group, and 17 patients with malignant melanoma with *NRAS* gene mutation in the 45 mg BID group), the causes of death were dyspnoea in 1 patient with malignant melanoma with BRAF V600 mutation in the 45 mg BID group, hepatic failure in 1 patient with malignant melanoma with BRAF V600 mutation in the 60 mg BID group, and euthanasia in 1 patient with malignant melanoma with *NRAS* gene mutation in the 45 mg BID group. A causal relation to the study drug could not be ruled out for hepatic failure in 1 patient with malignant melanoma with BRAF V600 mutation in the 60 mg BID group.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA concluded that, among the evaluation data submitted, the most important clinical study for evaluating the efficacy and safety of ENCO/BINI was the global phase III study (Study B2301) conducted to investigate the efficacy and safety of ENCO/BINI in patients with unresectable malignant melanoma with BRAF V600 mutation, and decided to evaluate the submitted data focusing on this study. The efficacy in Japanese patients was evaluated based on the consistency of data between the Japanese subpopulation and the overall study population in Study B2301, according to "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010; September 28, 2007) and "Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative Notice dated September 5, 2012), among others.

7.R.2 Efficacy

On the basis of the following review, PMDA concluded that the efficacy of ENCO/BINI has been demonstrated in patients with unresectable malignant melanoma with BRAF V600 mutation.

7.R.2.1 Control group

The applicant's explanation about justification for using VEM group as the control group for Study B2301:

At the time of planning Study B2301, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guideline; v.2.2013), etc., recommended the use of VEM in the target patient group for Study B2301, based on the report of superior efficacy of VEM to DTIC in this patient group (*N Engl J Med*. 2011;364:2507-16).

PMDA accepted the explanation of the applicant.

7.R.2.2 Efficacy endpoint

The applicant's explanation about justification for using PFS as the primary endpoint for Study B2301:

Prolongation of PFS in patients with unresectable malignant melanoma is expected to delay the aggravation of various symptoms due to metastasis to brain, lung, gastrointestinal tract, etc., associated with disease progression, thereby to keep patients under favorable clinical conditions, and to bring a result with clinical significance. It was thus considered appropriate that PFS was used as the primary endpoint for Study B2301.

PMDA's view:

Since patients with unresectable malignant melanoma with BRAF V600 mutation are treated with the expectation of prolonging their survival, overall survival (OS) should have been selected as the primary endpoint for Study B2301. However, PMDA understands the explanation of the applicant that prolongation of PFS in these patients is of certain clinical significance. It is therefore acceptable to evaluate the efficacy of ENCO/BINI based on PFS, the parameter used as the primary endpoint in this study, after confirmation of OS in Study B2301.

7.R.2.3 Results of efficacy evaluation

In Study B2301, superiority of the Combo 450 group to the VEM group was demonstrated in the primary endpoint, i.e., PFS by central assessment [see Section 7.1.3.2].

In case of a statistically significant difference observed in the primary analysis of PFS in the Combo 450 group and the VEM group, it had been planned to conduct hypothesis testing hierarchically in the order of (a) PFS between the Combo 450 group and the ENCO group (part 1 only), (b) PFS between the Combo 300 group and the ENCO group (pooled part 1 and part 2), and (c) OS between the Combo 450 group and the VEM group. In (a) above, the hazard ratio [95% CI] of PFS in the Combo 450 group relative to the ENCO group was 0.75 [0.56, 1.00] (stratified log-rank test, *P* value [one-sided] 0.026, significance level [one-sided] 0.025), failing to show a statistically significant difference in PFS in the Combo 450 group relative to the ENCO group. Table 48 shows the results of the interim analysis (data cut-off November 7, 2017) of OS in the Combo 450 group and the VEM group, and Figure 4 shows Kaplan-Meier curves.

Table 48. Results of the interim analysis of OS (FAS, data cut-off November 7, 2017)

	Combo 450	VEM
Number of patients	192	191
Number of events (%)	105 (54.7)	127 (66.5)
Median [95% CI] (months)	33.6 [24.4, 39.2]	16.9 [14.0, 24.5]
Hazard ratio [95% CI][*1]	0.61 [0.47, 0.79]	
P value (one-sided)[*2]	<0.001	

[*1] Stratified Cox regression analysis with disease stage (IIIB/C and IV [M1a/M1b], IV [M1c]) and ECOG PS (0, 1) as the stratification factors
[*2] Stratified log-rank test with disease stage (IIIB/C and IV [M1a/M1b], IV [M1c]) and ECOG PS (0, 1) as the stratification factors

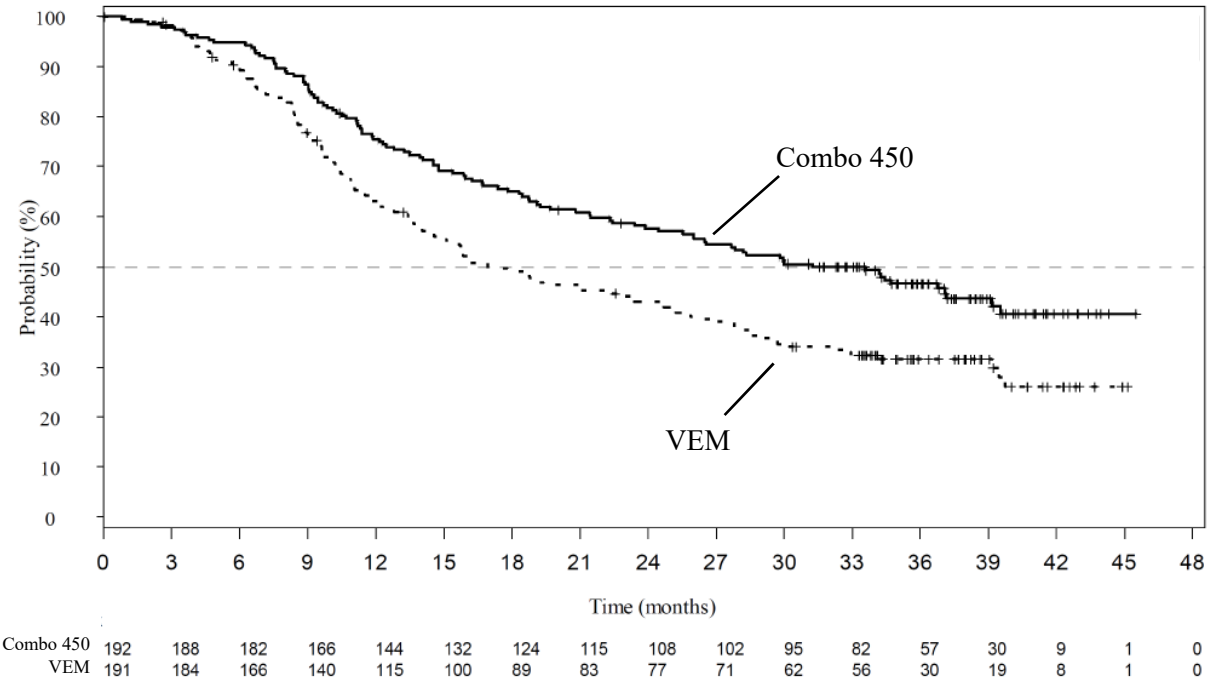

Figure 4. Kaplan-Meier curves of OS at the interim analysis (FAS, data cut-off November 7, 2017)

Table 49 shows PFS by central assessment in the Japanese subpopulation in Study B2301, and Figure 5 shows Kaplan-Meier curves.

Table 49. PFS in Japanese population in final analysis (central assessment, FAS, data cut-off May 19, 2016)

	Combo 450	VEM
Number of patients	3	5
Number of events (%)	2 (66.7)	4 (80.0)
Median [95% CI] (months)	5.5 [3.7, —]	3.7 [2.8, —]
Hazard ratio [95% CI][*1]	0.71 [0.12, 4.37]	
P value (one-sided)[*2]	0.357	

—, Not estimable; *[1], Non-stratified Cox regression analysis; *[2], Log-rank test

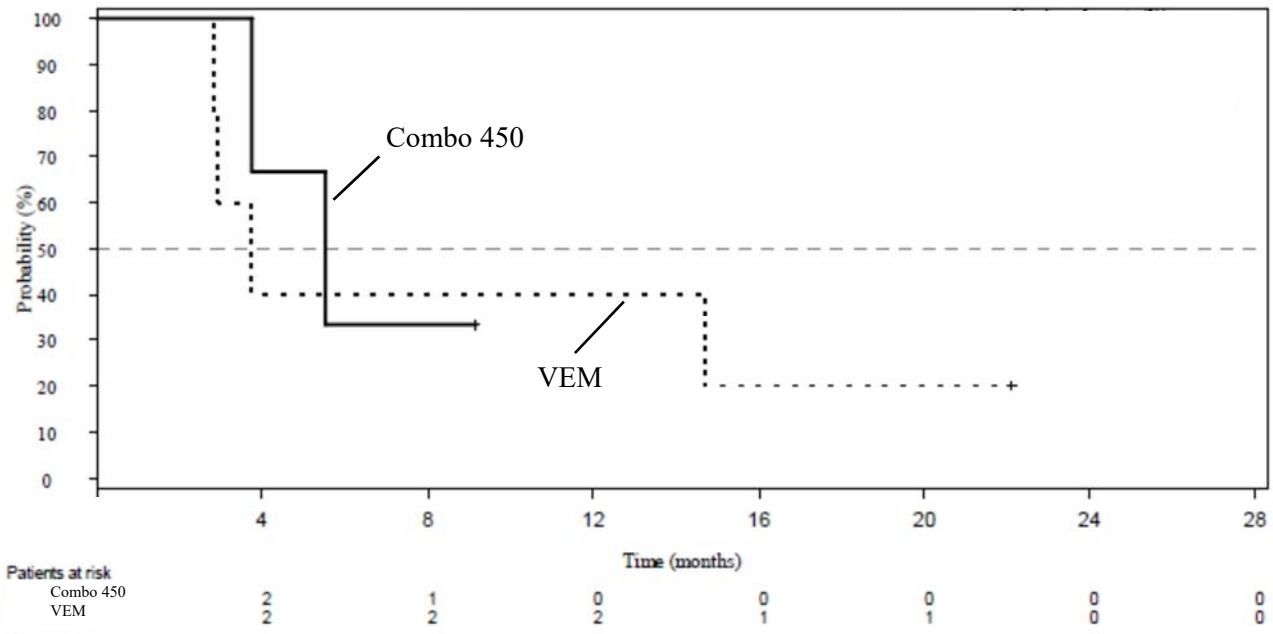

Figure 5. Kaplan-Meier curves of PFS in Japanese subpopulation at the final analysis (FAS, data cut-off May 19, 2016)

The applicant's explanation about the efficacy of ENCO or BINI monotherapy in patients with unresectable malignant melanoma with BRAF V600 mutation and the significance of concomitant use of ENCO and BINI:

Table 50 shows the results of the interim analysis (data cut-off May 19, 2016) on a secondary endpoint in Study B2301, i.e., PFS by central assessment in the ENCO group (part 1 only) and the VEM group, and Figure 6 shows Kaplan-Meier curves.

Table 50. Interim analysis of PFS (central assessment, ENCO group [part 1 only] and VEM group, data cut-off May 19, 2016)

	ENCO	VEM
Number of patients	194	191
Number of events (%)	96 (49.5)	106 (55.5)
Median [95% CI] (months)	9.6 [7.5, 14.8]	7.3 [5.6, 8.2]
Hazard ratio [95% CI][*1]	0.68 [0.52, 0.90]	
P value (one-sided)[*2]	0.0035	

*[1] Stratified Cox regression analysis with disease stage (IIIB/C and IV [M1a/M1b], IV [M1c]) and ECOG PS (0, 1) as the stratification factors
*[2] Stratified log-rank test with disease stage (IIIB/C and IV [M1a/M1b], IV [M1c]) and ECOG PS (0, 1) as the stratification factors

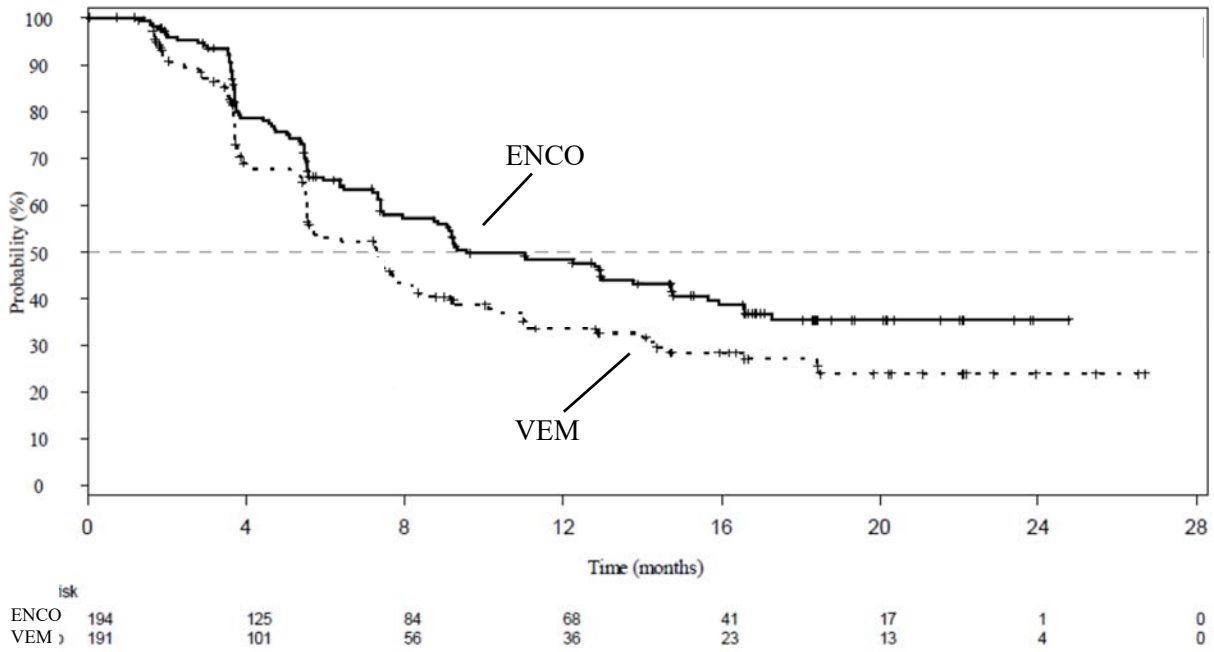

Figure 6. Kaplan-Meier curves of PFS at interim analysis
(central assessment, ENCO group [part 1 only] and VEM group, data cut-off May 19, 2016)

The above results show a tendency of greater PFS prolongation in the ENCO group compared with the VEM group. Therefore, even ENCO monotherapy is expected to have a certain level of efficacy in patients with unresectable malignant melanoma with BRAF V600 mutation.

In addition, Table 51 shows the results of the interim analysis (data cut-off November 9, 2016) on a secondary endpoint in Study B2301, i.e., PFS by central assessment, in the Combo 300 group and the ENCO group (pooled part 1 and part 2), the groups receiving the same dosage regimen of 300 mg QD, and Figure 7 shows its Kaplan-Meier curves. The hazard ratio [95% CI] of PFS by central assessment in the Combo 300 group relative to that in the ENCO group in part 2 was 0.57 [0.41, 0.78].

Table 51. PFS at interim analysis
(central assessment, Combo 300 group and ENCO group [pooled part 1 and part 2], data cut-off November 9, 2016)

	Combo 300	ENCO
Number of patients	258	280
Number of events (%)	133 (51.6)	160 (57.1)
Median [95% CI] (months)	12.9 [10.1, 14.0]	9.2 [7.4, 11.0]
Hazard ratio [95% CI][*1]	0.77 [0.61, 0.97]	
P value (one-sided)[*2]	0.015	

[*1] Stratified Cox regression analysis with disease stage (IIIB/C and IV [M1a/M1b], IV [M1c]) and ECOG PS (0, 1) as the stratification factors
[*2] Stratified log-rank test with disease stage (IIIB/C and IV [M1a/M1b], IV [M1c]) and ECOG PS (0, 1) as the stratification factors

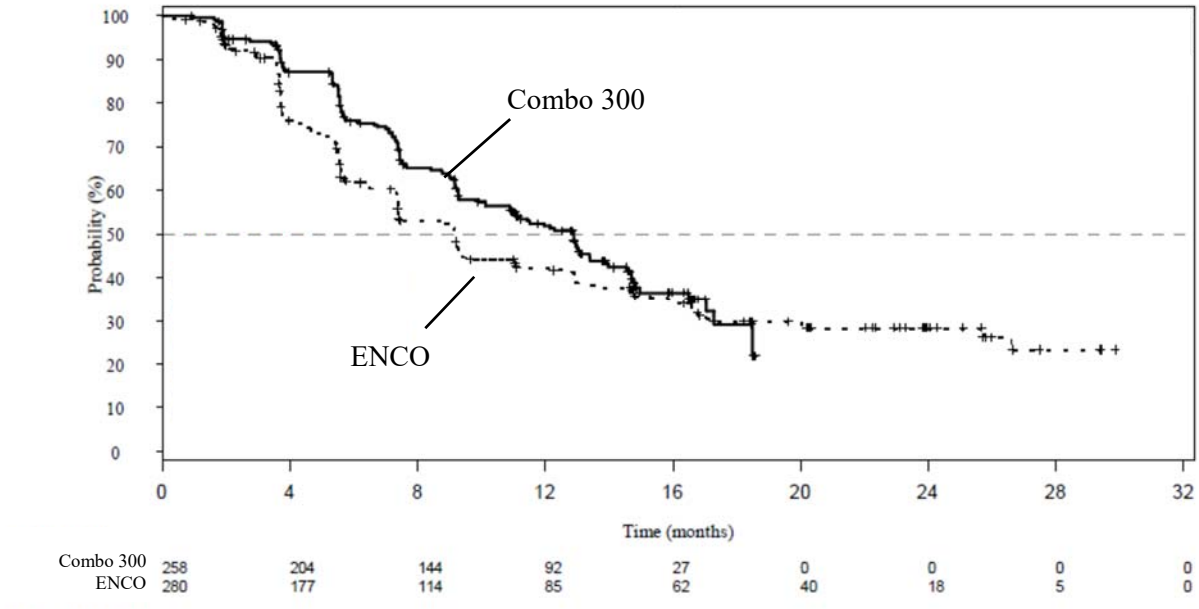

Figure 7. Kaplan-Meier curves of PFS at interim analysis (central assessment, Combo 300 group and ENCO group [combined part 1 and part 2], data cut-off November 9 2016)

The above results show a tendency of greater PFS prolongation in the Combo 300 group compared with the ENCO group. Since the dosage regimen of ENCO 300 mg QD is common to both groups, the above results demonstrate the clinical significance of concomitant use of ENCO and BINI.

The efficacy cannot be expected with BINI monotherapy in patients with unresectable malignant melanoma with BRAF V600 mutation, given the response rate in the foreign phase II study (X2201) [see Section 7.1.4.5], etc.

PMDA's view:
The efficacy of ENCO/BINI has been demonstrated in patients with unresectable malignant melanoma with BRAF V600 mutation, for the following reasons below. However, it is difficult to conclude the efficacy of ENCO monotherapy because results of an exploratory study are the only data available. As for BINI monotherapy, there are no data supporting efficacy.

- Study B2301 demonstrated the superiority of the Combo 450 group to the VEM group in the primary endpoint, i.e., PFS by central assessment, and the achieved PFS prolongation was clinically significant.
- Study B2301 suggested a tendency of greater OS prolongation in the Combo 450 group compared with the VEM group.
- Because of the limited number of Japanese patients investigated in Study B2301, there are limitations to the evaluation of efficacy of ENCO/BINI in Japanese patients based on the results obtained from the Japanese subpopulation in Study B2301. However, there was no clear tendency of difference in results in the Japanese subpopulation compared with those in the entire population.

7.R.3 Safety (for adverse events, see Section "7.2 Adverse events etc. observed in clinical studies")

PMDA's conclusion made after the review in the following subsections:

Adverse events requiring particular attention in treatment with ENCO/BINI in patients with unresectable malignant melanoma with BRAF V600 mutation are eye disorders, cardiac dysfunction, hepatic dysfunction, rhabdomyolysis, cutaneous malignancies, hypertension, haemorrhage, and palmar-plantar erythrodysaesthesia syndrome. Attention should be paid to these adverse events in using ENCO/BINI.

In addition, although attention should be paid to the above mentioned adverse events during treatment, ENCO/BINI is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring and controlling of adverse events; and interruption, dose reduction, or discontinuation of ENCO/BINI.

7.R.3.1 Safety profile and difference between Japanese and non-Japanese patients

The applicant's explanation about the safety profile of ENCO/BINI based on the safety information obtained from Study B2301:

Table 52 shows the outline of safety in Study B2301.

Table 52. Outline of safety (Study B2301)

	Number of patients (%)	
	Combo 450 (n = 192)	VEM (n = 186)
All adverse events	189 (98.4)	185 (99.5)
Grade ≥3 adverse events	111 (57.8)	118 (63.4)
Adverse events leading to death	9 (4.7)	6 (3.2)
Serious adverse events	66 (34.4)	69 (37.1)
Adverse events leading to treatment discontinuation	24 (12.5)	31 (16.7)
Adverse events leading to treatment interruption	88 (45.8)	98 (52.7)
Adverse events leading to dose reduction	22 (11.5)	42 (22.6)

In Study B2301, all adverse events with a ≥10% higher incidence in the Combo 450 group than in the VEM group were vomiting (57 patients [29.7%] in the Combo 450 group, 28 patients [15.1%] in the VEM group), blood CK increased (44 [22.9%], 4 [2.2%]), constipation (42 [21.9%], 12 [6.5%]), abdominal pain (32 [16.7%], 12 [6.5%]), and vision blurred (30 [15.6%], 4 [2.2%]). Grade ≥3 adverse events with a ≥2% higher incidence in the Combo 450 group than in the VEM group were γ-GTP increased (18 [9.4%), 6 [3.2%]), blood CK increased (13 [6.8%], 0), hypertension (11 [5.7%], 6 [3.2%]), ALT increased (10 [5.2%], 3 [1.6%]), anaemia (8 [4.2%], 4 [2.2%]), pyrexia (7 [3.6%], 0), abdominal pain (5 [2.6%], 1 [0.5%]), and hyperglycaemia (4 [2.1%], 0). The serious adverse event with a ≥2% higher incidence in the Combo 450 group than in the VEM group was pyrexia (6 [3.1%], 2 [1.1%]). Adverse events leading to treatment interruption with a ≥2% higher incidence in the Combo 450 group than in the VEM group were vomiting (13 [6.8%], 4 [2.2%]), ejection fraction decreased (10 [5.2%], 0), γ-GTP increased (9 [4.7%], 0), ALT increased (7 [3.6%], 2 [1.1%]), aspartate aminotransferase (AST) increased (6 [3.1%], 2 [1.1%]), blood CK increased (6 [3.1%], 1 [0.5%]), abdominal pain (5 [2.6%], 1 [0.5%]), and blood alkaline phosphatase increased (4 [2.1%], 0). The adverse event leading to dose reduction with a ≥2% higher incidence in the Combo 450 group than in the VEM group was retinal detachment (4 [2.1%], 0). There were no adverse events leading to death or treatment discontinuation that occurred with a ≥2% higher incidence in the Combo 450 group than in the VEM group.

The applicant's explanation about the difference in the safety of ENCO/BINI between Japanese and non-Japanese populations, based on the pooled data (10 Japanese patients, 439 non-Japanese patients)

of the Combo 450 group (3 Japanese patients, 189 non-Japanese patients) and the Combo 300 group (7 Japanese patients, 250 non-Japanese patients):
Table 53 shows the outline of safety in Japanese and non-Japanese populations in Study B2301.

Table 53. Outline of safety in Japanese and non-Japanese populations (Study B2301)

	Number of patients (%)	
	Japanese population (Combo 450 and Combo 300) n = 10	Non-Japanese population (Combo 450 and Combo 300) n = 439
All adverse events	10 (100)	431 (98.2)
Grade ≥3 adverse events	4 (40.0)	227 (51.7)
Adverse events leading to death	0	21 (4.8)
Serious adverse events	3 (30.0)	138 (31.4)
Adverse events leading to treatment discontinuation	2 (20.0)	54 (12.3)
Adverse events leading to treatment interruption	6 (60.0)	191 (43.5)
Adverse events leading to dose reduction	1 (10.0)	52 (11.8)

All-Grade adverse events reported by ≥2 Japanese patients were blood CK increased (6 Japanese patients [60.0%], 89 non-Japanese patients [20.3%]), retinal detachment (4 [40.0%], 30 [6.8%]), malaise (4 [40.0%], 7 [1.6%]), pyrexia (3 [30.0%], 75 [17.1%]), anaemia (3 [30.0%], 50 [11.4%]), seasonal allergy (3 [30.0%], 1 [0.2%]), neutropenia (2 [20.0%], 10 [2.3%]), diarrhoea (2 [20%], 141 [32.1%]), nasopharyngitis (2 [20%], 41 [9.3%]), and arthropod bite (2 [20%], 2 [0.5%]). Grade ≥3 adverse events reported by ≥1 Japanese patient were blood CK increased (1 [10%], 26 [5.9%]), anaemia (1 [10%], 14 [3.2%]), uveitis (1 [10%], 4 [0.9%]), and neutropenia (1 [10%], 2 [0.5%]). Serious adverse events reported by ≥1 Japanese patient were anaemia (1 [10%], 7 [1.6%]), uveitis (1 [10%], 2 [0.5%]), and facial nerve disorder (1 [10%], 0). Adverse events leading to treatment discontinuation reported by ≥1 Japanese patient were uveitis (1 [10.0%], 2 [0.5%]) and neutropenia (1 [10.0%], 0). Adverse events leading to treatment interruption reported by ≥1 Japanese patient were blood CK increased (2 [20.0%], 11 [2.5%]), retinal detachment (2 [20.0%], 9 [2.1%]), anaemia (1 [10.0%], 6 [1.4%]), myalgia (1 [10.0%], 4 [0.9%]), neutropenia (1 [10.0%], 0), neuropathy peripheral (1 [10.0%], 0), facial nerve disorder (1 [10.0%], 0), and alopecia (1 [10.0%], 0). The adverse event leading to dose reduction reported by ≥1 Japanese patient was retinal detachment (1 [10.0%], 4 [0.9%]). There was no adverse event leading to death reported in Japanese patient.

PMDA's view:
In Study B2301, there were Grade ≥3 adverse events with a higher incidence in the Combo 450 group than in the VEM group, but they could be managed by treatment interruption, dose reduction, etc. of ENCO or BINI. Taking account of the above, ENCO/BINI is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring and controlling of adverse events; and interruption, dose reduction of ENCO/BINI. Particular caution is required with ENCO/BINI against the events that occurred with a higher incidence in the Combo 450 group than in the VEM group in Study B2301. Information on the incidences of these events should be provided appropriately to healthcare professionals using the package insert, etc., to raise cautions.

There are limitations to discussing difference in the safety between Japanese and non-Japanese patients based on the results of Study B2301 due to the very limited number (10) of Japanese patients who

received ENCO/BINI. However, since there were no clear differences in the incidence of Grade ≥3 or serious adverse events between Japanese and non-Japanese patients, and there are no adverse events specific to Japanese patients, it is considered that there are no clear difference between Japanese and non-Japanese in the safety profile of ENCO/BINI at present. However, because of the limited information available on the safety in Japanese patients, relevant information should be continuously collected after the market launch of ENCO and BINI, and once available, new information should be provided appropriately to healthcare professionals.

In the following sections, PMDA reviewed the safety of ENCO/BINI based mainly on the safety results in Study B2301, focusing on the adverse events observed more frequently in the Combo 450 group than in the VEM group and the adverse events for which caution is required in administering DAB, the approved BRAF inhibitor, and TRA, the MEK inhibitor.

7.R.3.2 Eye disorders

The applicant's explanation about eye disorders associated with ENCO/BINI:
Events classified as "eye disorders" in MedDRA system organ class (SOC) were tabulated as eye disorders.

Table 54 shows the incidences of eye disorders in Study B2301.

Table 54. Incidences of eye disorders with an incidence of ≥2% of patients in either group (Study B2301)

PT (MedDRA ver. 19.0)	Number of patients (%)			
	Combo 450 (n = 192)		VEM (n = 186)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Eye disorder	104 (54.2)	5 (2.6)	62 (33.3)	1 (0.5)
Vision blurred	30 (15.6)	0	4 (2.2)	0
Retinal detachment	15 (7.8)	1 (0.5)	1 (0.5)	0
Cataract	12 (6.3)	0	4 (2.2)	1 (0.5)
Dry eye	11 (5.7)	0	12 (6.5)	0
Macular oedema	11 (5.7)	1 (0.5)	1 (0.5)	0
Photophobia	7 (3.6)	0	3 (1.6)	0
Subretinal fluid	7 (3.6)	0	0	0
Blepharitis	6 (3.1)	0	9 (4.8)	0
Eye disorder	6 (3.1)	0	0	0
Visual impairment	6 (3.1)	0	2 (1.1)	0
Uveitis	5 (2.6)	0	3 (1.6)	0
Chorioretinopathy	5 (2.6)	2 (1.0)	0	0
Iridocyclitis	4 (2.1)	1 (0.5)	3 (1.6)	0
Retinal disorder	4 (2.1)	0	0	0
Retinopathy	4 (2.1)	0	0	0
Visual acuity reduced	4 (2.1)	0	3 (1.6)	0
Keratitis	1 (0.5)	0	7 (3.8)	0
Episcleritis	0	0	4 (2.2)	0
Conjunctival hyperaemia	0	0	4 (2.2)	0

In Study B2301, there were no eye disorders leading to death. Serious eye disorders were observed in 2 of 192 patients (1.0%; retinal detachment and chorioretinopathy in 1 patient each) in the Combo 450 group and in 1 of 186 patients (0.5%; visual acuity reduced in 1 patient) in the VEM group. A causal relationship to the study drug could not be ruled out for retinal detachment and chorioretinopathy in 1 patient each in the Combo 450 group and for visual acuity reduced in 1 patient in the VEM group. Eye disorders leading to discontinuation of the study drug were not observed in the Combo 450 group but observed in 4 of 186 patients in the VEM group (2.2%; conjunctival irritation, keratitis, macular

degeneration, retinal haemorrhage, vision blurred, and corneal leukoma in 1 patient each [including duplicate counting]). Eye disorders leading to interruption of the study drug were observed in 16 of 192 patients in the Combo 450 group (8.3%; iridocyclitis and uveitis in 3 patients each, macular oedema, retinal detachment, visual acuity reduced, and chorioretinopathy in 2 patients each, blindness, chromatopsia, iritis, retinal disorder, retinopathy, visual impairment, and metamorphopsia in 1 patient each [including duplicate counting]) and in 7 of 186 patients in the VEM group (3.8%; uveitis in 3 patients, dry eye, iritis, macular oedema, retinal detachment, vitreous floaters, and autoimmune uveitis in 1 patient each [including duplicate counting]). Eye disorders leading to dose reduction of the study drug were observed in 6 of 192 patients in the Combo 450 group (3.1%; retinal detachment in 4 patients, iritis and chorioretinopathy in 1 patient each), but not in the VEM group.

In the Combo 450 group of Study B2301, the median time (range) to the first onset of eye disorder was 110.0 (1-623) days.

Table 55 shows the details of patients who had serious eye disorder associated with ENCO monotherapy or ENCO/BINI therapy in Study B2301.

Table 55. Patients who had serious eye disorder (Study B2301)

Treatment group	Age	Sex	Race	PT (MedDRA ver. 19.0)	Grade	Time of onset (day of administration)	Causal relationship to study drug	Duration (days)	Outcome
Combo 450	[redacted]	Male	[redacted]	Retinal detachment	2	1	Yes	85	Resolved
	[redacted]	Male	[redacted]	Chorio-retinopathy	3	1	Yes	3	Resolved
Combo 300	[redacted]	Male	[redacted]	Glaucoma	3	58	Yes	14	Resolved
		Female		Uveitis	3	84	Yes	101	Resolved
		Female		Uveitis	3	156	Yes	181	Resolving
	[redacted]	Male	[redacted]	Retinal detachment	4	335	No	21	Not resolved
	[redacted]	Male	[redacted]	Retinal vein occlusion	2	67	Yes	35	Not resolved
	[redacted]	Female	[redacted]	Uveitis	4	173	Yes	58	Resolving
ENCO	[redacted]	Male	[redacted]	Normal tension glaucoma	2	114	Yes	2	Resolved
	[redacted]	Male	[redacted]	Retinal artery occlusion	3	276	No	4	Resolved

PMDA's view:

Attention should be paid to occurrences of eye disorders associated with ENCO/BINI, in light of the observations in Study B2301 that the incidence of eye disorders was higher in the Combo 450 group than in the VEM group and that a causal relationship to ENCO/BINI therapy or to ENCO monotherapy could not be ruled out for some of the serious eye disorders observed. Incidences of eye disorders in clinical studies and measures that should be taken in case of onset should be communicated appropriately to healthcare professionals using the package insert, etc., to raise cautions.

7.R.3.3 Cardiac disorders (other than QT/QTc interval prolongation)

The applicant's explanation about cardiac disorders (other than QT/QTc interval prolongation) associated with ENCO/BINI:

Events classified as "cardiac failure (broad)" in standard MedDRA queries (SMQ) were tabulated as cardiac disorders.

Table 56 shows the incidences of cardiac disorders in Study B2301.

Table 56. Incidences of cardiac disorders (Study B2301)

PT (MedDRA ver. 19.0)	Number of patients (%)			
	Combo 450 (n = 192)		VEM (n = 186)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac disorder	39 (20.3)	5 (2.6)	29 (15.6)	2 (1.1)
Oedema peripheral	20 (10.4)	2 (1.0)	20 (10.8)	1 (0.5)
Ejection fraction decreased	11 (5.7)	2 (1.0)	1 (0.5)	0
Diastolic dysfunction	4 (2.1)	0	0	0
Peripheral swelling	3 (1.6)	0	7 (3.8)	1 (0.5)
Left ventricular dysfunction	2 (1.0)	0	0	0
Cardiac failure	2 (1.0)	1 (0.5)	0	0
Oedema	1 (0.5)	0	0	0

In Study B2301, there were no cardiac disorders leading to death. Serious cardiac disorders were not observed in the Combo 450 group but observed in 2 of 186 patients in the VEM group (1.1%; left ventricular failure and oedema peripheral in 1 patient each). Their causal relationship to the study drug was denied. There were no cardiac disorders leading to discontinuation of the study drug. Cardiac disorders leading to interruption of the study drug were observed in 14 of 192 patients in the Combo 450 group (7.3%; ejection fraction decreased in 10 patients, left ventricular dysfunction in 2 patients, oedema peripheral and diastolic dysfunction in 1 patient each), and in 2 of 186 patients in the VEM group (1.1%; left ventricular failure and oedema peripheral in 1 patient each). There were no cardiac disorders leading to dose reduction of the study drug.

In the Combo 450 group of Study B2301, the median time (range) to the first onset of cardiac disorder was 85.0 (1-648) days.

Table 57 shows the outline of the incidences of cardiac disorders in Study A2301.

Table 57. Outline of the incidences of cardiac disorders (Study A2301)

	Number of patients (%)	
	BINI (n = 269)	DTIC (n = 114)
All adverse events	131 (48.7)	6 (5.3)
Grade ≥3 adverse events	15 (5.6)	1 (0.9)
Adverse events leading to death	0	0
Serious adverse events	2 (0.7)	0
Adverse events leading to treatment discontinuation	13 (4.8)	0
Adverse events leading to treatment interruption	33 (12.3)	0
Adverse events leading to dose reduction	1 (0.4)	0

PMDA's view:

Attention should be paid to occurrences of cardiac disorders associated with ENCO/BINI, in light of the observations that the incidence of cardiac disorders tended to be higher in the Combo 450 group than in the VEM group in Study B2301, that cardiac disorders leading to treatment interruption were observed more frequently in the Combo 450 group in Study B2301, and that the incidence of cardiac disorders was higher in the BINI group than in DTIC group in Study A2301. Also, particular attention should be

paid to the occurrences of cardiac dysfunction, taking account of the frequent occurrences of cardiac dysfunction such as ejection fraction decreased among cardiac disorders observed in Study B2301. Cardiac function test should be performed as appropriate. Also, incidences of cardiac disorders in clinical studies and measures that should be taken in case of the onset should be communicated appropriately to healthcare professionals using the package insert, etc., to raise cautions.

7.R.3.4 Hepatic dysfunction

The applicant's explanation about hepatic dysfunction associated with ENCO/BINI administration:
Events classified as "liver related investigations, signs and symptoms," "cholestasis and jaundice of hepatic origin," "hepatitis, non-infectious," and "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions" in MedDRA SMQ were tabulated as hepatic dysfunction.

Table 58 shows the incidences of hepatic dysfunction in Study B2301.

Table 58. Incidences of hepatic dysfunction (Study B2301)

PT (MedDRA ver. 19.0)	Number of patients			
	Combo 450 (n = 192)		VEM (n = 186)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic dysfunction	50 (26.0)	31 (16.1)	43 (23.1)	9 (4.8)
γ-GTP increased	29 (15.1)	18 (9.4)	21 (11.3)	6 (3.2)
ALT increased	21 (10.9)	10 (5.2)	14 (7.5)	3 (1.6)
AST increased	16 (8.3)	4 (2.1)	15 (8.1)	3 (1.6)
Blood bilirubin increased	2 (1.0)	0	14 (7.5)	0
Cholestasis	2 (1.0)	2 (1.0)	0	0
Transaminases increased	2 (1.0)	1 (0.5)	1 (0.5)	0
Bilirubin conjugated increased	1 (0.5)	0	0	0
Hepatic failure	1 (0.5)	1 (0.5)	0	0
Hepatic function abnormal	1 (0.5)	0	0	0
Hepatocellular injury	1 (0.5)	0	2 (1.1)	0
Hepatotoxicity	1 (0.5)	0	2 (1.1)	2 (1.1)
Jaundice	1 (0.5)	1 (0.5)	0	0
Hepatic enzyme increased	1 (0.5)	1 (0.5)	4 (2.2)	1 (0.5)
Hypertransaminasaemia	1 (0.5)	0	0	0

In Study B2301, hepatic dysfunction leading to death was not observed in the Combo 450 group, but observed in 1 of 186 patients in the VEM group (0.5%; ascites in 1 patient). A causal relationship of the ascites to the study drug was denied. Serious hepatic dysfunction was observed in 1 of 192 patients in the Combo 450 group (0.5%; jaundice in 1 patient) and in 4 of 186 in the VEM group (2.2%; ascites, γ-GTP increased, hepatotoxicity, and hepatic enzyme increased in 1 patient each). A causal relationship to the study drug could not be ruled out for γ-GTP increased, hepatotoxicity, and hepatic enzyme increased in 1 patient each in the VEM group. Hepatic dysfunctions leading to discontinuation of the study drug were observed in 5 of 192 patients in the Combo 450 group (2.6%; ALT increased and AST increased in 5 patients each, and γ-GTP increased in 2 patients [including duplicate counting]) and in 5 of 186 patients in the VEM group (2.7%; γ-GTP increased in 3 patients, AST increased, ALT increased, and hepatotoxicity in 2 patients each, blood bilirubin increased, ascites, and hepatic enzyme increased in 1 patient each [including duplicate counting]). Hepatic disorder leading to interruption of the study drug was observed in 17 of 192 patients in the Combo 450 group (8.9%; γ-GTP increased in 9 patients, ALT increased in 7 patients, AST increased in 6 patients, bilirubin conjugated increased, blood bilirubin increased, cholestasis, hepatotoxicity, and hepatic enzyme increased in 1 patient each [including duplicate counting]) and in 3 of 186 patients in the VEM group (1.6%; AST increased and ALT increased

in 2 patients each, hepatotoxicity in 1 patient [including duplicate counting]). Hepatic dysfunctions leading to dose reduction of the study drug were observed in 1 of 192 patients in the Combo 450 group (0.5%; γ-GTP increased in 1 patient) and in 4 of 186 patients in the VEM group (2.2%; ALT increased and γ-GTP increased in 2 patients each, AST increased and hepatic enzyme increased in 1 patient each [including duplicate counting]).

In the Combo 450 group of Study B2301, the median time (range) to the first onset of hepatic dysfunction was 57.0 (1-534) days.

In any of the clinical studies administering ENCO/BINI, there were no hepatic dysfunctions with laboratory values that met Hy's law (defined in accordance with the Guidance for industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009).

Table 59 shows the details of patients who had serious hepatic dysfunction associated with ENCO/BINI therapy or ENCO or BINI monotherapy in Study B2301 or Study A2301.

Table 59. List of patients who had hepatic dysfunction that was serious or led to death (Studies B2301 and A2301)

Study	Treatment group	Age	Sex	PT (MedDRA ver. 19.0)	Grade	Time of onset (day of administration)	Causal relationship to study drug	Outcome
B2301	Combo 450	[redacted]	Male	Jaundice	3	268	No	Not resolved
	Combo 300	[redacted]	Female	γ-GTP increased	3	58	Yes	Resolved
		[redacted]	Male	Ascites	3	235	No	Resolving
		[redacted]	Female	Ascites	4	165	No	Unknown
	ENCO	[redacted]	Male	γ-GTP increased	3	29	Yes	Resolved
A2301	BINI	[redacted]	Male	Ascites	3	14	No	Not resolved
		[redacted]	Male	AST increased	3	48	Yes	Resolved
				ALT increased	3	48	Yes	Resolving
		[redacted]	Male	Hepatic failure	4	23	Yes	Death

PMDA's view:
Study B2301 showed that hepatic dysfunction occurred with a certain incidence in the Combo 450 group, and that the incidence of Grade ≥3 hepatic dysfunction was higher in the Combo 450 group than in the VEM group. Also, Study A2301 revealed hepatic failure leading to death for which a causal relationship to the study drug could not be ruled out. These results require caution against occurrences of hepatic dysfunction in administering ENCO/BINI. Liver function test should be performed periodically and incidence of hepatic dysfunction in clinical studies and measures that should be taken in case of onset should be communicated appropriately to healthcare professionals using the package insert, etc., to raise cautions.

7.R.3.5 Myositis/rhabdomyolysis (including blood CK increased)

The applicant's explanation about myositis/rhabdomyolysis (including blood CK increased) associated with ENCO/BINI:
Events classified as "rhabdomyolysis/myopathy (broad)" in MedDRA SMQ were tabulated as myositis/rhabdomyolysis.

Table 60 shows the incidences of myositis/rhabdomyolysis in Study B2301.

Table 60. Incidences of myositis/rhabdomyolysis (Study B2301)

PT (MedDRA ver. 19.0)	Number of patients (%)			
	Combo 450 (n = 192)		VEM (n = 186)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Myositis/rhabdomyolysis	81 (42.2)	18 (9.4)	63 (33.9)	7 (3.8)
Blood CK increased	44 (22.9)	13 (6.8)	4 (2.2)	0
Myalgia	26 (13.5)	0	34 (18.3)	1 (0.5)
Blood creatinine increased	12 (6.3)	2 (1.0)	11 (5.9)	1 (0.5)
Musculoskeletal pain	11 (5.7)	0	11 (5.9)	2 (1.1)
Muscular weakness	6 (3.1)	0	4 (2.2)	0
Renal failure	3 (1.6)	2 (1.0)	6 (3.2)	1 (0.5)
Acute kidney injury	3 (1.6)	2 (1.0)	2 (1.1)	1 (0.5)
Chromaturia	2 (1.0)	0	0	0
Myoglobin blood increased	2 (1.0)	0	0	0
Muscle rupture	1 (0.5)	0	0	0
Myositis	1 (0.5)	0	0	0
Rhabdomyolysis	1 (0.5)	1 (0.5)	0	0
Musculoskeletal discomfort	1 (0.5)	0	0	0
Renal impairment	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)

In Study B2301, myositis/rhabdomyolysis leading to death was not observed in the Combo 450 group but observed in 1 of 186 patients in the VEM group (0.5%; renal failure in 1 patient). Its causal relationship to the study drug was denied. Serious myositis/rhabdomyolysis was observed in 7 of 192 patients in the Combo 450 group (3.6%; acute kidney injury in 3 patients, blood creatinine increased, myositis, renal failure, rhabdomyolysis, and renal impairment in 1 patient each [including duplicate counting]) and in 4 of 186 patients in the VEM group (2.2%; musculoskeletal pain, renal failure, renal impairment, and acute kidney injury in 1 patient each). A causal relationship to the study drug could not be ruled out for acute kidney injury, rhabdomyolysis, renal failure, and myositis in 1 patient each (including duplicate counting) in the Combo 450 group and for acute kidney injury in 1 patient in the VEM group. Myositis/rhabdomyolysis leading to discontinuation of the study drug were observed in 4 of 192 patients in the Combo 450 group (2.1%; blood creatinine increased in 2 patients, blood CK increased and rhabdomyolysis in 1 patient each) and in 2 of 186 patients in the VEM group (1.1%; myalgia and acute kidney injury in 1 patient each). Myositis/rhabdomyolysis leading to interruption of the study drug were observed in 15 of 192 patients in the Combo 450 group (7.8%; blood CK increased in 6 patients, blood creatinine increased in 4 patients, renal failure and acute kidney injury in 2 patients each, myalgia and myositis in 1 patient each [including duplicate counting]) and in 10 of 186 patients in the VEM group (5.4%; blood creatinine increased in 4 patients, musculoskeletal pain and acute kidney injury in 2 patients each, blood CK increased, muscular weakness, myalgia, and chronic kidney disease in 1 patient each [including duplicate counting]). Myositis/rhabdomyolysis leading to dose reduction of the study drug was not observed in the Combo 450 group, but observed in 4 of 186 patients in the VEM group (2.2%; myalgia and renal failure in 2 patients each).

In the Combo 450 group of Study B2301, the median time (range) to the first onset of myositis/rhabdomyolysis was 141.5 (2-786) days.

Table 61 shows the details of patients who had serious myositis/rhabdomyolysis associated with ENCO/BINI in the Combo 450 group of Study B2301.

Table 61. List of patients who had serious myositis/rhabdomyolysis (Study B2301)

Age	Sex	PT (MedDRA ver. 19.0)	Grade	Time of onset (day of administration)	Causal relation to study drug	Outcome
[redacted]	Male	Acute kidney injury (accompanied by rhabdomyolysis)	4	11	Yes	Resolved
		Rhabdomyolysis (accompanied by CK increased)	3	30	Yes	Resolved
[redacted]	Female	Acute kidney injury	2	189	No	Resolved
[redacted]	Male	Renal impairment	3	163	No	Not resolved
[redacted]	Female	Renal failure	3	10	Yes	Resolved
[redacted]	Male	Blood creatinine increased	2	29	No	Resolved
[redacted]	Male	Myositis (accompanied by CK increased)	2	424	Yes	Resolved
[redacted]	Male	Acute kidney injury	3	391	No	Resolved

Table 62 shows the outline of incidences of myositis/rhabdomyolysis in Study A2301.

Table 62. Outline of incidences of myositis/rhabdomyolysis (Study A2301)

	Number of patients (%)	
	BINI (n = 269)	DTIC (n = 114)
All adverse events	131 (48.7)	10 (8.8)
Grade ≥3 adverse events	58 (21.6)	2 (1.8)
Adverse events leading to death	2 (0.7)	0
Serious adverse events	8 (3.0)	0
Adverse events leading to treatment discontinuation	9 (3.3)	0
Adverse events leading to treatment interruption	53 (19.7)	0
Adverse events leading to dose reduction	11 (4.1)	0

PMDA's view:

Results of Study B2301 showed the following findings: (1) Although CK increased was confirmed only in 2 patients among those with serious myositis/rhabdomyolysis for which a causal relationship to ENCO/BINI could not be ruled out, the incidence of myositis/rhabdomyolysis was higher in the Combo 450 group than in the VEM group, and (2) the incidence of blood CK increased was higher in the Combo 450 group than in the VEM group and, particularly, the incidence was higher in Japanese patients than non-Japanese patients [see Section 7.R.3.1]. Also, results of Study A2301 revealed a higher incidence of myositis/rhabdomyolysis in the BINI group than in the DTIC group. These results require caution against occurrences of myositis/rhabdomyolysis in administering ENCO/BINI. Rhabdomyolysis accompanied by serious acute renal failure was observed among patients who had serious myositis/rhabdomyolysis for which a causal relationship to ENCO/BINI could not be ruled out. These results require particular caution against the occurrence of rhabdomyolysis. Therefore, CK level should be monitored periodically, and incidence of rhabdomyolysis in clinical studies and measures that should be taken in case of onset should be communicated appropriately to healthcare professionals using the package insert, etc., to raise cautions.

7.R.3.6 Secondary malignancies

The applicant's explanation about secondary malignancies associated with ENCO/BINI:

Events classified as "malignant tumor" in MedDRA SMQ were tabulated as secondary malignancies.

Table 63 shows the incidences of secondary malignancies in Study B2301.

Table 63. Incidences of secondary malignancies (Study B2301)

PT (MedDRA ver. 19.0)	Number of patients (%)			
	Combo 450 (n = 192)		VEM (n = 186)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Secondary malignancies	13 (6.8)	4 (2.1)	45 (24.2)	22 (11.8)
Keratoacanthoma	4 (2.1)	0	21 (11.3)	6 (3.2)
Metastases to central nervous system	3 (1.6)	1 (0.5)	2 (1.1)	2 (1.1)
Basal cell carcinoma	3 (1.6)	0	3 (1.6)	1 (0.5)
Metastases to bone	1 (0.5)	1 (0.5)	0	0
Rectal adenocarcinoma	1 (0.5)	1 (0.5)	0	0
Squamous cell carcinoma	1 (0.5)	0	12 (6.5)	8 (4.3)
Metastases to meninges	1 (0.5)	1 (0.5)	1 (0.5)	0
Malignant melanoma	0	0	4 (2.2)	2 (1.1)
Metastatic malignant melanoma	0	0	3 (1.6)	3 (1.6)
Bowen's disease	0	0	1 (0.5)	1 (0.5)
Malignant melanoma in situ	0	0	1 (0.5)	1 (0.5)
Metastases to adrenals	0	0	1 (0.5)	1 (0.5)
Transitional cell carcinoma	0	0	1 (0.5)	1 (0.5)
Dermatofibrosarcoma protuberans	0	0	1 (0.5)	1 (0.5)
Metastasis	0	0	1 (0.5)	1 (0.5)
Paget's disease of nipple	0	0	1 (0.5)	0
Squamous cell carcinoma of skin	0	0	1 (0.5)	0
Lip squamous cell carcinoma	0	0	1 (0.5)	1 (0.5)

In Study B2301, secondary malignancies leading to death were not observed in the VEM group, but observed in 1 of 192 patients in the Combo 450 group (0.5%; metastases to meninges in 1 patient). A causal relationship of this event to the study drug was denied. Serious secondary malignancies were observed in 4 of 192 patients in the Combo 450 group (2.1%; metastases to bone, rectal adenocarcinoma, metastases to meninges, and metastases to central nervous system in 1 patient each) and in 11 of 186 patients in the VEM group (5.9%; metastatic malignant melanoma, squamous cell carcinoma, and metastases to central nervous system in 2 patients each and malignant melanoma in situ, metastases to adrenals, transitional cell carcinoma, metastases to meninges, dermatofibrosarcoma protuberans, and metastasis in 1 patient each). A causal relationship to the study drug could not be ruled out for squamous cell carcinoma in 2 patients, malignant melanoma in situ, and transitional cell carcinoma in 1 patient each in the VEM group. Secondary malignancies leading to discontinuation of the study drug were observed in 2 of 192 patients in the Combo 450 group (1.0%; metastases to meninges and metastases to central nervous system in 1 patient each) and in 1 of 186 patients in the VEM group (0.5%; transitional cell carcinoma in 1 patient). Secondary malignancies leading to interruption of the study drug were observed in 3 of 192 patients in the Combo 450 group (1.6%; basal cell carcinoma, metastases to bone, and rectal adenocarcinoma in 1 patient each), and in 2 of 186 patients in the VEM group (1.1%; metastatic malignant melanoma and metastases to central nervous system in 1 patient each). There were no secondary malignancies leading to dose reduction of the study drug.

In the Combo 450 group of Study B2301, the median time (range) to the first onset of secondary malignancies was 166.5 (30-638) days.

Table 64 shows the details of patients who had serious secondary malignancies associated with ENCO monotherapy or ENCO/BINI therapy in Study B2301.

Table 64. List of patients who had serious or fatal secondary malignancies (Study B2301)

Treatment group	Age	Sex	PT (MedDRA ver. 19.0)	Grade	Time of onset (day of administration)	Causal relationship to study drug	Outcome
Combo 450	[redacted]	Male	Metastases to bone	3	163	No	Not resolved
	[redacted]	Female	Metastases to meninges	4	97	No	Death
	[redacted]	Male	Metastases to central nervous system	3	107	No	Not resolved
	[redacted]	Male	Rectal adenocarcinoma	3	359	No	Resolved
Combo 300	[redacted]	Male	Metastases to central nervous system	4	365	No	Not resolved
	[redacted]	Male	Plasma cell myeloma	3	458	Yes	Not resolved
	[redacted]	Male	Metastases to spine	3	179	No	Not resolved
	[redacted]	Male	Metastases to bladder	3	80	No	Resolved
	[redacted]	Male	Metastases to central nervous system	3	218	No	Not resolved
	[redacted]	Male	Metastases to central nervous system	4	71	No	Death
ENCO	[redacted]	Male	Superficial spreading melanoma	4	100	Yes	Resolved
			Metastases to meninges	4	127	No	Death
	[redacted]	Male	Malignant melanoma in situ	3	85	Yes	Resolved
	[redacted]	Male	Basal cell carcinoma	3	112	Yes	Resolved
			Basal cell carcinoma	3	112	Yes	Resolved
			Basal cell carcinoma	3	112	Yes	Resolved
			Basal cell carcinoma	3	112	Yes	Resolved
	[redacted]	Female	Metastases to central nervous system	4	194	No	Death
	[redacted]	Male	Malignant melanoma	1	16	Yes	Resolved
	[redacted]	Male	Malignant melanoma	4	57	Yes	Resolved
	[redacted]	Male	Metastases to bone	3	209	No	Resolved
	[redacted]	Male	Metastases to central nervous system	4	227	No	Death
	[redacted]	Female	Metastases to central nervous system	4	269	No	Death
	[redacted]	Female	Superficial spreading melanoma	3	217	Yes	Resolved
	[redacted]	Male	Metastases to central nervous system	3	304	No	Resolved

PMDA's view:

In Study B2301, serious secondary malignancies were observed in the Combo 450 group, albeit at a lower incidence than in the VEM group, requiring caution against secondary malignancies in administering ENCO/BINI. Particular attention should be paid to secondary cutaneous malignancies, because of their occurrences at a high frequency among patients who experienced serious secondary malignancies for which a causal relationship to ENCO monotherapy or ENCO/BINI therapy could not be ruled out. In addition to the information on the incidences of these events in clinical studies, precautionary statement to monitor patient periodically and appropriate measures to be taken in case of a secondary malignancy should be provided appropriately to healthcare professionals using the package insert, etc.

7.R.3.7 Hypertension

The applicant's explanation about hypertension associated with ENCO/BINI:

Events classified as "hypertension" in MedDRA SMQ were tabulated as hypertension.

Table 65 shows the incidences of hypertension in Study B2301.

Table 65. Incidences of hypertension (Study B2301)

PT (MedDRA ver. 19.0)	Number of patients (%)			
	Combo 450 (n = 192)		VEM (n = 186)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypertension	22 (11.5)	11 (5.7)	21 (11.3)	6 (3.2)
Hypertension	21 (10.9)	11 (5.7)	21 (11.3)	6 (3.2)
Hypertensive crisis	1 (0.5)	0	0	0
Essential hypertension	1 (0.5)	0	0	0

In the Combo 450 group or in the VEM group of Study B2301, no hypertension led to death, was reported as serious, or led to treatment discontinuation. Hypertension leading to interruption of the study drug was observed in 4 of 192 patients in the Combo 450 group (2.1%; hypertension in 3 patients, hypertensive crisis in 1 patient) and 1 of 186 patients in the VEM group (0.5%; hypertension in 1 patient). Hypertension leading to dose reduction of the study drug was observed in 1 of 192 patients in the Combo 450 group (0.5%; hypertension in 1 patient) and 1 of 186 patients in the VEM group (0.5%; hypertension in 1 patient).

In the Combo 450 group of Study B2301, the median time (range) to the first onset of hypertension was 132.0 (1-509) days.

Table 66 shows the details of patients who had serious hypertension associated with ENCO/BINI therapy or with ENCO or BINI monotherapy in any of the clinical studies submitted.

Table 66. List of patients who had serious hypertension (Studies B2301, X2110, A2301, and X2201)

Study	Treatment group	Age	Sex	PT (MedDRA ver. 19.0)	Grade	Time of onset (day of administration)	Causal relationship to study drug	Outcome
B2301	Combo 300	[redacted]	Female	Hypertension	3	22	No	Resolved
		[redacted]	Male	Hypertensive encephalopathy	1	204	No	Resolved
X2110	ENCO 450 mg	[redacted]	Male	Retinopathy hypertensive	1	282	Yes	Unknown
A2301	BINI	[redacted]	Male	Hypertension	3	44	Yes	Resolved
		[redacted]	Female	Hypertensive crisis	3	17	No	Resolving
		[redacted]	Male	Hypertensive crisis	4	28	Yes	Resolved
X2201	BINI 45 mg	[redacted]	Female	Hypertensive crisis	3	5	Yes	Unknown

PMDA's view:
Although hypertension occurred in only a limited number of patients in Study B2301, the incidence of Grade ≥3 hypertension was higher in the Combo 450 group than in the VEM group, and there were cases of serious hypertension for which a causal relationship to the study drug could not be ruled out in clinical studies other than Study B2301. It is therefore necessary to pay attention to the occurrence of hypertension in administering ENCO/BINI. Incidences of hypertension in clinical studies should be communicated appropriately to healthcare professionals using the package insert, etc.

7.R.3.8 Haemorrhage

The applicant's explanation about haemorrhage associated with ENCO/BINI:
Events classified as "haemorrhage terms (excl laboratory terms)" in MedDRA SMQ were tabulated as haemorrhage.

Table 67 shows the incidences of haemorrhage in Study B2301.

Table 67. Incidences of haemorrhage (Study B2301)

PT (MedDRA ver. 19.0)	Number of patients (%)			
	Combo 450 (n = 192)		VEM (n = 186)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Haemorrhage	38 (19.8)	6 (3.1)	15 (8.1)	3 (1.6)
Rectal haemorrhage	8 (4.2)	1 (0.5)	1 (0.5)	0
Haematochezia	6 (3.1)	0	0	0
Haematuria	5 (2.6)	0	3 (1.6)	0
Cerebral haemorrhage	3 (1.6)	3 (1.6)	1 (0.5)	1 (0.5)
Epistaxis	2 (1.0)	0	4 (2.2)	1 (0.5)
Menorrhagia	2 (1.0)	0	0	0
Metrorrhagia	2 (1.0)	0	0	0
Retinal haemorrhage	2 (1.0)	0	1 (0.5)	0
Contusion	2 (1.0)	0	0	0
Haemorrhoidal haemorrhage	2 (1.0)	0	0	0
Conjunctival haemorrhage	1 (0.5)	0	0	0
Ecchymosis	1 (0.5)	0	0	0
Gastric ulcer haemorrhage	1 (0.5)	0	0	0
Gastrointestinal haemorrhage	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Gingival bleeding	1 (0.5)	0	0	0
Haematoma	1 (0.5)	0	1 (0.5)	0
Haematospermia	1 (0.5)	0	0	0
Blood urine present	1 (0.5)	0	0	0
Intracranial tumour haemorrhage	1 (0.5)	1 (0.5)	0	0
Subdural haematoma	1 (0.5)	0	0	0
Uterine haemorrhage	1 (0.5)	0	0	0
Haemorrhagic cyst	1 (0.5)	0	0	0
Vaginal haemorrhage	0	0	2 (1.1)	0
Post procedural haemorrhage	0	0	1 (0.5)	0
Wound haemorrhage	0	0	1 (0.5)	0
Postmenopausal haemorrhage	0	0	1 (0.5)	0

In Study B2301, haemorrhage leading to death did not occur in the VEM group, but was observed in 4 of 192 patients in the Combo 450 group (2.1%; cerebral haemorrhage in 3 patients, gastric ulcer haemorrhage in 1 patient). Their causal relationship to the study drug was denied. Serious haemorrhage was observed in 7 of 192 patients in the Combo 450 group (3.6%; cerebral haemorrhage in 3 patients, gastric ulcer haemorrhage, gastrointestinal haemorrhage, intracranial tumour haemorrhage, and rectal haemorrhage in 1 patient each) and in 3 of 186 patients in the VEM group (1.6%; cerebral haemorrhage, epistaxis, and gastrointestinal haemorrhage in 1 patient each). A causal relationship to the study drug could not be ruled out for gastrointestinal haemorrhage in 1 patient in the Combo 450 group. Haemorrhage leading to discontinuation of the study drug was observed in 3 of 192 patients in the Combo 450 group (1.6%; gastric ulcer haemorrhage, intracranial tumour haemorrhage, and rectal haemorrhage in 1 patient each) and in 1 of 186 patients in the VEM group (0.5%; retinal haemorrhage in 1 patient). Haemorrhage leading to interruption of the study drug was observed in 2 of 192 patients in the Combo 450 group (1.0%; rectal haemorrhage in 2 patients, gastrointestinal haemorrhage and metrorrhagia in 1 patient each [including duplicate counting]) and in 2 of 186 patients in the VEM group (1.1%; epistaxis and gastrointestinal haemorrhage in 1 patient each). There was no haemorrhage leading to dose reduction of the study drug.

In the Combo 450 group of Study B2301, the median time (range) to the first onset of haemorrhage was 157.0 (1-673) days.

Table 68 shows the details of patients who had serious haemorrhage associated with ENCO/BINI therapy or with BINI monotherapy in the Combo 450 group of Study B2301 or in the BINI group of Study A2301.

Table 68. List of patients who had serious or fatal haemorrhage (Studies B2301 and A2301)

Study	Treatment group	Age	Sex	PT (MedDRA ver. 19.0)	Grade	Time of onset (day of administration)	Causal relationship to study drug	Outcome
B2301	Combo 450	[redacted]	Male	Rectal haemorrhage	3	24	No	Resolved
		[redacted]	Male	Intracranial tumour haemorrhage	4	258	No	Not resolved
		[redacted]	Male	Gastric ulcer haemorrhage	2	14	No	Death
		[redacted]	Female	Cerebral haemorrhage	4	202	No	Death
		[redacted]	Male	Cerebral haemorrhage	3	237	No	Death
		[redacted]	Female	Gastrointestinal haemorrhage	3	22	Yes	Resolved
		[redacted]	Female	Cerebral haemorrhage	4	185	No	Death
A2301	BINI	[redacted]	Male	Haemorrhage	4	16	No	Death
		[redacted]	Male	Skin haemorrhage	3	59	No	Resolved
		[redacted]	Male	Haemoptysis	1	8	No	Resolved
		[redacted]	Female	Tumour haemorrhage	3	124	Yes	Resolving
		[redacted]	Female	Haemorrhage intracranial	3	259	No	Resolved

Table 69 shows the outline of the incidences of haemorrhage in Study A2301.

Table 69. Outline of incidences of haemorrhage (Study A2301)

	Number of patients (%)	
	BINI (n = 269)	DTIC (n = 114)
All adverse events	30 (11.2)	5 (4.4)
Grade ≥3 adverse events	4 (1.5)	2 (1.8)
Adverse events leading to death	1 (0.4)	1 (0.9)
Serious adverse events	5 (1.9)	2 (1.8)
Adverse events leading to treatment discontinuation	2 (0.7)	0
Adverse events leading to treatment interruption	2 (0.7)	2 (1.8)
Adverse events leading to dose reduction	0	0

PMDA's view:

Attention should be paid to occurrences of haemorrhage in administering ENCO/BINI, because (1) the incidence of haemorrhage was higher in the Combo 450 group than in the VEM group in Study B2301, (2) the incidence of haemorrhage was high in the BINI group of Study A2301, and (3) there were cases of serious haemorrhage for which a causal relationship to ENCO/BINI therapy or to BINI monotherapy could not be ruled out in Studies B2301 and A2301. Incidences of haemorrhage in clinical studies should be communicated appropriately to healthcare professionals using the package insert, etc., to raise cautions.

7.R.3.9 Palmar-plantar erythrodysaesthesia syndrome

The applicant's explanation about palmar-plantar erythrodysaesthesia syndrome associated with ENCO/BINI:

Events classified as "palmar-plantar erythrodysaesthesia syndrome" in MedDRA preferred term (PT) were tabulated as palmar-plantar erythrodysaesthesia syndrome.

Table 70 shows the incidences of palmar-plantar erythrodysaesthesia syndrome in Study B2301.

Table 70. Incidences of palmar-plantar erythrodysaesthesia syndrome (Study B2301)

PT (MedDRA ver. 19.0)	Number of patients (%)					
	Combo 450 (n = 192)		ENCO (n = 276)		VEM (n = 186)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Palmar-plantar erythrodysaesthesia syndrome	13 (6.8)	0	129 (46.7)	30 (10.9)	26 (14.0)	2 (1.1)

In study B2301, there was no fatal or serious palmar-plantar erythrodysaesthesia syndrome. Palmar-plantar erythrodysaesthesia syndrome leading to discontinuation of the study drug was not observed in the Combo 450 group or the VEM group, but observed in 8 of 276 patients in the ENCO group (2.9%; palmar-plantar erythrodysaesthesia syndrome in 8 patients). Palmar-plantar erythrodysaesthesia syndrome leading to interruption of the study drug was observed in 1 of 192 patients in the Combo 450 group (0.5%; palmar-plantar erythrodysaesthesia syndrome in 1 patient), 54 of 276 patients in the ENCO group (19.6%; palmar-plantar erythrodysaesthesia syndrome in 54 patients), and 2 of 186 patients in the VEM group (1.1%; palmar-plantar erythrodysaesthesia syndrome in 2 patients). Palmar-plantar erythrodysaesthesia syndrome leading to dose reduction of the study drug was not observed in the Combo 450 group, but observed in 27 of 276 patients in the ENCO group (9.8%; palmar-plantar erythrodysaesthesia syndrome in 27 patients), and in 2 of 186 patients in the VEM group (1.1%; palmar-plantar erythrodysaesthesia syndrome in 2 patients).

In the Combo 450 group and the ENCO group of Study B2301, the median time (range) to the first onset of palmar-plantar erythrodysaesthesia syndrome was 153.0 (57-438) days and 57.0 (1-870) days, respectively.

PMDA's view:
Attention should be paid to occurrence of palmar-plantar erythrodysaesthesia syndrome in administering ENCO/BINI, because (1) the syndrome occurred at a high incidence in the ENCO group of Study B2301 and (2) the syndrome was observed in the Combo 450 group at a certain level, albeit at a lower frequency than the ENCO group. Incidences of palmar-plantar erythrodysaesthesia syndrome in clinical studies should be communicated appropriately to healthcare professionals using the package insert, etc., to raise cautions.

7.R.3.10 Others

Taking account of the mechanisms of action of ENCO and BINI and of the incidences of adverse events for which caution is required in administering a BRAF inhibitor of DAB and a MEK inhibitor of TRA, PMDA asked the applicant to explain the incidences of the following adverse events which are conceivable in administering ENCO/BINI: (a) Interstitial lung disease (ILD), (b) venous thromboembolism, (c) bone marrow depression, (d) pyrexia, (e) renal impairment, and (f) QT/QTc interval prolongation.

The applicant's response:
(a) ILD:
Events classified as "interstitial lung disease (broad)" in MedDRA SMQ or as "Lung disorder" in MedDRA PT were tabulated as ILD.

Table 71 shows the incidences of ILD in Study B2301.

Table 71. Incidences of ILD (Study B2301)

PT (MedDRA ver. 19.0)	Number of patients (%)			
	Combo 450 (n = 192)		VEM (n = 186)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
ILD	1 (0.5)	0	2 (1.1)	1 (0.5)
ILD	1 (0.5)	0	0	0
Lung infiltration	0	0	1 (0.5)	1 (0.5)
Lung disorder	0	0	1 (0.5)	0

In Study B2301, there was no ILD leading to death. Serious ILD was not observed in the Combo 450 group but observed in 1 of 186 patients in the VEM group (0.5%; lung infiltration in 1 patient). Its causal relationship to the study drug was denied. There were no cases of ILD leading to discontinuation of the study drug. ILD leading to interruption of the study drug was observed in 1 of 192 patients in the Combo 450 group (0.5%; ILD in 1 patient), but not in the VEM group. There were no cases of ILD leading to dose reduction of the study drug.

In the Combo 450 group of Study B2301, the median time (range) to the first onset of ILD was 53 (53-53) days.

Table 72 shows the details of patients who had serious ILD associated with ENCO/BINI therapy or with ENCO or BINI monotherapy in any of the clinical studies submitted.

Table 72. List of patients who had serious ILD (Studies B2301, X2101, A2301, X2109, and X2201)

Study	Treatment group	Age	Sex	Race	PT (MedDRA ver. 19.0)	Grade	Time of onset (day of administration)	Causal relationship to study drug	Outcome
B2301	ENCO	[redacted]	Male	[redacted]	Pulmonary alveolar haemorrhage	3	203	No	Resolved
X2101	ENCO 300 mg	[redacted]	Male	[redacted]	Pneumonitis	2	182	No	Unknown
A2301	BINI	[redacted]	Male	[redacted]	Lung disorder	3	72	Yes	Resolved
		[redacted]	Male	[redacted]	Pneumonitis	2	104	Yes	Resolved
		[redacted]	Female	[redacted]	Pneumonitis	3	54	Yes	Not resolved
X2109	ENCO/BINI	[redacted]	Male	[redacted]	Pulmonary alveolar haemorrhage	3	3	No	Resolved
X2201	BINI 45 mg	[redacted]	Male	[redacted]	Lung disorder	3	77	No	Unknown

(b) Venous thromboembolism:
Events classified as “embolic and thrombotic events, venous” in MedDRA SMQ were tabulated as venous thromboembolism.

Table 73 shows the incidences of venous thromboembolism in Study B2301.

Table 73. Incidences of venous thromboembolism (Study B2301)

PT (MedDRA ver. 19.0)	Number of patients (%)			
	Combo 450 (n = 192)		VEM (n = 186)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Venous thromboembolism	10 (5.2)	2 (1.0)	3 (1.6)	2 (1.1)
Pulmonary embolism	6 (3.1)	2 (1.0)	2 (1.1)	2 (1.1)
Superior vena cava syndrome	1 (0.5)	0	0	0
Thrombophlebitis	1 (0.5)	0	0	0
Thrombophlebitis superficial	1 (0.5)	0	0	0
Deep vein thrombosis	1 (0.5)	0	0	0
Hepatic vein thrombosis	0	0	1 (0.5)	0

In Study B2301, venous thromboembolism leading to death was not observed in the Combo 450 group, but observed in 1 of 186 patients in the VEM group (0.5%; pulmonary embolism), and its causal relationship to the study drug was denied. Serious venous thromboembolism was observed in 5 of 192 patients in the Combo 450 group (2.6%; pulmonary embolism in 3 patients, thrombosis venous superficial and deep vein thrombosis in 1 patient each) and in 2 of 186 patients in the VEM group (1.1%; pulmonary embolism in 2 patients). A causal relationship to the study drug was denied for all of these events. Venous thromboembolism leading to discontinuation of the study drug was not observed in the Combo 450 group, but observed in 1 of 186 patients in the VEM group (0.5%; pulmonary embolism in 1 patient). Venous thromboembolism leading to interruption of the study drug was observed in 2 of 192 patients in the Combo 450 group (1.0%; pulmonary embolism in 2 patients) but not in the VEM group. There were no cases of venous thromboembolism leading to dose reduction of the study drug.

In the Combo 450 group of Study B2301, the median time (range) to the first onset of venous thromboembolism was 105.0 (1-543) days.

Table 74 shows the details of patients who had serious venous thromboembolism associated with ENCO/BINI therapy or with ENCO or BINI monotherapy in Studies B2301 and A2301.

Table 74. List of patients who had serious venous thromboembolism (Studies B2301 and A2301)

Study	Treatment group	Age	Sex	PT (MedDRA ver. 19.0)	Grade	Time of onset (day of administration)	Causal relationship to study drug	Outcome
B2301	Combo 450	[redacted]	Male	Thrombophlebitis superficial	2	542	No	Resolved
		[redacted]	Male	Deep vein thrombosis	1	1	No	Resolved
		[redacted]	Female	Pulmonary embolism	3	96	No	Resolved
		[redacted]	Male	Pulmonary embolism	4	88	No	Resolved
		[redacted]	Male	Pulmonary embolism	2	1	No	Resolved
	Combo 300	[redacted]	Female	Deep vein thrombosis	2	63	No	Resolving
		[redacted]	Male	Pulmonary embolism	3	109	No	Not resolved
		[redacted]	Female	Pulmonary embolism	3	504	No	Not resolved
		[redacted]	Male	Retinal vein occlusion	2	67	Yes	Not resolved
A2301	BINI	[redacted]	Male	Retinal vein occlusion	4	86	Yes	Resolving
		[redacted]	Male	Retinal vein occlusion	2	192	Yes	Not resolved
		[redacted]	Male	Pulmonary embolism	2	81	No	Resolving
		[redacted]	Male	Pulmonary embolism	3	16	No	Resolved
		[redacted]	Female	Deep vein thrombosis	3	27	No	Resolved
		[redacted]	Male	Retinal vein occlusion	3	44	Yes	Resolved
		[redacted]	Male	Pulmonary embolism	3	37	Yes	Resolved
		[redacted]	Male	Retinal vein occlusion	3	114	Yes	Resolving
		[redacted]	Male	Pulmonary embolism	3	44	Yes	Resolved
		[redacted]	Male	Retinal vein occlusion	4	89	Yes	Not resolved
		[redacted]	Male	Mesenteric vein thrombosis	2	85	No	Resolving

(c) Bone marrow depression:

Events classified as “haematopoietic cytopenias (broad)” in MedDRA SMQ were tabulated as bone marrow depression.

Table 75 shows the incidences of bone marrow depression in Study B2301.

Table 75. Incidences of bone marrow depression (Study B2301)

PT (MedDRA ver. 19.0)	Number of patients (%)			
	Combo 450 (n = 192)		VEM (n = 186)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Bone marrow depression	40 (20.8)	13 (6.8)	28 (15.1)	9 (4.8)
Anaemia	29 (15.1)	8 (4.2)	14 (7.5)	4 (2.2)
Neutropenia	5 (2.6)	2 (1.0)	3 (1.6)	1 (0.5)
Thrombocytopenia	3 (1.6)	1 (0.5)	1 (0.5)	0
White blood cell count decreased	3 (1.6)	0	1 (0.5)	0
Neutrophil count decreased	2 (1.0)	0	1 (0.5)	0
Lymphopenia	2 (1.0)	0	5 (2.7)	3 (1.6)
Platelet count decreased	2 (1.0)	1 (0.5)	0	0
Haemoglobin decreased	1 (0.5)	0	4 (2.2)	0
Leukopenia	1 (0.5)	0	3 (1.6)	0
Lymphocyte count decreased	1 (0.5)	1 (0.5)	5 (2.7)	1 (0.5)
Normochromic normocytic anaemia	1 (0.5)	0	0	0
Red blood cell count decreased	0	0	1 (0.5)	0

In Study B2301, there was no bone marrow depression leading to death either in the Combo 450 group or in the VEM group. Serious bone marrow depression was observed in 4 of 192 patients in the Combo 450 group (2.1%; anaemia in 4 patients, thrombocytopenia in 1 patient [including duplicate counting]) and in 3 of 186 patients in the VEM group (1.6%; anaemia in 2 patients, lymphopenia in 1 patient). A causal relationship to the study drug could not be ruled out for anaemia in 2 patients in the Combo 450 group. Bone marrow depression leading to discontinuation of the study drug was observed in 1 of 192

patients in the Combo 450 group (0.5%; neutropenia in 1 patient), but not in the VEM group. Bone marrow depression leading to interruption of the study drug were observed in 5 of 192 patients in the Combo 450 group (2.6%; anaemia in 4 patients, neutropenia in 1 patient) and in 3 of 186 patient in the VEM group (1.6%; anaemia in 2 patients, neutropenia in 1 patient). Bone marrow depression leading to dose reduction of the study drug was not observed in the Combo 450 group but observed in 1 of 186 patients in the VEM group (0.5%; lymphopenia in 1 patient).

Table 76 shows the details of patients who had serious bone marrow depression associated with ENCO/BINI in the Combo 450 group of Study B2301.

Table 76. List of patients who had serious bone marrow depression (Study B2301)

Age	Sex	PT (MedDRA ver. 19.0)	Grade	Time of onset (day of administration)	Causal relationship to study drug	Outcome
[redacted]	Male	Anaemia	3	312	No	Not resolved
[redacted]	Male	Anaemia	3	217	Yes	Resolved
[redacted]	Female	Anaemia	4	15	Yes	Resolving
[redacted]	Male	Anaemia	3	251	No	Not resolved
[redacted]	Male	Thrombocytopenia	2	255	No	Resolved

(d) Pyrexia:
Events classified as “pyrexia,” “body temperature increased,” “febrile neutropenia,” “puerperal pyrexia,” or “fever neonatal” in MedDRA PT were tabulated as pyrexia.

In Study B2301, there was no pyrexia leading to death. Serious pyrexia was observed in 6 of 192 patients in the Combo 450 group (3.1%; pyrexia in 6 patients) and in 2 of 186 patients in the VEM group (1.1%; pyrexia in 2 patients). A causal relationship to the study drug could not be ruled out for pyrexia in 1 patient in the Combo 450 group and 1 patient in the VEM group. Pyrexia leading to discontinuation of the study drug was observed in 1 of 192 patients in the Combo 450 group (0.5%; pyrexia in 1 patient), but not in the VEM group. Pyrexia leading to interruption of the study drug was observed in 8 of 192 patients in the Combo 450 group (4.2%; pyrexia in 8 patients) and in 11 of 186 patients in the VEM group (5.9%; pyrexia in 11 patients). Pyrexia leading to dose reduction of the study drug was observed in 1 of 192 patients in the Combo 450 group (0.5%; pyrexia in 1 patient) and in 3 of 186 patients in the VEM group (1.6%; pyrexia in 3 patients).

Table 77 shows the details of patients who had serious pyrexia associated with ENCO/BINI in the Combo 450 group of Study B2301.

Table 77. List of patients who had serious pyrexia (Study B2301)

Age	Sex	PT (MedDRA ver. 19.0)	Grade	Time of onset (day of administration)	Causal relationship to study drug	Outcome
[redacted]	Male	Pyrexia	3	310	No	Resolved
[redacted]	Female	Pyrexia	3	179	No	Resolved
[redacted]	Female	Pyrexia	2	106	No	Resolved
[redacted]	Male	Pyrexia	3	47	Yes	Resolved
[redacted]	Male	Pyrexia	3	72	No	Resolved
[redacted]	Male	Pyrexia	3	147	No	Resolved
[redacted]	Male	Pyrexia	3	124	No	Not resolved

(e) Renal impairment:
Events classified as “acute renal failure (broad)” in MedDRA SMQ were tabulated as renal impairment.

In Study B2301, renal impairment leading to death was not observed in the Combo 450 group, but observed in 1 of 186 patients in the VEM group (0.5%; renal failure in 1 patient). Its causal relationship to the study drug was denied. Serious renal impairment was observed in 6 of 192 patients in the Combo 450 group (3.1%; acute kidney injury in 3 patients, blood creatinine increased, renal failure, and renal impairment in 1 patient each), and in 3 of 186 patients in the VEM group (1.6%; renal failure, renal impairment, and acute kidney injury in 1 patient each). A causal relationship to the study drug could not be ruled out for acute kidney injury and renal failure in 1 patient each in the Combo 450 group and acute kidney injury in 1 patient in the VEM group. Renal impairment leading to discontinuation of the study drug was observed in 2 of 192 patients in the Combo 450 group (1.0%; blood creatinine increased in 2 patients) and in 1 of 186 patients in the VEM group (0.5%; acute kidney injury in 1 patient). Renal impairment leading to interruption of the study drug was observed in 8 of 192 patients in the Combo 450 group (4.2%; blood creatinine increased in 4 patients, renal failure and acute kidney injury in 2 patients each) and in 6 of 186 patients in the VEM group (3.2%; blood creatinine increased in 4 patients, acute kidney injury in 2 patients, and proteinuria in 1 patient [including duplicate counting]). Renal impairment leading to dose reduction of the study drug was not observed in the Combo 450 group but observed in 2 of 186 patients in the VEM group (1.1%; renal failure in 2 patients).

Table 78 shows the details of patients who had serious renal impairment associated with ENCO/BINI in the Combo 450 group of Study B2301.

Table 78. List of patients who had serious renal impairment (Study B2301)

Age	Sex	PT (MedDRA ver. 19.0)	Grade	Time of onset (day of administration)	Causal relationship to study drug	Outcome
[redacted]	Male	Acute kidney injury	4	11	Yes	Resolved
[redacted]	Female	Acute kidney injury	2	189	No	Resolved
[redacted]	Male	Renal impairment	3	163	No	Not resolved
[redacted]	Female	Renal failure	3	10	Yes	Resolved
[redacted]	Male	Blood creatinine increased	2	29	No	Resolved
[redacted]	Male	Acute kidney injury	3	391	No	Resolved

(f) QT/QTc interval prolongation
Events classified as “torsade de pointes/QT prolongation (narrow)” in MedDRA SMQ were tabulated as QT/QTc interval prolongation.

In Study B2301, there were no cases of fatal or serious QT/QTc prolongation. QT/QTc prolongation leading to discontinuation of the study drug was not observed in the Combo 450 group but observed in 1 of 186 patients in the VEM group (0.5%; electrocardiogram QT prolonged in 1 patient). There was no QT/QTc prolongation leading to interruption or dose reduction of the study drug.

Table 79 shows changes in QT interval corrected by Fridericia’s method (QTcF) associated with ENCO/BINI in Study B2301. Among patients who showed change in QTcF, there were no patients who experienced symptoms related to serious QT/QTc interval prolongation.

Table 79. Changes in QTcF associated with ENCO/BINI (Study B2301)

	Number of patients (%)		
	Japanese subpopulation (n = 3)	Non-Japanese subpopulation (n = 189)	Entire population (n = 192)
Maximum			
>480 ms	1 (33.3)	6 (3.2)	7 (3.6)
>500 ms	0	1 (0.5)	1 (0.5)
>550 ms	0	0	0
Maximum increase from baseline			
>30 ms	2 (66.7)	48 (25.4)	50 (26.0)
>60 ms	0	10 (5.3)	10 (5.2)
>100 ms	0	1 (0.5)	1 (0.5)
Mean maximum increase from baseline [90% CI] (ms)			
	26.8 [5.6, 47.9]	21.3 [18.9, 23.8]	21.4 [19.0, 23.9]

PMDA's view:

Serious events of ILD, venous thromboembolism, bone marrow depression, pyrexia, and renal impairment for which a causal relationship to ENCO/BINI therapy or to BINI monotherapy could not be ruled out were observed in clinical studies. In addition, changes in QTcF were observed as events classified as QT/QTc interval prolongation. Because the number of occurrences of each event is limited, no specific precautions against these events are necessary currently. However, relevant post-marketing information should be collected continuously, and once available, new information should be provided appropriately to healthcare professionals.

7.R.4 Clinical positioning and indication

The proposed indication for ENCO and BINI was "unresectable malignant melanoma with *BRAF* gene mutation." The following descriptions were included in the "Precautions for Indications" section:

- ENCO and BINI should be administered to patients with known *BRAF* gene mutation through tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic should be used in the test.
- Suitable patients should be selected based on a thorough understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of ENCO and BINI.
- The efficacy and safety of ENCO and BINI in adjuvant chemotherapy have not been established.

Upon reviewing Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the discussion described in the following sections, PMDA concluded that the indication for ENCO and BINI should be "unresectable malignant melanoma with *BRAF* gene mutation" as proposed, with the following cautions in the "Precautions for Indication" section:

- ENCO and BINI should be administered to patients with known *BRAF* gene mutation through tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic should be used in the test.
- Suitable patients should be selected based on a thorough understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of ENCO and BINI.
- The efficacy and safety of ENCO and BINI in adjuvant chemotherapy have not been established.

7.R.4.1 Target patients and indication of ENCO/BINI

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

Clinical practice guidelines

- NCCN Guideline (v.3.2018):
  ENCO/BINI is recommended as the first-line treatment for patients with unresectable malignant melanoma with BRAF V600 mutation. Also, ENCO/BINI is a treatment option for second- and further-line treatment.
- ESMO Guideline (2015)
  ENCO is included as a BRAF inhibitor, and BINI as a MEK inhibitor, both of which are concomitantly administered for the treatment of metastatic malignant melanoma.

The applicant's explanation about the target patients for treating with ENCO/BINI indicated for unresectable malignant melanoma with BRAF V600 mutation:
Clinical usefulness of ENCO/BINI was demonstrated by Study B2301. Therefore, the target patients should include the patient group investigated in Study B2301, namely patients with unresectable malignant melanoma who are confirmed to have BRAF V600E or V600K mutation by "THxID BRAF kit" of bioMérieux Japan Ltd.

Use of ENCO/BINI as an adjuvant therapy is not recommended because there are no data of clinical studies that investigated the efficacy and safety of ENCO/BINI as an adjuvant therapy.

On the basis of the above, the indication for ENCO and BINI was proposed as "unresectable malignant melanoma with *BRAF* gene mutation," with the description in the "Clinical Studies" section that patients enrolled in Study B2301 were those with BRAF V600E or V600K mutation, and with the following cautions in the "Precautions for Indication" section, of the package insert:

- ENCO and BINI should be administered to patients with known *BRAF* gene mutation through tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic should be used in the test.
- Suitable patients should be selected based on a thorough understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of ENCO and BINI.
- The efficacy and safety of ENCO and BINI in adjuvant chemotherapy have not been established.

The applicant's explanation about the choice between ENCO/BINI and approved antineoplastic agents:
Treatments approved in Japan for the target patients of ENCO/BINI, i.e., patients with unresectable malignant melanoma with BRAF V600 mutation, are treatment with combination of DAB and TRA (DAB/TRA), DAB monotherapy, VEM monotherapy, treatment with combination of nivolumab (genetical recombination) (NIVO) and ipilimumab (genetical recombination) (IPI) (NIVO/IPI), NIVO monotherapy, IPI monotherapy, and pembrolizumab (genetical recombination) monotherapy. The choice between ENCO/BINI and each of the above antineoplastic agents should be as follows:

- Choice between ENCO/BINI and DAB/TRA or DAB monotherapy: The priority as the antineoplastic agent is unclear currently because comparison of the efficacy and safety between ENCO/BINI and

DAB/TRA or DAB monotherapy has not been performed in the same clinical study. Either of the treatments should be selected according to the patient conditions with the knowledge of the efficacy and safety of each treatment.

- Choice between ENCO/BINI and VEM monotherapy: ENCO/BINI should be used in preference to VEM monotherapy because Study B2301 demonstrated the superiority of ENCO/BINI to VEM monotherapy in efficacy.
- Choice between ENCO/BINI and NIVO/IPI, NIVO monotherapy, IPI monotherapy, or pembrolizumab (genetical recombination) monotherapy: The priority of the antineoplastic agent is currently unclear because comparison of the efficacy and safety between ENCO/BINI and these antineoplastic agents has not been performed in the same study. NCCN Guideline (v.3.2018) states that BRAF and MEK inhibitors should be used in preference if a prompt response is considered to be of clinical significance. The treatment should be selected according to the patient conditions, such as by giving preference to ENCO/BINI or to DAB/TRA.

PMDA's view:

PMDA accepted the applicant's explanation and concluded that the indication for ENCO and BINI should be "unresectable malignant melanoma with *BRAF* gene mutation" as proposed, with the following cautions in the "Precautions for Indication" section:

- ENCO and BINI should be administered to patients with known *BRAF* gene mutation through tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic should be used in the test.
- Suitable patients should be selected based on a thorough understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of ENCO and BINI.
- The efficacy and safety of ENCO and BINI in adjuvant chemotherapy have not been established.

7.R.5 Dosage and administration

The following table shows the "Dosage and Administration" and the "Precautions for Dosage and Administration" for ENCO and BINI for the treatment of unresectable malignant melanoma with *BRAF* gene mutation, proposed by the applicant.

	Dosage and administration	Precautions for dosage and administration
ENCO	In combination with BINI, the usual adult dosage is 450 mg of ENCO administered orally once daily.	• When BINI is discontinued, ENCO may be administered continuously at a 1-level lower dose (300 mg once daily), taking account of the clinical usefulness in patients. • The dose reduction of ENCO should be considered during the period of interruption of BINI (ENCO 450 mg monotherapy is not recommended because of decreased tolerability). • Guide for interruption, dose reduction, and discontinuation of ENCO in case of adverse drug reactions
BINI	In combination with ENCO, the usual adult dosage is 45 mg of BINI administered orally twice daily at intervals of approximately 12 hours.	• The dose should be reduced to 15 mg twice daily in patients with moderate or severe hepatic impairment. • BINI should be discontinued when ENCO is discontinued. • BINI should be interrupted when ENCO is interrupted. • Guide for interruption, dose reduction, and discontinuation of BINI in case of adverse drug reactions

Upon reviewing Sections "6.R.1 Administration of ENCO to patients with hepatic impairment," "6.R.3 Administration of BINI in patients with hepatic impairment," "7.R.2 Efficacy," "7.R.3 Safety," and the discussion described in the following sections, PMDA concluded that the "Dosage and Administration"

and “Precautions for Dosage and Administration sections” should be specified as shown in the following table.

	Dosage and administration	Precautions for dosage and administration
ENCO	In combination with BINI, the usual adult dosage is 450 mg of ENCO administered orally once daily. The dose may be reduced according to the patient’s condition.	• Increased blood ENCO concentration has been reported in patients with hepatic impairment. The dose reduction of ENCO should be considered in these patients, and patients should be monitored more carefully for occurrence of adverse events. • In clinical studies investigating the tolerability of ENCO monotherapy, it is suggested that once daily administration of 450 mg may exceed the maximum tolerated dose of ENCO. When BINI is interrupted or discontinued, the dose reduction of ENCO should be considered, and patient should be closely monitored for occurrences of adverse events. • Guide for interruption, dose reduction, and discontinuation of ENCO in case of adverse drug reactions
BINI	In combination with ENCO, the usual adult dosage is 45 mg of BINI administered orally twice daily. The dose may be reduced according to the patient’s condition.	• Increased blood BINI concentration has been reported in patients with moderate or severe hepatic impairment. The dose reduction of BINI should be considered in these patients, and patients should be monitored more carefully for occurrences of adverse events. • When ENCO is interrupted or discontinued, BINI should also be interrupted or discontinued, respectively. • Guide for interruption, dose reduction, and discontinuation of BINI in case of adverse drug reactions

7.R.5.1 Dosage and administration of ENCO and BINI

The applicant’s explanation about justification for the proposed dosage and administration of ENCO and BINI for unresectable malignant melanoma with BRAF V600 mutation:

Study B2301, which was conducted using the dosage regimen based on the following study results, demonstrated the clinical usefulness of ENCO/BINI in patients with unresectable malignant melanoma with BRAF V600 mutation. The proposed dosage and administration for ENCO and BINI were specified according to those used in Study B2301. Clinical usefulness was demonstrated only with ENCO/BINI, but not with ENCO or BINI monotherapy or with concomitant use of ENCO or BINI with other antineoplastic agents. As a result, only ENCO/BINI was recommended as the dosage regimen whereas other regimens were not.

- In the global phase I study (Study X2101), RP2D of ENCO was determined to be 300 mg QD [see Section 7.1.3.1].
- In the foreign phase I study (Study 162-111), RP2D of BINI was determined to be 45 mg BID [see Section 7.1.4.1].
- In the foreign phase Ib/II study (Study X2110) which was conducted using the dosage regimen determined according to the above study results, RP2D of ENCO in ENCO/BINI was determined to be 450 mg QD [see Section 7.1.4.2]. When BINI was concomitantly administered with ENCO, PFS tended to increase with the increase in AUC of BINI under the steady state, although the evaluation was performed only at the dosage regimen of BINI 45 mg BID [see Section 6.2.10.3.1].

In addition to the above, the following descriptions were included in the “Precautions for Dosage and Administration” section for reasons described below: (a) The dose reduction of ENCO should be considered when BINI is interrupted or discontinued, and (b) BINI should be interrupted or discontinued if ENCO is interrupted or discontinued, respectively.

- In Study B2301, the dose reduction of ENCO had not been specified in case of the interruption or discontinuation of BINI. However, in the expanded part of Study X2101, DLT occurred in 10 of first 34 patients who started the treatment with ENCO 450 mg QD, the MTD in ENCO monotherapy,

necessitating dose reduction to 300 mg QD in 7 of these patients [see Section 7.1.3.1]. Despite this information of safety concerns, Study B2301 demonstrated the following efficacy results: (1) response to treatment was observed in 1 of 2 patients who continued ENCO at a reduced dose of 300 mg after discontinuation of BINI, and (2) PFS tended to increase in the ENCO group (300 mg QD) compared with the VEM group. Since these results suggest the efficacy of ENCO 300 mg QD, a precautionary statement on the dose reduction of ENCO in case of interruption or discontinuation of BINI was included.

- In Study B2301, the dose interruption of BINI had not been specified in case of the interruption of ENCO. However, since the efficacy and safety of BINI monotherapy in case of the interruption or discontinuation of ENCO had not been established, a precautionary statement requiring interruption or discontinuation of BINI was included.

PMDA's view:

PMDA generally accepted the applicant's explanation. However, no clinical study was conducted to investigate the efficacy and safety of the treatment where the dose of ENCO was adjusted after the interruption or discontinuation of BINI. Therefore, the optimum dose of ENCO after interruption or discontinuation of BINI remains unknown. Thus, there is insufficient evidence to include dose reduction of ENCO to 300 mg QD in the "Precautions for Dosage and Administration" section.

On the basis of the above, descriptions in the "Dosage and administration" and "Precautions for Dosage and Administration" sections of ENCO and BINI should be modified as shown below.

ENCO

- Dosage and administration
  In combination with BINI, the usual adult dosage is 450 mg of ENCO administered orally once daily. The dose may be reduced according to the patient's condition.
- Precautions for dosage and administration
  In clinical studies investigating the tolerability of ENCO monotherapy, it is suggested that once daily administration of 450 mg may exceed the maximum tolerated dose. When BINI is interrupted or discontinued, the dose reduction of ENCO should be considered, and patient should be closely monitored for occurrences of adverse events.

BINI

- Dosage and administration
  In combination with ENCO, the usual adult dosage is 45 mg of BINI administered orally twice daily. The dose may be reduced according to the patient's condition.
- Precautions for dosage and administration
  When ENCO is interrupted or discontinued, BINI should also be interrupted or discontinued, respectively.

7.R.5.2 Dose adjustment of ENCO and BINI

The applicant's explanation about the guide for interruption, dose reduction, and discontinuation of ENCO and BINI:

In Study B2301, the criteria for the interruption, dose reduction, and discontinuation of ENCO and BINI, as well as specific countermeasures for adverse drug reactions were established, and the clinical usefulness of ENCO/BINI was confirmed when these criteria were followed. Therefore, the guides of dose adjustment will be included in the "Precautions for Dosage and Administration" section of ENCO and BINI based on the above criteria.

PMDA's view:

PMDA accepted the applicant's explanation and concluded that the guides for dose reduction, interruption, and discontinuation of ENCO and BINI should be specified in the "Precautions for Dosage and Administration" section, with the following modifications from those proposed.

ENCO

- In case of adverse drug reactions associated with ENCO, ENCO should be interrupted, reduced in dose, or discontinued by referring to the following criteria.

Table 80. Dose reduction of ENCO in continued administration

Dose reduction level*	Dose
Normal dose	450 mg QD
1-level dose reduction	300 mg QD
2-level dose reduction	200 mg QD
3-level dose reduction	100 mg QD
4-level dose reduction	50 mg QD
5-level dose reduction	Discontinue

* If the adverse event requiring dose reduction has improved to Grade ≤1, and there are no other concomitant adverse events, the dose may be increased according to the reverse steps.

Table 81. Criteria for dose adjustment of ENCO in case of adverse drug reactions

Adverse drug reaction	Severity*	Measure
Retinal disease, uveitis	Grade 2	Interrupt ENCO until recovery to Grade ≤1. Resume ENCO at same dose or at 1-level lower dose.
	Grade 3	Interrupt ENCO until recovery to Grade ≤2. Resume ENCO at 1-level lower dose. Discontinue ENCO if Grade 3 persists.
	Grade 4	Discontinue ENCO.
Retinal vein occlusion	Grade ≥1	Discontinue ENCO.
Eye disorders (other than above)	Grade 3	Interrupt ENCO until recovery to Grade ≤1. If recovered within 28 days, resume ENCO at 1-level lower dose. Discontinue ENCO if not recovered within 28 days.
	Grade 4	Discontinue ENCO.
AST increased, ALT increased	Grade 2 (not accompanied by serum bilirubin increased)	If the symptom persists for >14 days, interrupt ENCO until recovery to Grade ≤1. Resume ENCO at same dose. If recurrent, interrupt ENCO until recovery and then resume at 1-level lower dose.
	Grade 2 (accompanied by serum bilirubin increased)	Interrupt ENCO until recovery to Grade ≤1. If recovered within 7 days, resume ENCO at 1-level lower dose. Discontinue ENCO if not recovered within 7 days.
	Grade 3 (not accompanied by serum bilirubin increased)	Interrupt ENCO until recovery to Grade ≤1. If recovered within 14 days, resume ENCO at same dose. If recovered after >14 days, resume ENCO at 1-level lower dose.
	Grade 3 (accompanied by serum bilirubin increased) and Grade 4	Discontinue ENCO.
Serum CK increased	Grade 3-4 (accompanied by serum creatinine increased)	Interrupt ENCO until recovery to Grade ≤1. If recovered within 28 days, resume ENCO at 1-level lower dose. Discontinue ENCO if not recovered within 28 days.
Electrocardiogram QT prolonged	QTc exceeds 500 ms, and the change from baseline is ≤60 ms.	Interrupt ENCO until QTc decreases to <500 ms. Resume ENCO at 1-level lower dose. Discontinue ENCO if recurrent.
	QTc exceeds 500 ms, and the change from baseline is >60 ms.	Discontinue ENCO.
Dermatitis	Grade 2	If the symptom persists or worsens, interrupt ENCO until recovery to Grade ≤1. Resume ENCO at same dose.
	Grade 3	Interrupt ENCO until recovery to Grade ≤1. Resume ENCO at same dose. If recurrent, interrupt ENCO until recovery and then resume at 1-level lower dose.
	Grade 4	Discontinue ENCO.
Palmar-plantar erythrodysaesthesia syndrome	Grade 2	If the symptom persists for >15 days, interrupt ENCO until recovery to Grade ≤1. Resume ENCO at same dose. If recurrent, interrupt ENCO until recovery and then consider resumption at 1-level lower dose.
	Grade 3	Interrupt ENCO until recovery to Grade ≤1. Resume ENCO at 1-level lower dose. If repeatedly recurrent, consider resumption at 1-level lower dose or discontinuation.
Other adverse drug reactions	Grade 2	If Grade 2 adverse reaction persists, consider interruption or dose reduction.
	Grade 3	Consider interruption until recovery to Grade ≤1. If recovered within 28 days, consider resumption at 1-level lower dose.
	Grade 4	Discontinue ENCO.

* Grade is determined according to NCI-CTCAE ver4.03.

BINI

- In case of adverse drug reactions associated with BINI, BINI should be interrupted, reduced in dose, or discontinued by referring to the following criteria.

Table 82. Dose reduction of BINI in continued administration

Dose reduction level*	Dose
Normal dose	45 mg BID
1-level dose reduction	30 mg BID
2-level dose reduction	15 mg BID
3-level dose reduction	Discontinue

* If the adverse event requiring dose reduction has improved to Grade ≤1, and there are no other concomitant adverse events, the dose may be increased according to the reverse steps.

Table 83. Criteria for dose adjustment of BINI in case of adverse drug reactions

Adverse drug reaction	Severity*	Measure
Retinal disease, uveitis	Grade 2	Interrupt BINI until recovery to Grade ≤1. Resume BINI at same dose or at 1-level lower dose.
	Grade 3	Interrupt BINI until recovery to Grade ≤2. Resume BINI at 1-level lower dose. Discontinue BINI if Grade 3 persists.
	Grade 4	Discontinue BINI.
Retinal vein occlusion	Grade ≥1	Discontinue BINI.
Eye disorders (other than above)	Grade 3	Interrupt BINI until recovery to Grade ≤1. If recovered within 28 days, resume BINI at 1-level lower dose. Discontinue BINI if not recovered within 28 days.
	Grade 4	Discontinue BINI.
AST increased, ALT increased	Grade 2 (not accompanied by serum bilirubin increased)	Interrupt BINI until recovery to Grade ≤1. If recovered within 14 days, resume BINI at same dose. If recovered after ≥14 days, resume BINI at 1-level lower dose.
	Grade 2 (accompanied by serum bilirubin increased)	Interrupt BINI until recovery to Grade ≤1. If recovered within 7 days, resume BINI at 1-level lower dose. Discontinue BINI if not recovered within 7 days.
	Grade 3 (not accompanied by serum bilirubin increased)	Interrupt BINI until recovery to Grade ≤1. Resume BINI at 1-level lower dose.
	Grade 3 (accompanied by serum bilirubin increased) and Grade 4	Discontinue BINI.
Serum CK increased	Grade 3 (accompanied by muscular symptom or creatinine increased) and Grade 4	Interrupt BINI until recovery to Grade ≤1. If recovered within 28 days, resume BINI at 1-level lower dose. Discontinue BINI if not recovered within 28 days.
Cardiac ejection fraction decreased	Asymptomatic with decrease in left ventricular ejection fraction from baseline by ≥10% or to below the lower limit of normal	Interrupt BINI until recovery. If recovered within 28 days, resume BINI at 1-level lower dose. Discontinue BINI if not recovered within 28 days.
	Grade 3-4	Discontinue BINI.
Electrocardiogram QT prolonged	QTc exceeds 500 ms, and the change from baseline is ≤60 ms.	Interrupt BINI until QTc decreases to <500 ms. Resume BINI at 1-level lower dose. Discontinue BINI if QTc prolongation recurs.
	QTc exceeds 500 ms, and the change from baseline is >60 ms.	Discontinue BINI.
Dermatitis	Grade 2	If the symptom persists or worsens, interrupt BINI until recovery to Grade ≤1. Resume BINI at same dose. If recurrent, interrupt BINI until recovery and then resume at 1-level lower dose.
	Grade 3	Interrupt BINI until recovery to Grade ≤1. Resume BINI at same dose. If recurrent, interrupt BINI until recovery and then resume at 1-level lower dose.
	Grade 4	Discontinue BINI.
Other adverse drug reactions	Grade 2	If Grade 2 symptom persists, consider interruption or dose reduction.
	Grade 3	Consider interruption until recovery to Grade ≤1. If recovered within 28 days, consider resumption at 1-level lower dose.
	Grade 4	Discontinue BINI.

* Grade is determined according to NCI-CTCAE ver4.03.

7.R.6 Post-marketing investigations

The applicant's explanation about their post-marketing surveillance plan:
The applicant plans to conduct post-marketing surveillance covering all patients treated with ENCO and BINI to evaluate the safety, etc. of ENCO and BINI in post-marketing clinical use.

Because very limited number of Japanese patients were enrolled in Study B2301, it is planned to collect information of not only the safety specifications but also every type of adverse event that occur in patients receiving ENCO/BINI in clinical use.

The target sample size is 150 for feasibility reason, taking account of the limited number of patients with unresectable malignant melanoma with *BRAF* gene mutation in Japan.

The observation period is 12 months, taking into consideration that most of the adverse events in Study B2301 occurred within 12 months.

PMDA's view:
Because of the limited information available on the safety of ENCO/BINI in Japanese patients, a post-marketing surveillance covering all patients receiving ENCO/BINI should be conducted for a certain period after the market launch, thereby to collect safety information promptly and in an unbiased manner, and to provide safety information thus obtained to healthcare professionals without delay.

As for, based on the incidences of adverse events in Study B2301 and other studies, the following adverse events requiring particular caution in administering ENCO/BINI should be included in the safety specifications for this surveillance: Eye disorders, cardiac dysfunction, hepatic dysfunction, rhabdomyolysis, cutaneous malignancies, hypertension, haemorrhage, and palmar-plantar erythrodysaesthesia syndrome.

The planned sample size and the observation period should be reconsidered taking account of the incidences of events included in the safety specifications for this surveillance.

Since ENCO and BINI are expected to be used in combination in most cases, a survey plan should be designed to enable investigation of safety etc., in concomitant use of ENCO with BINI.

7.2 Adverse events, etc. observed in clinical studies

Deaths reported in the safety evaluation data were detailed in Section "7.1 Evaluation data." The following subsections summarize major adverse events excluding deaths.

7.2.1 Japanese phase I study (Study X1101)

Adverse events were observed in all patients, and adverse events for which a causal relationship to the study drug could not be ruled out were also observed in all patients. Adverse events with an incidence of ≥60% in either group were hypoalbuminaemia and blood alkaline phosphatase increased in 5 patients (83.3%) each, decreased appetite, retinal detachment, diarrhoea, dry skin, pyrexia, ALT increased, AST increased, blood CK increased, and lipase increased in 4 patients (66.7%) each in the 30 mg group; and

blood CK increased in 13 patients (86.7%), AST increased in 11 patients (73.3%), and retinal detachment in 9 patients (60.0%) in the 45 mg group.

Serious adverse events were observed in 4 of 6 patients (66.7%) in the 30 mg group and in 6 of 15 patients (40.0%) in the 45 mg group. There were no serious adverse events reported by ≥2 patients in either group.

Adverse events leading to discontinuation of the study drug were observed in 1 of 6 patients (16.7%) in the 30 mg group and in 5 of 15 patients (33.3%) in the 45 mg group. The adverse event leading to discontinuation of the study drug reported by ≥2 patients in either group was blood CK increased in 2 patients (13.3%) in the 45 mg group. A causal relationship to the study drug could not be ruled out for all events.

7.2.2 Global phase I study (Study X2101)

7.2.2.1 Dose-titration part

Adverse events were observed in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 4 of 4 patients (100%) in the 50 mg QD group (a), 10 of 10 patients (100%) in the 100 mg QD group (b), 6 of 6 patients (100%) in the 150 mg QD group (c), 3 of 3 patients (100%) in the 75 mg BID group (d), 4 of 4 patients (100%) in the 200 mg QD group (e), 4 of 5 patients (80.0%) in the 100 mg BID group (f), 5 of 5 patients (100%) in the 300 mg QD group (g), 4 of 4 patients (100%) in the 150 mg BID group (h), 6 of 6 patients (100%) in the 450 mg QD group (i), 4 of 5 patients (80.0%) in the 550 mg QD group (j), and 2 of 2 patients (100%) in the 700 mg QD group (k). Adverse events with an incidence of ≥80% in any group were nausea, hyperkeratosis, and keratosis pilaris in 3 patients (100%) each in (d), pain in extremity in 4 patients (80.0%) in (f), palmar-plantar erythrodysaesthesia syndrome in 4 patients (80.0%) in (g), decreased appetite and vomiting in 4 patients (80.0%) each in (j), and vomiting and myalgia in 2 patients (100%) each in (k).

Serious adverse events were observed in 2 of 4 patients (50.0%) in (a), 7 of 10 patients (70.0%) in (b), 3 of 6 patients (50.0%) in (c), 2 of 3 patients (66.7%) in (d), 3 of 4 patients (75.0%) in (e), 2 of 5 patients (40.0%) in (f), 4 of 5 patients (80.0%) in (g), 2 of 4 patients (50.0%) in (h), 2 of 6 patients (33.3%) in (i), 3 of 5 patients (60.0%) in (j), and 1 of 2 patients (50.0%) in (k). Serious adverse events reported by ≥2 patients in any group were intracranial pressure increased in 2 patients (20.0%) in (b) and general physical condition decreased in 2 patients (40.0%) in (g). A causal relationship to the study drug could not be ruled out for general physical condition decreased in 1 patient in (g).

Adverse events leading to discontinuation of the study drug were observed in 1 of 10 patients (10.0%) in (b), 1 of 5 patients (20.0%) in (g), 1 of 6 patients (16.7%) in (i), 1 of 5 patients (20.0%) in (j), and 1 of 2 patients (50.0%) in (k). There were no adverse events leading to discontinuation of the study drug reported by ≥2 patients in any group.

7.2.2.2 Expanded part

Adverse events were observed in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 34 of 35 patients with malignant melanoma (97.1%) and

in 17 of 18 patients with CRC (94.4%). Table 84 shows adverse events with an incidence of ≥40% in either patient group.

Table 84. Adverse events with an incidence of ≥40% in either patient group

SOC PT (MedDRA ver. 17.0)	Number of patients			
	Malignant melanoma (n = 35)		CRC (n = 18)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	35 (100)	28 (80.0)	18 (100)	13 (72.2)
Psychiatric disorders				
Insomnia	16 (45.7)	2 (5.7)	6 (33.3)	1 (5.6)
Gastrointestinal disorders				
Nausea	23 (65.7)	4 (11.4)	3 (16.7)	0
Vomiting	17 (48.6)	3 (8.6)	8 (44.4)	2 (11.1)
Skin and subcutaneous tissue disorders				
Alopecia	15 (42.9)	0	5 (27.8)	0
Dry skin	15 (42.9)	1 (2.9)	7 (38.9)	0
Hyperkeratosis	14 (40.0)	1 (2.9)	7 (38.9)	0
Palmar-plantar erythrodysaesthesia syndrome	19 (54.3)	4 (11.4)	12 (66.7)	3 (16.7)
Pruritus	13 (37.1)	1 (2.9)	8 (44.4)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	17 (48.6)	7 (20.0)	7 (38.9)	2 (11.1)
Myalgia	22 (62.9)	5 (14.3)	8 (44.4)	2 (11.1)

Serious adverse events were observed in 18 of 35 patients with malignant melanoma (51.4%) and in 8 of 18 patients with CRC (44.4%). Serious adverse events reported by ≥2 patients in either patient group were nausea in 7 patients (20.0%), myalgia in 4 patients (11.4%), vomiting, fatigue, and arthralgia in 3 patients (8.6%) each, and asthenia and pyrexia in 2 patients (5.7%) each among patients with malignant melanoma; and intestinal obstruction in 3 patients (16.7%), and vomiting, abdominal pain, and back pain in 2 patients (11.1%) each among patients with CRC. A causal relationship to the study drug could not be ruled out for nausea in 6 patients (17.1%), myalgia in 4 patients (11.4%), fatigue and arthralgia in 3 patients (8.6%) each, vomiting and asthenia in 2 patients (5.7%) each, and pyrexia in 1 patient (2.9%) among patients with malignant melanoma.

Adverse events leading to discontinuation of the study drug were observed in 8 of 35 patients with malignant melanoma (22.9%) and in 3 of 18 patients with CRC (16.7%). Adverse events leading to discontinuation of the study drug reported by ≥2 patients in either group were myalgia and arthralgia in 2 patients (5.7%) each of patients with malignant melanoma. A causal relationship to the study drug could not be ruled out for all events.

7.2.3 Global phase III study (Study B2301)

Adverse events were observed in 189 of 192 patients (98.4%) in the Combo 450 group, 191 of 192 patients (99.5%) in the ENCO group, and 185 of 186 patients (99.5%) in the VEM group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 169 of 192 patients (88.0%) in the Combo 450 group, 191 of 192 patients (99.5%) in the ENCO group, and 180 of 186 patients (96.8%) in the VEM group. Table 85 shows adverse events with an incidence of ≥30% in any group.

Table 85. Adverse events with an incidence of ≥30% in any group

SOC PT (MedDRA ver. 19.0)	Number of patients (%)					
	Combo 450 (n = 192)		ENCO (n = 192)		VEM (n = 186)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	189 (98.4)	111 (57.8)	191 (99.5)	127 (66.1)	185 (99.5)	118 (63.4)
Gastrointestinal disorders						
Diarrhoea	70 (36.5)	5 (2.6)	26 (13.5)	3 (1.6)	63 (33.9)	4 (2.2)
Nausea	79 (41.1)	3 (1.6)	74 (38.5)	8 (4.2)	63 (33.9)	3 (1.6)
Skin and subcutaneous tissue disorders						
Alopecia	26 (13.5)	0	107 (55.7)	0	68 (36.6)	0
Dry skin	27 (14.1)	0	58 (30.2)	0	42 (22.6)	0
Hyperkeratosis	27 (14.1)	1 (0.5)	72 (37.5)	7 (3.6)	54 (29.0)	0
Palmar-plantar erythrodysaesthesia syndrome	13 (6.8)	0	98 (51.0)	26 (13.5)	26 (14.0)	2 (1.1)
Musculoskeletal and connective tissue disorders						
Arthralgia	49 (25.5)	1 (0.5)	84 (43.8)	18 (9.4)	83 (44.6)	11 (5.9)
General disorders and administration site conditions						
Fatigue	55 (28.6)	4 (2.1)	48 (25.0)	1 (0.5)	57 (30.6)	4 (2.2)

Serious adverse events were observed in 66 of 192 patients (34.4%) in the Combo 450 group, 65 of 192 patients (33.9%) in ENCO group, and 69 of 186 patients (37.1%) in the VEM group. Serious adverse events reported by ≥3 patients in any group were pyrexia in 6 patients (3.1%), anaemia and abdominal pain in 4 patients (2.1%) each, pneumonia, cerebral haemorrhage, pulmonary embolism, vomiting, acute kidney injury, and general physical condition decreased in 3 patients (1.6%) each in the Combo 450 group; nausea and vomiting in 6 patients (3.1%) each, back pain and pain in 4 patients (2.1%) each, metastases to central nervous system, hyperglycaemia, facial paralysis, musculoskeletal pain, myalgia, and pyrexia in 3 patients (1.6%) each in the ENCO group; and general physical condition decreased in 6 patients (3.2%), hemiparesis, dyspnoea, and arthralgia in 3 patients (1.6%) each in the VEM group. A causal relationship to the study drug could not be ruled out for anaemia and abdominal pain in 2 patients each, vomiting, acute kidney injury, pyrexia, and general physical condition decreased in 1 patient each in the Combo 450 group; facial paralysis, nausea, vomiting, and pyrexia in 3 patients each, hyperglycaemia, back pain, myalgia, and pain in 2 patients each, and musculoskeletal pain in 1 patient in the ENCO group; and arthralgia in 3 patients, general physical condition decreased in 2 patients, and hemiparesis and dyspnoea in 1 patient each in the VEM group.

Adverse events leading to discontinuation of the study drug were observed in 24 of 192 patients (12.5%) in the Combo 450 group, 27 of 192 patients (14.1%) in the ENCO group, and 31 of 186 patients (16.7%) in the VEM group. Adverse events leading to discontinuation of the study drug reported by ≥3 patients were ALT increased and AST increased in 5 patients (2.6%) each in the Combo 450 group; palmar-plantar erythrodysaesthesia syndrome in 5 patients (2.6%) and vomiting in 3 patients (1.6%) in the ENCO group; and photosensitivity reaction, arthralgia, and γ-GTP increased in 3 patients (1.6%) each in the VEM group. A causal relationship to the study drug could not be ruled out for ALT increased and AST increased in 4 patients each in the Combo 450 group; palmar-plantar erythrodysaesthesia syndrome in 5 patients and vomiting in 3 patients in the ENCO group; and photosensitivity reaction, arthralgia, and γ-GTP increased in 3 patients each in the VEM group.

7.2.4 Global phase III study (Study A2301)

Adverse events were observed in 269 of 269 patients (100%) in the BINI group and 104 of 114 patients (91.2%) in the DTIC group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 260 of 269 patients (96.7%) in the BINI group and 78 of 114 patients (68.4%) in the DTIC group. Table 86 shows adverse events with an incidence of ≥20% in either group.

Table 86. Adverse events with an incidence of ≥20% in either group

SOC PT (MedDRA ver. 18.1)	Number of patients (%)			
	BINI (n = 269)		DTIC (n = 114)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	269 (100)	183 (68.0)	104 (91.2)	52 (45.6)
Gastrointestinal disorders				
Diarrhoea	108 (40.1)	4 (1.5)	13 (11.4)	1 (0.9)
Nausea	79 (29.4)	4 (1.5)	37 (32.5)	1 (0.9)
Vomiting	57 (21.2)	6 (2.2)	14 (12.3)	0
Skin and subcutaneous tissue disorders				
Dermatitis acneiform	95 (35.3)	7 (2.6)	1 (0.9)	0
Rash	98 (36.4)	11 (4.1)	1 (0.9)	0
General disorders and administration site conditions				
Fatigue	60 (22.3)	6 (2.2)	36 (31.6)	3 (2.6)
Oedema peripheral	97 (36.1)	1 (0.4)	3 (2.6)	0
Investigations				
Blood CK increased	113 (42.0)	52 (19.3)	3 (2.6)	0

Serious adverse events were observed in 91 of 269 patients (33.8%) in the BINI group and in 25 of 114 patients (21.9%) in the DTIC group. Serious adverse events reported by ≥3 patients in either group were general physical health deterioration in 12 patients (4.5%), retinal vein occlusion in 5 patients (1.9%), pulmonary embolism in 4 patients (1.5%), sepsis, skin infection, anaemia, dyspnoea, vomiting, and blood CK increased in 3 patients (1.1%) each in the BINI group. A causal relationship to the study drug could not be ruled out for retinal vein occlusion in 5 patients, blood CK increased in 3 patients, pulmonary embolism and vomiting in 2 patients each, skin infection, anaemia, and dyspnoea in 1 patient in the BINI group.

Adverse events leading to discontinuation of the study drug were observed in 66 of 269 patients (24.5%) in the BINI group and in 9 of 114 patients (7.9%) in the DTIC group. Adverse events leading to discontinuation of the study drug reported by ≥3 patients were ejection fraction decreased in 10 patients (3.7%), retinal vein occlusion and blood CK increased in 5 patients (1.9%) each, retinal detachment in 4 patients (1.5%), dermatitis acneiform, muscular weakness, general physical condition decreased, and ALT increased and AST increased in 3 patients (1.1%) each in the BINI group. A causal relationship to the study drug could not be ruled out for ejection fraction decreased in 10 patients, retinal vein occlusion and blood CK increased in 5 patients each, retinal detachment in 4 patients, and dermatitis acneiform, muscular weakness, ALT increased, and AST increased in 3 patients each in the BINI group.

7.2.5 Foreign phase I study (Study A2101)

Adverse events were observed in 2 of 4 subjects (50.0%). Adverse events for which a causal relationship to the study drug could not be ruled out were also observed in 2 of 4 subjects (50.0%). The adverse event reported by ≥2 subjects was flushing in 2 subjects (50.0%).

There were no serious adverse events nor those leading to discontinuation of the study drug.

7.2.6 Foreign phase I study (Study A2101J)

Adverse events were observed in 9 of 37 subjects (24.3%). Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 6 of 37 subjects (16.2%). Adverse events with an incidence of ≥5% were neutrophil count decreased in 3 subjects (8.1%) and presyncope in 2 subjects (5.4%).

There were no serious adverse events.

An adverse event leading to discontinuation of the study drug was observed in 1 of 37 subjects (2.7%). The event was visual acuity reduced in 1 subject, and its causal relationship to the study drug could not be ruled out.

7.2.7 Foreign phase I study (Study A2102)

Adverse events were observed in 3 of 6 subjects (50.0%). Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 2 of 6 subjects (33.3%). There were no adverse events reported by ≥2 subjects.

There were no serious adverse events nor those leading to discontinuation of the study drug.

7.2.8 Foreign phase I study (Study A2103)

Adverse events were observed in 4 of 12 subjects (33.3%). Adverse events for which a causal relationship to the study drug could not be ruled out were also observed in 4 of 12 subjects (33.3%). The adverse event reported by ≥2 subjects was nausea in 2 subjects (16.7%).

There were no serious adverse events nor those leading to discontinuation of the study drug.

7.2.9 Foreign phase I study (Study A2104)

Adverse events were observed in 5 of 10 subjects with normal hepatic function (50.0%), 2 of 6 patients with mild hepatic impairment (33.3%), 2 of 6 patients with moderate hepatic impairment (33.3%), and 3 of 5 patients with severe hepatic impairment (60.0%). Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 5 of 10 subjects with normal hepatic function (50.0%), 1 of 6 patients with mild hepatic impairment (16.7%), 1 of 6 patients with moderate hepatic impairment (16.7%), and 1 of 5 patients with severe hepatic impairment (20.0%). Adverse events reported by ≥2 patients in any patient groups were headache in 2 patients (33.3%) among those with mild hepatic impairment and headache in 2 patients (40.0%) among those with severe hepatic impairment.

Serious adverse events were observed in 1 patient (20.0%) among those with severe hepatic impairment. The observed serious adverse events were road traffic accident and syncope in 1 patient each, and their causal relationship to the study drug was denied.

There were no adverse events leading to discontinuation of the study drug.

7.2.10 Foreign phase I study (Study A2105)

Adverse events were observed in 14 of 15 subjects (93.3%). Adverse events for which a causal relationship to the study drug could not be ruled out were also observed in 14 of 15 subjects (93.3%). Adverse events with an incidence of ≥30% were pruritus in 12 subjects (80.0%), dermatitis acneiform in 10 subjects (66.7%), application site irritation in 8 subjects (53.3%), and abdominal pain in 6 subjects (40.0%).

There were no serious adverse events.

Adverse events leading to discontinuation of the study drug were observed in 3 of 15 subjects (20.0%). The observed events were vomiting, rash maculo-papular, and dermatitis acneiform in 1 subject each. A causal relationship to the study drug could not be ruled out for any of these events.

7.2.11 Foreign phase I study (Study 162-0601)

Adverse events were observed in 1 of 4 subjects (25.0%) in the 5 mg group, 2 of 4 subjects (50.0%) in the 20 mg group, 1 of 4 subjects (25.0%) in the 40 mg group, and 4 of 5 subjects (80.0%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 1 of 4 subjects (25.0%) in the 20 mg group, 1 of 4 subjects (25.0%) in the 40 mg group, and 1 of 5 subjects (20.0%) in the placebo group. The adverse event reported by ≥2 subjects in any treatment group was headache in 2 patients (40.0%) in the placebo group.

There were no serious adverse events nor those leading to discontinuation of the study drug.

7.2.12 Foreign phase I study (Study 162-0602)

Adverse events were observed in 6 of 6 subjects (100%) in the 5 mg QD group (a), 6 of 6 subjects (100%) in the 10 mg QD group (b), 4 of 4 subjects (100%) in the 20 mg QD group (c), 6 of 6 subjects (100%) in the 20 mg BID group (d), 3 of 4 subjects (75.0%) in the 80 mg single dose group (e), 6 of 6 subjects (100%) in the 40 mg QD group (f), 6 of 6 subjects (100%) in the 60 mg QD group (g), and 9 of 12 subjects (75.0%) in the placebo group (h). Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 5 subjects (83.3%) in (a), 6 subjects (100%) in (b), 4 subjects (100%) in (c), 6 subjects (100%) in (d), 1 subject (25.0%) in (e), 6 subjects (100%) in (f), 6 subjects (100%) in (g), and 8 subjects (66.7%) in (h). Adverse events reported by ≥4 subjects in any group were headache in 5 subjects (83.3%) in (a), diarrhoea in 4 subjects (66.7%) in (b), rash in 6 subjects (100%) in (d), acne in 6 subjects (100%), diarrhoea in 5 subjects (83.3%), and rash erythematous in 4 subjects (66.7%) in (f), headache and rash in 4 subjects (66.7%) each in (g), and headache and diarrhoea in 4 subjects (33.3%) each in (h).

There were no serious adverse events.

Adverse events leading to discontinuation of the study drug were observed in 1 of 6 subjects (16.7%) in (d), 1 of 6 subjects (16.7%) in (f), 2 of 6 subjects (33.3%) in (g), and 1 of 12 subjects (8.3%) in (h). The observed events were rash and swelling face in 1 subject (16.7%) each in (d), rash macular in 1 subject (16.7%) in (f), acne, rash, and rash maculo-papular in 1 subject (16.7%) each in (g), and vision blurred

in 1 subject (8.3%) in (h). A causal relationship to the study drug could not be ruled out for all of these events except for vision blurred in 1 subject in the placebo group.

7.2.13 Foreign phase I study (Study 162-104)

An adverse event was observed in 1 of 12 subjects (8.3%). An adverse event for which a causal relationship to the study drug could not be ruled out was also observed in 1 of 12 subjects (8.3%). The observed adverse event was headache in 1 subject (8.3%).

There were no serious adverse events nor those leading to discontinuation of the study drug.

7.2.14 Foreign phase I study (Study 162-105)

Adverse events were observed in 1 of 15 subjects (6.7%) in the BINI group and in 15 of 15 subjects (100%) in the ENCO group. Adverse events for which a causal relationship to the study drug could not be ruled out were also observed in 1 of 15 subjects (6.7%) in the BINI group and in 15 of 15 subjects (100%) in the ENCO group. Adverse events with an incidence of ≥30% in either group were headache in 14 subjects (93.3%), flushing in 12 subjects (80.0%), feeling hot in 8 subjects (53.3%), nausea and chills in 7 subjects (46.7%) each, and abdominal pain in 5 subjects (33.3%) in the ENCO group.

There were no serious adverse events.

An adverse event leading to discontinuation of the study drug was observed in 1 of 14 subjects (7.1%) in the ENCO group. The event was vomiting in 1 subject, and its causal relationship to the study drug could not be ruled out.

7.2.15 Foreign phase I study (Study 162-106)

Adverse events were observed in 2 of 6 patients with severe renal impairment (33.3%), and adverse events for which a causal relationship to the study drug could not be ruled out were observed in 1 of 6 patients with severe renal impairment (16.7%). Adverse events observed in either population were headache and myalgia in 1 patient (16.7%) each among those with severe renal impairment.

There were no serious adverse events nor those leading to discontinuation of the study drug.

7.2.16 Foreign phase I study (Study 818-101)

Adverse events were observed in 5 of 6 subjects with normal hepatic function (83.3%) and in 6 of 7 patients with mild hepatic impairment (85.7%). Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 5 of 6 subjects with normal hepatic function (83.3%) and in 4 of 7 patients with mild hepatic impairment (57.1%). Adverse events reported by ≥2 patients in either group were headache in 2 subjects with normal hepatic function (33.3%) and headache and drug eruption in 2 patients each with mild hepatic impairment (28.6%).

There were no serious adverse events nor those leading to discontinuation of the study drug.

7.2.17 Foreign phase I study (Study 818-102)

Adverse events were observed in 27 of 34 subjects (79.4%) in the fasted group and 34 of 37 subjects (91.9%) in the fed group. Adverse events for which a causal relationship to the study drug could not be ruled out were also observed in 27 of 34 subjects (79.4%) in the fasted group and 34 of 37 subjects (91.9%) in the fed group. Adverse events with an incidence of ≥10% in either group were flushing in 24 subjects (70.6%), headache in 15 subjects (44.1%), feeling hot in 6 subjects (17.6%), and hyperaesthesia in 4 subjects (11.8%) in the fasted group; flushing in 26 subjects (70.3%), headache in 24 subjects (64.9%), paraesthesia in 9 subjects (24.3%), nausea and feeling hot in 6 subjects (16.2%) each, and sensory disturbance in 4 subjects (10.8%) in the fed group.

There were no serious adverse events.

Adverse events leading to discontinuation of the study drug were observed in 2 of 34 subjects (5.9%) in the fasted group and in 4 of 37 subjects (10.8%) in the fed group. The observed adverse events were diarrhoea and blood pressure increased in 1 subject (2.9%) each in the fasted group; and oral herpes in 2 subjects (5.4%), conjunctivitis and haematuria in 1 subject (2.7%) each in the fed group. A causal relationship to the study drug could not be ruled out for oral herpes in 2 subjects in the fed group.

7.2.18 Foreign phase I study (Study 818-105)

Adverse events were observed in 15 of 16 subjects (93.8%) in part 1 and in 13 of 16 subjects (81.3%) in part 2. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 15 of 16 subjects (93.8%) in part 1 and in 12 of 16 subjects (75.0%) in part 2. Adverse events with an incidence of ≥30% in either part were erythema in 14 subjects (87.5%), feeling hot in 12 subjects (75.0%), headache in 11 subjects (68.8%), chills and face oedema in 9 subjects (56.3%) each, pruritus and skin exfoliation in 7 subjects (43.8%) each, and periorbital oedema in 5 subjects (31.3%) in part 1; and headache in 7 subjects (43.8%) in part 2.

There were no serious adverse events nor those leading to discontinuation of the study drug.

7.2.19 Foreign phase I study (Study 162-111)

Adverse events were observed in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 4 of 4 patients (100%) in the 30 mg group, 41 of 44 patients (93.2%) in the 45 mg group, 38 of 41 patients (92.7%) in the 60 mg group, and 4 of 4 patients (100%) in the 80 mg group. Adverse events with an incidence of ≥50% in any group were diarrhoea in 4 patients (100%), nausea, vomiting, and rash in 3 patients (75.0%) each, dyspnoea, constipation, pruritus, fatigue, and pyrexia in 2 patients (50.0%) each in the 30 mg group; nausea in 27 patients (61.4%), and vomiting in 23 patients (52.3%) in the 45 mg group; rash in 32 patients (78.0%), diarrhoea in 25 patients (61.0%), nausea and oedema peripheral in 21 patients (51.2%) each in the 60 mg group; and retinopathy, haematochezia, vomiting, and oedema peripheral in 2 patients (50.0%) each in the 80 mg group.

Serious adverse events were observed in 2 of 4 patients (50.0%) in the 30 mg group, 9 of 44 patients (20.5%) in the 45 mg group, and 17 of 41 patients (41.5%) in the 60 mg group. Serious adverse events reported by ≥2 patients in any group were anaemia in 4 patients (9.8%), and bacteraemia and ulcer

haemorrhage in 2 patients (4.9%) each in the 60 mg group. A causal relationship to the study drug was denied for all of them.

Adverse events leading to discontinuation of the study drug were observed in 10 of 44 patients (22.7%) in the 45 mg group, 10 of 41 patients (24.4%) in the 60 mg group, and 1 of 4 patients (25.0%) in the 80 mg group. Adverse events leading to discontinuation of the study drug reported by ≥2 patients were malignant neoplasm progression and fatigue in 3 patients (6.8%) each, nausea and dermatitis acneiform in 2 patients (4.5%) each in the 45 mg group; and malignant neoplasm progression in 4 patients (9.8%) in the 60 mg group. A causal relationship to the study drug could not be ruled out for dermatitis acneiform and fatigue in 2 patients each and nausea in 1 patient in the 45 mg group.

7.2.20 Foreign phase Ib/II study (Study X2110)

7.2.20.1 Phase Ib part

Adverse events were observed in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 6 of 6 patients (100%) in the 50 mg group, 4 of 5 patients (80.0%) in the 100 mg group, 3 of 4 patients (75.0%) in the 200 mg group, 4 of 5 patients (80.0%) in the 400 mg group, 13 of 13 patients (100%) in the 450 mg group, 8 of 8 patients (100%) in the 600 mg group, and 6 of 6 patients (100%) in the 800 mg group. Adverse events with an incidence of ≥60% in any group were fatigue in 4 patients (66.7%) in the 50 mg group; nausea in 4 patients (80.0%), cough, constipation, and arthralgia in 3 patients (60.0%) each in the 100 mg group; vomiting in 4 patients (100%) in the 200 mg group; abdominal pain, nausea, and vomiting in 3 patients (60.0%) each in the 400 mg group; diarrhoea in 7 patients (87.5%) and nausea in 5 (62.5%) in the 600 mg group; and headache in 5 patients (83.3%), constipation, diarrhoea, and nausea in 4 patients (66.7%) in the 800 mg group.

Serious adverse events were observed in 3 of 6 patients (50.0%) in the 50 mg group, 1 of 5 patients (20.0%) in the 100 mg group, 2 of 4 patients (50.0%) in the 200 mg group, 2 of 5 patients (40.0%) in the 400 mg group, 4 of 13 patients (30.8%) in the 450 mg group, 4 of 8 patients (50.0%) in the 600 mg group, and 3 of 6 patients (50.0%) in the 800 mg group. There were no serious adverse events reported by ≥2 patients in any group.

Adverse events leading to discontinuation of the study drug were observed in 1 of 6 patients (16.7%) in the 50 mg group, 1 of 5 patients (20.0%) in the 400 mg group, 1 of 13 patients (7.7%) in the 450 mg group, and 1 of 8 patients (12.5%) in the 600 mg group. There were no adverse events leading to discontinuation of the study drug reported by ≥2 patients in any group.

7.2.20.2 Phase II part

Adverse events were observed in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 11 of 11 patients (100%) in the CRC group, 26 of 26 patients (100%) in the previously treated malignant melanoma group, and 40 of 42 patients (95.2%) in the treatment naïve malignant melanoma group. Table 87 shows adverse events with an incidence of ≥40% in any group.

Table 87. Adverse events with an incidence of ≥40% in any group

SOC PT (MedDRA ver. 18.1)	Number of patients (%)					
	CRC (n = 11)		Previously treated malignant melanoma (n = 26)		Treatment naïve malignant melanoma (n = 42)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	11 (100)	4 (36.4)	26 (100)	15 (57.7)	42 (100)	25 (59.5)
Eye disorders						
Retinopathy	7 (63.6)	0	4 (15.4)	0	6 (14.3)	2 (4.8)
Gastrointestinal disorders						
Diarrhoea	8 (72.7)	2 (18.2)	14 (53.8)	1 (3.8)	19 (45.2)	1 (2.4)
Nausea	6 (54.5)	0	11 (42.3)	3 (11.5)	20 (47.6)	2 (4.8)
Vomiting	6 (54.5)	0	9 (34.6)	3 (11.5)	14 (33.3)	2 (4.8)
General disorders and administration site conditions						
Asthenia	6 (54.5)	0	3 (11.5)	0	3 (7.1)	0
Pyrexia	6 (54.5)	0	6 (23.1)	0	14 (33.3)	2 (4.8)

Serious adverse events were observed in 4 of 11 patients (36.4%) in the CRC group, 12 of 26 patients (46.2%) in the previously treated malignant melanoma group, and 15 of 42 patients (35.7%) in the treatment naïve malignant melanoma group. Serious adverse events reported by ≥2 patients in any group were hypercreatininaemia and intestinal obstruction in 2 patients (18.2%) each in the CRC group; nausea and vomiting in 3 patients (11.5%) each, and hyponatraemia and pyrexia in 2 patients (7.7%) each in the previously treated malignant melanoma group; and pyrexia in 3 patients (7.1%), and headache, nausea, and vomiting in 2 patients (4.8%) each in the treatment naïve malignant melanoma group. A causal relationship to the study drug could not be ruled out for hypercreatininaemia in 2 patients in the CRC group, pyrexia in 1 patient in the previously treated malignant melanoma group, and pyrexia in 1 patient in the treatment naïve malignant melanoma group.

Adverse events leading to discontinuation of the study drug were observed in 1 of 11 patients (9.1%) in the CRC group, 2 of 26 patients (7.7%) in the previously treated malignant melanoma group, and 4 of 42 patients (9.5%) in the treatment naïve malignant melanoma group. There were no adverse events leading to discontinuation of the study drug reported by ≥2 patients in any group.

7.2.21 Foreign phase II study (Study X2102)

Adverse events were observed in all patients, and adverse events for which a causal relationship to the study drug could not be ruled out were also observed in all patients. Adverse events with an incidence of ≥40% in either part were hyperkeratosis in 12 patients (80.0%), insomnia and alopecia in 10 patients (66.7%) each, palmar-plantar erythrodysaesthesia syndrome in 9 patients (60.0%), fatigue in 8 patients (53.3%), and arthralgia in 6 patients (40.0%) in part 1; and convulsion, decreased appetite, fatigue, and vaginal haemorrhage in 1 patient (100%) each in part 2.

Serious adverse events were observed in 3 of 15 patients (20.0%) in part 1. They were pneumonia, metastatic pain, metastases to central nervous system, coagulopathy, dehydration, panic attack, atrial fibrillation, hypotension, dyspnoea, acute renal failure, and urinary retention in 1 patient (6.7%) each in part 1. A causal relationship to the study drug could not be ruled out for any of them.

Adverse events leading to discontinuation of the study drug were observed in 7 of 15 patients (46.7%) in part 1. They were palmar-plantar erythrodysaesthesia syndrome in 2 patients (13.3%), and pneumonia, hypertriglyceridaemia, paraesthesia, hyperkeratosis, and asthenia in 1 patient (6.7%) each. A causal

relationship to the study drug could not be ruled out for palmar-plantar erythrodysaesthesia syndrome in 2 patients, and paraesthesia, hyperkeratosis, and asthenia in 1 patient each in part 1.

7.2.22 Foreign phase II study (Study X2109)

Adverse events were observed in 75 of 75 patients (100%) in the treatment naïve group and 77 of 83 patients (92.8%) in the previously treated group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 70 of 75 patients (93.3%) in the treatment naïve group and 64 of 83 patients (77.1%) in the previously treated group. Table 88 shows adverse events with an incidence of ≥30% in either group.

Table 88. Adverse events with an incidence of ≥30% in either group

SOC PT (MedDRA ver. 19.0)	Number of patients (%)			
	Treatment naïve patients N = 75		Previously treated patients N = 83	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	75 (100)	44 (58.7)	77 (92.8)	45 (54.2)
Gastrointestinal disorders				
Diarrhoea	27 (36.0)	4 (5.3)	21 (25.3)	1 (1.2)
Nausea	26 (34.7)	4 (5.3)	30 (36.1)	4 (4.8)
General disorders and administration site conditions				
Fatigue	26 (34.7)	2 (2.7)	22 (26.5)	3 (3.6)
Investigations				
Blood CK increased	23 (30.7)	2 (2.7)	6 (7.2)	1 (1.2)

Serious adverse events were observed in 31 of 75 patients (41.3%) in the treatment naïve group and 28 of 83 patients (33.7%) in the previously treated group. Serious adverse events reported by ≥2 patients in either group were nausea in 4 patients (5.3%), pneumonia and diarrhoea in 3 patients (4.0%) each, and epilepsy, partial seizures, Crohn's disease, and vomiting in 2 patients (2.7%) each in the treatment naïve group; vomiting in 6 patients (7.2%), pyrexia and general physical condition decreased in 4 patients (4.8%) each, sepsis and nausea in 3 patients (3.6%) each, and tumour pain, dehydration, and lipase increased in 2 patients (2.4%) each in the previously treated group. A causal relationship to the study drug could not be ruled out for Crohn's disease, diarrhoea, and nausea in 1 patient each in the treatment naïve group; and vomiting in 5 patients, nausea in 3 patients, pyrexia in 2 patients, and sepsis, general physical condition decreased, and lipase increased in 1 patient each in the previously treated group.

Adverse events leading to discontinuation of the study drug were observed in 4 of 75 patients (5.3%) in the treatment naïve group and 9 of 83 patients (10.8%) in the previously treated group. Adverse events leading to discontinuation of the study drug reported by ≥2 patients in either group were vomiting, pyrexia, and blood creatinine increased in 2 patients (2.4%) each in the previously treated group. A causal relationship to the study drug could not be ruled out for blood creatinine increased in 2 patients, and vomiting and pyrexia in 1 patient each in the previously treated group.

7.2.23 Foreign phase II study (Study X2201)

Adverse events were observed in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 40 of 41 patients (97.6%) in the BRAF 45 mg group, 114 of 117 patients (97.4%) in the NRAS 45 mg group, and 24 of 25 patients (96.0%) in the BRAF 60 mg group. Table 89 shows adverse events with an incidence of ≥30% in any group.

Table 89. Adverse events with an incidence of ≥30% in any group

SOC PT (MedDRA ver. 16.1)	Number of patients (%)					
	BRAF 45 mg (n = 41)		NRAS 45 mg (n = 117)		BRAF 60 mg (n = 25)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	41 (100)	27 (65.9)	117 (100)	73 (62.4)	25 (100)	18 (72.0)
Eye disorders						
Retinopathy	1 (2.4)	0	12 (10.3)	0	10 (40.0)	1 (4.0)
Gastrointestinal disorders						
Diarrhoea	18 (43.9)	1 (2.4)	57 (48.7)	3 (2.6)	13 (52.0)	0
Nausea	10 (24.4)	0	37 (31.6)	1 (0.9)	12 (48.0)	3 (12.0)
Vomiting	5 (12.2)	1 (2.4)	21 (17.9)	1 (0.9)	9 (36.0)	3 (12.0)
Skin and subcutaneous tissue disorders						
Dermatitis acneiform	15 (36.6)	3 (7.3)	63 (53.8)	1 (0.9)	8 (32.0)	0
Rash	16 (39.0)	0	24 (20.5)	1 (0.9)	5 (20.0)	0
General disorders and administration site conditions						
Fatigue	12 (29.3)	2 (4.9)	39 (33.3)	6 (5.1)	12 (48.0)	0
Oedema peripheral	17 (41.5)	1 (2.4)	57 (48.7)	1 (0.9)	14 (56.0)	0
Investigations						
Blood CK increased	12 (29.3)	9 (22.0)	60 (51.3)	29 (24.8)	14 (56.0)	6 (24.0)

Serious adverse events were observed in 11 of 41 patients (26.8%) in the BRAF 45 mg group, 35 of 117 patients (29.9%) in the NRAS 45 mg group, and 9 of 25 patients (36.0%) in the BRAF 60 mg group. Serious adverse events reported by ≥2 patients were hypokalaemia in 2 patients (4.9%) in the BRAF 45 mg group; erysipelas in 4 patients (3.4%), general physical condition decreased in 3 patients (2.6%), and dehydration, diarrhoea, and blood CK increased in 2 patients (1.7%) each in the NRAS 45 mg group; and gastritis in 2 patients (8.0%) in the BRAF 60 mg group. A causal relationship to the study drug could not be ruled out for diarrhoea and blood CK increased in 2 patients each and general physical condition decreased in 1 patient in the NRAS 45 mg group.

Adverse events leading to discontinuation of the study drug were observed in 12 of 41 patients (29.3%) in the BRAF 45 mg group, 16 of 117 patients (13.7%) in the NRAS 45 mg group, and 5 of 25 patients (20.0%) in the BRAF 60 mg group. Adverse events leading to discontinuation of the study drug reported by ≥2 patients were dermatitis acneiform in 2 patients (4.9%) in the BRAF 45 mg group; ejection fraction decreased in 4 patients (3.4%), and retinal vein occlusion and general physical condition decreased in 2 patients (1.7%) each in the NRAS 45 mg group; and blood CK increased in 2 patients (8.0%) in the BRAF 60 mg group. A causal relationship to the study drug could not be ruled out for dermatitis acneiform in 2 patients in the BRAF 45 mg group; ejection fraction decreased in 4 patients and retinal vein occlusion in 2 patients in the NRAS 45 mg group; and blood CK increased in 2 patients in the BRAF 60 mg group.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices. On the basis of the inspection and

assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.3.2-4, CTD 5.3.5.1-1, CTD 5.3.5.1-2, CTD 5.3.5.1-3) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. PMDA identified the following findings requiring corrective action at some of the study sites and the sponsor (clinical trial in-country representative), although they had no significant impact on the review of the overall clinical studies. PMDA notified the head of the study site and the sponsor (clinical trial in-country representative) to seek improvement.

Inspection findings

Study site

- Some of the informed consent forms of patients participating in the study were not signed (nor affixed with name and seal) and dated by the investigator, etc., who provided the explanation of the study.

Sponsor (clinical trial in-country representative)

- Delay in annual report of safety information to the investigator and to the head of study sites

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

On the basis of the data submitted, PMDA has concluded that ENCO/BINI has efficacy in the treatment of unresectable malignant melanoma with *BRAF* gene mutation, and that ENCO/BINI has acceptable safety in view of its benefit. ENCO and BINI are drugs with new active ingredients that inhibit kinase activity of BRAF and MEK, respectively, and they are considered to inhibit the growth of tumors with *BRAF* gene mutation by inhibiting the phosphorylation of signal transduction molecules on MAPK pathway (e.g., ERK). ENCO and BINI have clinical significance as a treatment option for unresectable malignant melanoma with *BRAF* gene mutation. The safety, dosage and administration, and post-marketing investigations are subject to further discussion.

PMDA has concluded that both ENCO and BINI may be approved if they are not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 19, 2018

Product Submitted for Approval

(a)	**Brand Name**	Braftovi Capsules 50 mg
	Non-proprietary Name	Encorafenib
	Applicant	Ono Pharmaceutical Co., Ltd.
	Date of Application	April 25, 2018
(b)	**Brand Name**	Mektovi Tablets 15 mg
	Non-proprietary Name	Binimetinib
	Applicant	Ono Pharmaceutical Co., Ltd.
	Date of Application	April 25, 2018

List of Abbreviations
See Appendix.

1. Content of the Review

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

1.1 Efficacy

Following the review on Section "7.R.2 Efficacy" of the Review Report (1), PMDA concluded that the efficacy of ENCO/BINI was demonstrated in patients, with unresectable malignant melanoma with BRAF V600E or V600K mutation, previously untreated with BRAF or MEK inhibitor (treatment naïve), by the superiority of Combo 450 (concomitant use of ENCO 450 mg and BINI 45 mg) to VEM in the primary endpoint, i.e., PFS by central assessment, in the global phase III study (Study B2301).

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

1.2 Safety

Following the review on Section "7.R.3 Safety" of the Review Report (1), PMDA concluded that the treatment with ENCO/BINI in patients with unresectable malignant melanoma with BRAF V600 mutation requires particular attention to eye disorders, cardiac dysfunction, hepatic dysfunction, rhabdomyolysis, cutaneous malignancies, hypertension, haemorrhage, and palmar-plantar erythrodysaesthesia syndrome.

Despite these adverse events requiring close attention, PMDA concluded that ENCO/BINI is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring and controlling adverse events; and interruption of ENCO and BINI.

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

1.3 Clinical positioning and indication

As a result of the review on Section "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA concluded that ENCO and BINI should be indicated for "unresectable malignant melanoma with *BRAF* gene mutation," as proposed by the applicant. The "Clinical Studies" section of the package insert should contain the information that the patients treated in Study B2301 were those with BRAF V600E or V600K mutation and that test for BRAF V600E or V600K was performed by using "THxID BRAF kit" which is approved as a companion diagnostic. Also, the "Precautions for Indication" section should contain the following precautionary statements:

Precautions for Indication section

- ENCO and BINI should be administered to patients with known *BRAF* gene mutation through tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic should be used in the test.
- Suitable patients should be selected based on a thorough understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of ENCO and BINI.
- The efficacy and safety of ENCO and BINI in adjuvant chemotherapy have not been established.

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

On the basis of the above, PMDA instructed the applicant to finalize the descriptions in the "Indications" and "Precautions for Indications" sections as above. The applicant agreed.

1.4 Dosage and administration

Following the review on Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA concluded that the "Dosage and Administration" and "Precautions for Dosage and Administration" sections of ENCO and BINI should be defined as shown below.

	Dosage and Administration	Precautions for Dosage and Administration
ENCO	In combination with BINI, the usual adult dosage is 450 mg of ENCO administered orally once daily. The dose may be reduced according to the patient's condition.	• Increased blood ENCO concentration has been reported in patients with hepatic impairment. The dose reduction of ENCO should be considered in these patients, and patients should be monitored more carefully for occurrence of adverse events. • In clinical studies investigating the tolerability of ENCO monotherapy, it is suggested that once daily administration of 450 mg may exceed the maximum tolerated dose of ENCO. When BINI is interrupted or discontinued, the dose reduction of ENCO should be considered, and patient should be closely monitored for occurrences of adverse events. • Guide for interruption, dose reduction, and discontinuation of ENCO in case of adverse drug reactions [see Section "7.R.5.2 Dose adjustment of ENCO and BINI" of the Review Report (1)].
BINI	In combination with ENCO, the usual adult dosage is 45 mg of BINI administered orally twice daily. The dose may be reduced according to the patient's condition.	• Increased blood BINI concentration has been reported in patients with moderate or severe hepatic impairment. The dose reduction of BINI should be considered in these patients, and patients should be monitored more carefully for occurrences of adverse events. • When ENCO is interrupted or discontinued, BINI should also be interrupted or discontinued, respectively. • Guide for interruption, dose reduction, and discontinuation of BINI in case of adverse drug reactions [see Section "7.R.5.2 Dose adjustment of ENCO and BINI" of the Review Report (1)].

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- The "Precautions for Dosage and Administration" section for ENCO contains the precautionary statement requiring consideration of dose reduction of ENCO in case of the interruption or discontinuation of BINI. The information that justifies such requirement [see Section "7.R.5.1 Dosage and administration of ENCO and BINI" of the Review Report (1)] should be provided appropriately to healthcare professionals using the package insert.

Accordingly, PMDA instructed the applicant to state the "Dosage and Administration" and "Precautions for Dosage and Administration" sections as above, and to include the results of the global phase I study (Study X2101) investigating the tolerability of ENCO monotherapy in the "Clinical Studies" section of the package insert for ENCO. The applicant agreed.

1.5 Risk management plan (draft)

To evaluate the safety, etc., of ENCO/BINI in post-marketing clinical use by collecting the information of not only the safety specifications but also overall adverse events, the applicant plans to conduct post-marketing surveillance covering all patients treated with ENCO/BINI, with the planned sample size of 150 patients and the observation period of 12 months.

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA concluded that it is essential to conduct post-marketing surveillance covering all patients treated with ENCO/BINI over a certain period to collect safety data promptly in an unbiased manner and to provide available safety data to healthcare professionals without delay.

Also, PMDA concluded the surveillance plan as follows:

- The safety specifications should include eye disorders, cardiac dysfunction, hepatic dysfunction, rhabdomyolysis, cutaneous malignancies, hypertension, haemorrhage, and palmar-plantar erythrodysaesthesia syndrome.

- The planned sample size and the observation period should be revised in light of the incidences of adverse events included in the safety specifications for this surveillance.

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

In view of the comments from the Expert Discussion, PMDA instructed the applicant to re-consider the post-marketing surveillance plan.

The applicant's explanation:
- The safety specifications will include eye disorders, cardiac dysfunction, hepatic dysfunction, rhabdomyolysis, cutaneous malignancies, hypertension, haemorrhage, and palmar-plantar erythrodysaesthesia syndrome. Incidence of these events in clinical use will be investigated.
- The planned sample size is 150 as a result of the reconsideration, taking account of the incidences of the above events in Study B2301.
- The observation period is 12 months as a result of the reconsideration, taking account of the incidences of the above events in Study B2301.

PMDA accepted the applicant's explanation.

In view of the discussions above, PMDA has concluded that the risk management plan (draft) for ENCO/BINI should include the safety specifications presented in Tables 90 and 91, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 92 and 93.

Table 90. Safety and efficacy specifications in the risk management plan (draft) of ENCO

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Cutaneous malignancies • Palmar-plantar erythrodysaesthesia syndrome • Eye disorders	• Secondary malignancies other than cutaneous malignancies • Cardiac dysfunction • Hypertension • Rhabdomyolysis • Hepatic dysfunction • Haemorrhage • ILD/pneumonitis • Renal impairment • QT prolongation • Drug-drug interactions in concomitant use with moderate or potent CYP3A inhibitors • Embryo-fetal toxicity	Not applicable
Efficacy specification		
Not applicable		

Table 91. Safety and efficacy specifications in the risk management plan (draft) of BINI

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Cardiac dysfunction • Hypertension • Rhabdomyolysis • Hepatic dysfunction • Eye disorders • Haemorrhage	• ILD/pneumonitis • Venous thromboembolism • Renal impairment • QT prolongation • Safety in patients with moderate or severe hepatic impairment • Embryo-fetal toxicity	Not applicable
Efficacy specification		
Not applicable		

Table 92. Summary of additional pharmacovigilance activities, efficacy surveillance and studies, and additional risk minimization activities included under the risk management plan (draft) for ENCO/BINI

Additional pharmacovigilance activities	Efficacy surveillance and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey	Not applicable	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate materials for healthcare professionals

Table 93. Outline of use-results survey (draft)

Objective	To investigate the incidences of eye disorders, cardiac dysfunction, hepatic dysfunction, rhabdomyolysis, cutaneous malignancies, hypertension, haemorrhage, and palmar-plantar erythrodysaesthesia syndrome under routine clinical practice.
Survey method	All-case surveillance
Population	All patients treated with ENCO/BINI
Observation period	12 months
Planned sample size	150 patients
Main survey items	Safety specifications: Eye disorders, cardiac dysfunction, hepatic dysfunction, rhabdomyolysis, cutaneous malignancies, hypertension, haemorrhage, and palmar-plantar erythrodysaesthesia syndrome Other main survey items: Patient characteristics (age, sex, disease stage, medical history, concurrent illness, etc.), the details on administration of ENCO and BINI, concomitant drugs, etc.

2. Overall Evaluation

As a result of the above review, PMDA concluded that the products may be approved for the following indication and dosage and administration with the following approval conditions, provided that appropriate cautions will be included in the package insert and information on the proper use of the products will be provided appropriately after the market launch, and the proper use of ENCO and BINI will be ensured under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions with adequate facilities for emergency care. Because both the products are designated as orphan drugs, their re-examination period is 10 years. The products are not classified as biological products or specified biological products. The drug products and their drug substances are both classified as powerful drugs.

Braftovi Capsules 50 mg

Indication

Unresectable malignant melanoma with *BRAF* gene mutation

Dosage and Administration

In combination with binimetinib, the usual adult dosage is 450 mg of encorafenib administered orally once daily. The dose may be reduced according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics of patients treated with the product. The applicant is also required to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.

Warning

Encorafenib should be administered only to patients suitable for the treatment with the product under the supervision of a physician with adequate knowledge and experience in the treatment of cancer chemotherapy at a medical institution with adequate facilities for emergency care. Prior to treatment, patients or their family members should be thoroughly informed of the potential risks and benefits of the treatment, and informed consent should be obtained before starting treatment.

Contraindication

Patients with a history of hypersensitivity to encorafenib or to any of its components

Precautions for Indications

(1) Encorafenib should be administered to patients with known *BRAF* gene mutation through tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic should be used in the test.
(2) Suitable patients should be selected based on a thorough understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of the product.
(3) The efficacy and safety of the product in adjuvant chemotherapy have not been established.

Precautions for Dosage and Administration

(1) In case of adverse drug reactions associated with encorafenib, treatment should be interrupted, reduced in dose, or discontinued by referring to the following criteria.
(2) In clinical studies investigating the tolerability of encorafenib monotherapy, it is suggested that once daily administration of 450 mg may exceed the maximum tolerated dose of encorafenib. When binimetinib is interrupted or discontinued, the dose reduction of encorafenib should be considered, and patient should be closely monitored for occurrences of adverse drug reactions.
(3) Increased blood encorafenib concentration has been reported in patients with hepatic impairment. The dose reduction of encorafenib should be considered in these patients, and patients should be monitored more carefully for occurrence of adverse drug reactions.

Dose reduction in continued administration

Dose reduction level[*1]	Dose
Normal dose	450 mg once daily
1-level dose reduction	300 mg once daily
2-level dose reduction	200 mg once daily
3-level dose reduction	Discontinue

[*1] If the adverse drug reaction requiring dose reduction has improved to Grade ≤1, and there are no other concomitant adverse drug reactions, the dose may be increased according to the reverse steps.

Criteria for dose adjustment in case of adverse drug reactions

Adverse drug reaction	Severity[*2]	Measure
Retinal disease, uveitis	Grade 2	Interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose or at 1-level lower dose.
	Grade 3	Interrupt encorafenib until recovery to Grade ≤2. Resume encorafenib at 1-level lower dose. Discontinue encorafenib if Grade 3 persists.
	Grade 4	Discontinue encorafenib.
Retinal vein occlusion	Grade ≥1	Discontinue encorafenib.
Eye disorders (other than above)	Grade 3	Interrupt encorafenib until recovery to Grade ≤1. If recovered within 28 days, resume encorafenib at 1-level lower dose. Discontinue encorafenib if not recovered within 28 days.
	Grade 4	Discontinue encorafenib.
AST increased, ALT increased	Grade 2 (not accompanied by serum bilirubin increased)	If the symptom persists for >14 days, interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose. If recurrent, interrupt encorafenib until recovery and then resume at 1-level lower dose.
	Grade 2 (accompanied by serum bilirubin increased)	Interrupt encorafenib until recovery to Grade ≤1. If recovered within 7 days, resume encorafenib at 1-level lower dose. Discontinue encorafenib if not recovered within 7 days.
	Grade 3 (not accompanied by serum bilirubin increased)	Interrupt encorafenib until recovery to Grade ≤1. If recovered within 14 days, resume encorafenib at same dose. If recovered after >14 days, resume encorafenib at 1-level lower dose.
	Grade 3 (accompanied by serum bilirubin increased) and Grade 4	Discontinue encorafenib.
Serum CK increased	Grade 3-4 (accompanied by serum creatinine increased)	Interrupt encorafenib until recovery to Grade ≤1. If recovered within 28 days, resume encorafenib at 1-level lower dose. Discontinue encorafenib if not recovered within 28 days.
Electrocardiogram QT prolonged	QTc exceeds 500 ms, and the change from baseline is ≤60 ms.	Interrupt encorafenib until QTc decreases to <500 ms. Resume encorafenib at 1-level lower dose. Discontinue encorafenib if recurrent.
	QTc exceeds 500 ms, and the change from baseline is >60 ms.	Discontinue encorafenib.
Dermatitis	Grade 2	If the symptom persists or worsens, interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose.
	Grade 3	Interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose. If recurrent, interrupt encorafenib until recovery and then resume at 1-level lower dose.
	Grade 4	Discontinue encorafenib.
Palmar-plantar erythrodysaesthesia syndrome	Grade 2	If the symptom persists for >14 days, interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at same dose. If recurrent, interrupt encorafenib until recovery and then consider resumption at 1-level lower dose.
	Grade 3	Interrupt encorafenib until recovery to Grade ≤1. Resume encorafenib at 1-level lower dose. If repeatedly recurrent, consider resumption at 1-level lower dose or discontinuation.
Other adverse drug reactions	Grade 2	If Grade 2 persists, consider interruption or dose reduction.
	Grade 3	Consider interruption until recovery to Grade ≤1. If recovered within 28 days, consider resumption at 1-level lower dose.
	Grade 4	Discontinue encorafenib.

[*2] Grade is determined according to NCI-CTCAE ver4.03.

Mektovi Tablets 15 mg

Indication

Unresectable malignant melanoma with *BRAF* gene mutation

Dosage and Administration

In combination with encorafenib, the usual adult dosage is 45 mg of binimetinib administered orally twice daily. The dose may be reduced according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics of patients treated with the product. The applicant is also required to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.

Warning

Binimetinib should be administered only to patients suitable for the treatment with the product under the supervision of a physician with adequate knowledge and experience in the treatment of cancer chemotherapy at a medical institution with adequate facilities for emergency care. Prior to treatment, patients or their family members should be thoroughly informed of the potential risks and benefits of the treatment, and informed consent should be obtained before starting treatment.

Contraindication

Patients with a history of hypersensitivity to binimetinib or to any of its components

Precautions for Indication

(1) Binimetinib should be administered to patients with known *BRAF* gene mutation through tests performed by a thoroughly experienced pathologist or testing laboratory. An approved *in vitro* diagnostic should be used in the test.
(2) Suitable patients should be selected based on a thorough understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of the product.
(3) The efficacy and safety of the product in adjuvant chemotherapy have not been established.

Precautions for dosage and administration

(1) In case of adverse drug reactions associated with binimetinib, treatment should be interrupted, reduced in dose, or discontinued by referring to the following criteria.
(2) When encorafenib is interrupted or discontinued, binimetinib should also be interrupted or discontinued, respectively.
(3) Increased blood binimetinib concentration has been reported in patients with moderate or severe hepatic impairment. The dose reduction of binimetinib should be considered, and patients should be monitored more carefully for occurrences of adverse events.

Dose reduction in continued administration

Dose reduction level[*1]	Dose
Normal dose	45 mg twice daily
1-level dose reduction	30 mg twice daily
2-level dose reduction	15 mg twice daily
3-level dose reduction	Discontinue.

[*1] If the adverse drug reaction requiring dose reduction has improved to Grade ≤1, and there are no other concomitant adverse drug reactions, the dose may be increased according to the reverse steps.

Criteria for dose adjustment in case of adverse drug reactions

Adverse drug reaction	Severity[*2]	Measure
Retinal disease, uveitis	Grade 2	Interrupt binimetinib until recovery to Grade ≤1. Resume binimetinib at same dose or at 1-level lower dose.
	Grade 3	Interrupt binimetinib until recovery to Grade ≤2. Resume binimetinib at 1-level lower dose. Discontinue binimetinib if Grade 3 persists.
	Grade 4	Discontinue binimetinib.
Retinal vein occlusion	Grade ≥1	Discontinue binimetinib.
Eye disorders (other than above)	Grade 3	Interrupt binimetinib until recovery to Grade ≤1. If recovered within 28 days, resume binimetinib at 1-level lower dose. Discontinue binimetinib if not recovered within 28 days.
	Grade 4	Discontinue binimetinib.
AST increased, ALT increased	Grade 2 (not accompanied by serum bilirubin increased)	Interrupt binimetinib until recovery to Grade ≤1. If recovered within 14 days, resume binimetinib at same dose. If recovered after ≥14 days, resume binimetinib at 1-level lower dose. If recurrent, interrupt binimetinib until recovery and then resume at 1-level lower dose.
	Grade 2 (accompanied by serum bilirubin increased)	Interrupt binimetinib until recovery to Grade ≤1. If recovered within 7 days, resume binimetinib at 1-level lower dose. Discontinue binimetinib if not recovered within 7 days.
	Grade 3 (not accompanied by serum bilirubin increased)	Interrupt binimetinib until recovery to Grade ≤1. Resume binimetinib at 1-level lower dose.
	Grade 3 (accompanied by serum bilirubin increased) and Grade 4	Discontinue binimetinib.
Serum CK increased	Grade 3 (accompanied by muscular symptom or creatinine increased) and Grade 4	Interrupt binimetinib until recovery to Grade ≤1. If recovered within 28 days, resume binimetinib at 1-level lower dose. Discontinue binimetinib if not recovered within 28 days.
Ejection fraction decreased	Decrease in left ventricular ejection fraction from baseline by ≥10% or to below the lower limit of normal	Interrupt binimetinib until recovery. If recovered within 28 days, resume binimetinib at 1-level lower dose. Discontinue binimetinib if not recovered within 28 days.
	Grade 3-4	Discontinue binimetinib.
Electrocardiogram QT prolonged	QTc exceeds 500 ms, and the change from baseline is ≤60 ms.	Interrupt binimetinib until QTc decreases to <500 ms. Resume binimetinib at 1-level lower dose. Discontinue binimetinib if recurrent.
	QTc exceeds 500 ms, and the change from baseline is >60 ms.	Discontinue binimetinib.
Dermatitis	Grade 2	If the symptom persists or worsens, interrupt binimetinib until recovery to Grade ≤1. Resume binimetinib at same dose. If recurrent, interrupt binimetinib until recovery and then resume at 1-level lower dose.
	Grade 3	Interrupt binimetinib until recovery to Grade ≤1. Resume binimetinib at same dose. If recurrent, interrupt binimetinib until recovery and then resume at 1-level lower dose.
	Grade 4	Discontinue binimetinib.
Other adverse drug reactions	Grade 2	If Grade 2 persists, consider interruption or dose reduction.
	Grade 3	Consider interruption until recovery to Grade ≤1. If recovered within 28 days, consider resumption at 1-level lower dose.
	Grade 4	Discontinue binimetinib.

[*2] Grade is determined according to NCI-CTCAE ver4.03.

Appendix

List of Abbreviations

^{14}C-BINI	^{14}C-labeled BINI
^{14}C-ENCO	^{14}C-labeled ENCO
A/G ratio	albumin/globulin ratio
AGP	α1-acid glycoprotein
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BA	bioavailability
BCRP	breast cancer resistance protein
BID	bis in die
BINI	binimetinib
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BRAF V600 mutation	BRAF mutation involving amino acid substitution of valine to other amino acid at codon 600
BRAF V600D mutation	BRAF mutation involving amino acid substitution of valine to aspartic acid at codon 600
BRAF V600E mutation	BRAF mutation involving amino acid substitution of valine to glutamic acid at codon 600
BRAF V600K mutation	BRAF mutation involving amino acid substitution of valine to lysine at codon 600
BSEP	bile salt export pump
CI	confidence interval
CK	creatine phosphokinase
CL2/F	apparent inter-compartmental clearance
CMC	carboxymethylcellulose
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CRAF	Raf-1 proto-oncogene, serine/threonine kinase
CRC	colorectal cancer
CYP	cytochrome P450
Cobimetinib	Cobimetinib fumarate
Cobimetinib/VEM	Combination of cobimetinib and VEM
DAB	dabrafenib mesilate
DAB/TRA	Combination of DAB and TRA
DLT	dose-limiting toxicity
DMSO	dimethyl sulfoxide
DTIC	dacarbazine
Diltiazem	Diltiazem hydrochloride
ECOG	Eastern Cooperative Oncology Group
efflux ratio	Ratio of permeability coefficient in the direction of secretion to that in the direction of absorption
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ENCO	encorafenib
ENCO/BINI	Combination of encorafenib and binimetinib
ERK	extracellular signal-regulated kinase

ETPGS	Vitamin E d-α-tocopheryl polyethylene glycol succinate
FAS	Full analysis set
FGF	fibroblast growth factor
FOB	functional observation battery
FRET	fluorescence resonance energy transfer
GC	gas chromatography
hERG	human *ether-a-go-go* related gene
HLT	high level term
HSA	human serum albumin
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q1E Guideline	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ICH S9 Guideline	"Nonclinical Evaluation for Anticancer Pharmaceuticals (PFSB/ELD Notification No. 0604-(1) dated June 4, 2010).
ILD	interstitial lung disease
IPI	Ipilimumab (genetical recombination)
IR	infrared absorption spectrum
Japanese Guidelines for Clinical Practice	Guideline for evidence-based diagnosis and treatment of skin cancer, edited by Japanese Dermatological Association and Japanese Skin Cancer Society, 2nd edition
K_I	inhibitor concentration at 50% of maximum inhibition rate
k_{inact}	maximum inactivation rate constant
KRAS	KRAS proto-oncogene, GTPase
LC	liquid chromatography
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LDH	lactate dehydrogenase
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusion
MEK	mitogen-activated protein kinase/extracellular signal-regulated kinase kinase
mRNA	messenger ribonucleic acid
MRP	multidrug resistance associated protein
MTD	maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN Guideline	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Melanoma
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NE	not evaluable
NIVO	Nivolumab (genetical recombination)
NIVO/IPI	Combination of NIVO and IPI
NMR	nuclear magnetic resonance spectrum
NRAS	NRAS proto-oncogene, GTPase
NRAS Q61 mutation	NRAS mutation involving amino acid substitution of glutamine to other amino acid at codon 61
NZW	New Zealand White
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
P-gp	P-glycoprotein

PCR	polymerase chain reaction
PD	progressive disease
PDE4D	phosphodiesterase 4D
PEG	polyethylene glycol
PFS	Progression-free survival
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
PTP	press through packaging
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basolateral direction
QD	quaque die
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia method
QbD	quality by design
RP2D	recommended Phase 2 dose
SD	stable disease
SMQ	standard MedDRA queries
SOC	system organ class
SPA	scintillation proximity assay
STK36	serine/threonine kinase 36
Study 162-0601	Study ARRY-162-0601
Study 162-0602	Study ARRY-162-0602
Study 162-104	Study ARRAY-162-104
Study 162-105	Study ARRAY-162-105
Study 162-106	Study ARRAY-162-106
Study 162-111	Study ARRAY-162-111
Study 818-101	Study ARRAY-818-101
Study 818-102	Study ARRAY-818-102
Study 818-103	Study ARRAY-818-103
Study 818-105	Study ARRAY-818-105
Study A2101	Study CLGX818A2101
Study A2101J	Study CMEK162A2101J
Study A2102	Study CMEK162A2102
Study A2103	Study CMEK162A2103
Study A2104	Study CMEK162A2104
Study A2105	Study CMEK162A2105
Study A2301	Study CMEK162A2301
Study B2301	Study CMEK162B2301
Study X1101	Study CMEK162X1101
Study X2101	Study CLGX818X2101
Study X2102	Study CLGX818X2102
Study X2109	Study CLGX818X2109
Study X2110	Study CMEK162X2110
Study X2201	Study CMEK162X2201
TG	triglycerides

TRA	trametinib dimethyl sulfoxide
UDPGA	uridine diphosphate glucuronic acid
UGT	uridine diphosphate glucuronosyl transferase
UV-A	ultraviolet A
VEM	vemurafenib
ΔQTcF	Change in QTcF from baseline