Report on the Deliberation Results

February 7, 2014

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

[Brand name]	(1) Lonsurf combination tablets T15
	(2) Lonsurf combination tablets T20
[Non-proprietary name]	Trifluridine and Tipiracil Hydrochloride (JAN*)
[Name of applicant]	Taiho Pharmaceutical Co., Ltd.
[Date of application]	February 26, 2013

[Results of deliberation]
In the meeting held on February 3, 2014, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period for the product is 8 years. Trifluridine, one of the drug substances, and the drug product are classified as powerful drugs. The product is not classified as a biological product or a specified biological product.

[Conditions for approval]
The applicant is required to submit the results of the ongoing phase III study that is conducted to confirm the efficacy and safety of the product in patients with unresectable advanced or recurrent colorectal cancer without delay after the completion of the study for review.

**Japanese Accepted Name (modified INN)*

Review Report

January 15, 2014

The Pharmaceuticals and Medical Devices Agency

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

[Brand name] (1) Lonsurf combination tablets T15,
(2) Lonsurf combination tablets T20

[Non-proprietary name] Trifluridine and Tipiracil Hydrochloride

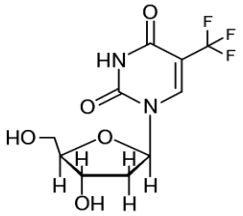
[Name of applicant] Taiho Pharmaceutical Co., Ltd.

[Date of application] February 26, 2013

[Dosage form/Strength] (1) Each tablet contains 15 mg of trifluridine and 7.065 mg of tipiracil hydrochloride.
(2) Each tablet contains 20 mg of trifluridine and 9.42 mg of tipiracil hydrochloride.

[Application classification] Prescription drug (1) Drug with a new active ingredient, (2) New prescription combination product

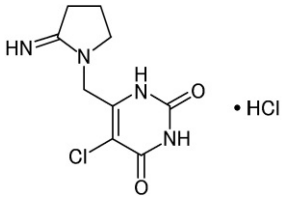
[Chemical structure]



Molecular formula: $C_{10}H_{11}F_3N_2O_5$

Molecular weight: 296.20

Chemical name: 2'-Deoxy-5-(trifluoromethyl)uridine



Molecular formula: $C_9H_{11}ClN_4O_2 \cdot HCl$

Molecular weight: 279.12

Chemical name: 5-Chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-dione monohydrochloride

[Items warranting special mention] None

[Reviewing office] Office of New Drug V

Review Results

January 15, 2014

[Brand name] Lonsurf combination tablets T15 and Lonsurf combination tablets T20
[Non-proprietary name] Trifluridine and Tipiracil Hydrochloride
[Name of applicant] Taiho Pharmaceutical Co., Ltd.
[Date of application] February 26, 2013

[Results of review]
Based on the data submitted by the applicant, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product is expected for the treatment of unresectable advanced or recurrent colorectal cancer (only if refractory to standard therapies), and the safety of the product is acceptable in view of the observed benefits. The occurrence of bone marrow suppression and infections needs to be further investigated via post-marketing surveillance.

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

[Indication] Unresectable advanced or recurrent colorectal cancer (only if refractory to standard therapies)

[Dosage and administration] The usual initial adult dose of the combination product of trifluridine and tipiracil tydrochloride (FTD-TPI) is determined based on body surface area (BSA) and shown in the dosing table below, which presents predefined ranges of BSA and the corresponding initial doses (on the basis of trifluridine at approximately 35 mg/m^2/dose). FTD-TPI is orally administered twice daily, after breakfast and after supper, in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period.
The dose may be reduced according to the patient's condition.

Body surface area (m^2)	Initial dose (as trifluridine)
<1.07	35 mg/dose (70 mg/day)
1.07 - <1.23	40 mg/dose (80 mg/day)
1.23 - <1.38	45 mg/dose (90 mg/day)
1.38 - <1.53	50 mg/dose (100 mg/day)
1.53 - <1.69	55 mg/dose (110 mg/day)
1.69 - <1.84	60 mg/dose (120 mg/day)
1.84 - <1.99	65 mg/dose (130 mg/day)
1.99 - <2.15	70 mg/dose (140 mg/day)
≥2.15	75 mg/dose (150 mg/day)

[Conditions for approval]

The applicant is required to submit the results of ongoing phase III study that is conducted to confirm the efficacy and safety of the product in patients with unresectable advanced or recurrent colorectal cancer without delay after the completion of the study for review.

Review Report (1)

November 13, 2013

I. Product Submitted for Registration

[Brand name] (1) Lonsurf combination tablets T15,
(2) Lonsurf combination tablets T20

[Non-proprietary name] Trifluridine and Tipiracil Hydrochloride

[Name of applicant] Taiho Pharmaceutical Co., Ltd.

[Date of application] February 26, 2013

[Dosage form/Strength] (1) Each tablet contains 15 mg of trifluridine and 7.065 mg of tipiracil hydrochloride.
(2) Each tablet contains 20 mg of trifluridine and 9.42 mg of tipiracil hydrochloride.

[Proposed indication] Unresectable advanced or recurrent colorectal cancer

[Proposed dosage and administration]

The usual initial adult dose of the combination product of trifluridine and tipiracil tydrochloride (FTD-TPI) is determined based on body surface area (BSA) and shown in the dosing table below, which presents predefined ranges of BSA and the corresponding initial doses (on the basis of trifluridine at approximately 35 mg/m^2/dose). FTD-TPI is orally administered twice daily, after breakfast and after supper, in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period.

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

Body surface area (m^2)	Initial dose (as trifluridine)
<1.07	35 mg/dose (70 mg/day)
1.07 - <1.23	40 mg/dose (80 mg/day)
1.23 - <1.38	45 mg/dose (90 mg/day)
1.38 - <1.53	50 mg/dose (100 mg/day)
1.53 - <1.69	55 mg/dose (110 mg/day)
1.69 - <1.84	60 mg/dose (120 mg/day)
1.84 - <1.99	65 mg/dose (130 mg/day)
1.99 - <2.15	70 mg/dose (140 mg/day)
≥2.15	75 mg/dose (150 mg/day)

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

A summary of the data submitted by the applicant and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

(1) Drug overview

Trifluridine (FTD) is an antineoplastic nucleoside analog discovered by Heidelberger and others at the University of Wisconsin as a drug that inhibits thymidylate synthetase (TS) similarly to existing fluoropyrimidines but exerts a growth inhibitory effect mainly by being incorporated into DNA of tumor cells. FTD has not been developed as a single-component antitumor drug because of its rapid metabolism in the body and other reasons. Tipiracil hydrochloride (TPI), discovered by the applicant, is considered to inhibit thymidine phosphorylase (TPase), an enzyme that degrades FTD.

Lonsurf combination tablets T15 and T20 are a combination of FTD and TPI at a molar ratio of 2:1 (hereinafter referred to as FTD-TPI). The applicant developed the combination product in and outside Japan on the basis of the expectation that the combination with TPI helps maintain plasma FTD concentration over time and thereby enhance the tumor growth inhibitory effect of FTD.

(2) Pharmaceutical development

[redacted]

Outside Japan, a phase I study in patients with solid tumors (TAS102-9801) was initiated in [redacted], and additional 4 phase I studies in patients with solid tumors (TAS102-9802, TAS102-9803, TAS102-9804, and TAS102-9805) have been conducted through [redacted].

In Japan, a phase I study in patients with solid tumors (TAS102-J001) was initiated in [redacted], and a phase II study in patients with unresectable advanced or recurrent colorectal cancer (TAS102-J003) was initiated in [redacted]. A global phase III study in patients with unresectable advanced or recurrent colorectal cancer (TPU-TAS-102-301), initiated in [redacted], is ongoing in 13 countries including Japan.

In February 2013, the applicant submitted a new drug application for the combination product in Japan mainly on the basis of the results of Study TAS102-J003.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Trifluridine

[redacted]

i) Characterization

FTD is white crystals or crystalline powder, and its properties including description, solubility, hygroscopicity, melting point, decomposition point, ultraviolet-visible absorption spectrum, optical

rotation, pH, acid dissociation constant, partition coefficient, and polymorphism have been determined. [redacted].

The chemical structure of FTD has been confirmed by elemental analysis, mass spectrometry, ultraviolet–visible spectrophotometry (UV/VIS), infrared spectrophotometry (IR), nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR), and X-ray crystallography.

ii) Manufacturing process

See Appendix.

iii) Control of FTD

The proposed specifications for FTD include content, appearance, identification (UV/VIS, IR), optical rotation, purity (heavy metals, related substances [high-performance liquid chromatography (HPLC)], and residual solvents [gas chromatography (GC)]), water content, residue on ignition, and assay (HPLC).

iv) Stability of FTD

The following stability studies were conducted for FTD. The photostability testing showed FTD is photostable.

Stability studies of FTD

	Primary batches	Temperature	Humidity	Storage form	Duration of storage
Long-term testing	3 production batches	25°C	60%RH	Double low-density polyethylene pouches and a polyethylene bottle	18 months
Accelerated testing	3 production batches	40°C	75%RH		6 months

On the basis of the results of the above studies, a re-test period of [redacted] months has been proposed for FTD if the drug substance is packaged with double low-density polyethylene pouches and a polyethylene bottle or an equivalent polyethylene drum and is stored at room temperature, according to the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003 [hereafter referred to the ICH Q1E guidelines]). The long-term testing will be continued up to [redacted] months.

2.A.(1).2) Tipiracil hydrochloride

i) Characterization

Tipiracil hydrochloride (TPI) is white crystals or crystalline powder, and its properties including description, solubility, hygroscopicity, melting point, decomposition point, ultraviolet-visible absorption spectrum, optical rotation, pH, acid dissociation constant, partition coefficient, and polymorphism have been determined. [redacted]

The chemical structure of TPI has been confirmed by elemental analysis, mass spectrometry, ultraviolet–

visible spectrophotometry (UV/VIS), infrared spectrophotometry (IR), nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR), and X-ray crystallography.

ii) Manufacturing method

[redacted]

iii) Control of TPI

The proposed specifications for TPI include content, appearance, identification (UV/VIS, IR, chlorides), purity (heavy metals, related substances [HPLC], residual solvents [GC]), water content, residue on ignition, and assay (HPLC).

iv) Stability of TPI

The following stability studies were conducted for TPI. The photostability testing showed the drug substance is photostable.

Stability studies of TPI

	Primary batches	Temperature	Humidity	Storage form	Duration of storage
Long-term testing	3 pilot scale batches	25°C	60%RH	Double low-density polyethylene pouches and a fiber drum	18 months
Accelerated testing	3 pilot scale batches	40°C	75%RH		6 months

On the basis of the results of the above studies, a re-test period of [redacted] months has been proposed for TPI if the drug substance is packaged with double low-density polyethylene pouches and a fiber drum and is stored at room temperature, according to the ICH Q1E guideline. The long-term testing will be continued up to [redacted] months.

2.A.(2) Drug product

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

The drug product is immediate-release film-coated tablets containing 15 mg of FTD and 7.065 mg of TPI or 20 mg of FTD and 9.42 mg of TPI in each tablet. The drug product contains lactose hydrate, partially pregelatinized starch, stearic acid, hypromellose, macrogol 6000, titanium oxide, red ferric oxide (only in T20), and magnesium stearate as excipients.

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

[redacted]

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

The proposed specifications for the drug product include contents, appearance, identification (HPLC, UV), purity (related substances [HPLC]), uniformity of dosage units (content uniformity testing [HPLC]), dissolution (HPLC), microbial limits, and assay (HPLC).

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

The following stability studies were conducted for the drug product. The photostability testing showed the drug product is photostable.

Stability studies of the drug product

	Primary batches	Temperature	Humidity	Storage form	Duration of storage
Long-term testing	3 pilot scale batches	25°C	60%RH	PTP sheet + an aluminum pouch with desiccant	18 months
Accelerated testing	3 pilot scale batches	40°C	75%RH	PTP sheet + an aluminum pouch with desiccant	6 months

[redacted] The long-term testing will be continued up to [redacted] months.

2.B. Outline of the review by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substances and drug product is controlled appropriately.

3. Non-clinical data

In this section, the doses of combination products are described as the amounts of the following active ingredients that inhibit tumor growth: trifluridine (FTD) for the combination product of FTD and tipiracil hydrochloride (TPI) (FTD-TPI); and tegafur for the combination product of tegafur, gimeracil and oteracil potassium (hereinafter referred to as TS-1).

3.(i) Summary of pharmacology studies

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

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

3.(i).A.(1).1) Tumor growth inhibition

in vitro:

Antiproliferative effect of FTD on colon cancer cell line (Report 20061-004)

The antiproliferative effects of FTD and 5-fluorouracil (5-FU) on the human colon cancer cell line HCT-15 were investigated. The IC_{50} values of FTD and 5-FU were 10.7 and 4.96 μmol/L, respectively (n = 1).

Based on the results, the applicant explained that FTD has an antiproliferative effect similar to that of 5-FU on the colon cancer cell line.

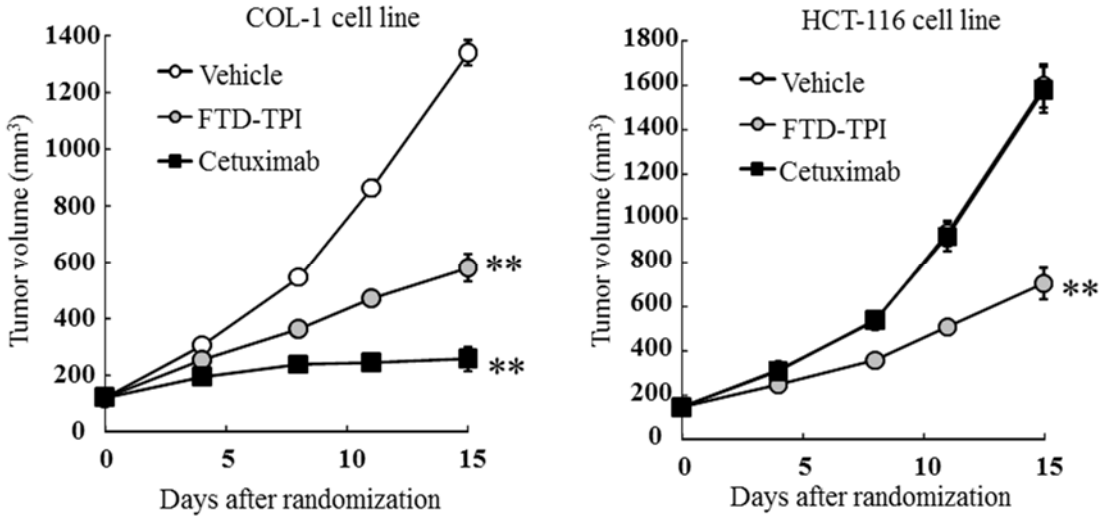
in vivo:

i) Antiproliferative effect of FTD-TPI on colon cancer cell lines (Reports 11TA01 and 03-09-008)

The antiproliferative effect of FTD-TPI was investigated in athymic mice (nude mice) by subcutaneous implantation of the human colon cell line COL-1 (KRAS wild-type cell line) or HCT-116 (KRAS mutant cell line). The mice were randomized on the day when the tumor volume reached about 120 mm^3 for COL-1 cells (13 days after implantation) and about 145 mm^3 for HCT-116 cells (10 days after implantation), and started to receive FTD-TPI at a dose of 75 mg/kg twice daily (BID) orally for 14 consecutive days from the day after randomization. The tumor volume was calculated during the treatment period. Control animals received the vehicle or cetuximab (genetic recombination) (hereinafter referred to as cetuximab) intraperitoneally at a dose of 40 mg/kg twice a week for 2 weeks.

The FTD-TPI and the cetuximab groups showed statistically significant growth inhibition on COL-1 cells as compared with the vehicle control 15 days after randomization [see the left figure below]. The FTD-TPI group significantly inhibited the tumor growth of HCT-116 cells as compared with the vehicle control 15 days after randomization [see the right figure below].

The applicant explained that the results above suggested that FTD-TPI has an antiproliferative effect on colon cancer cells.



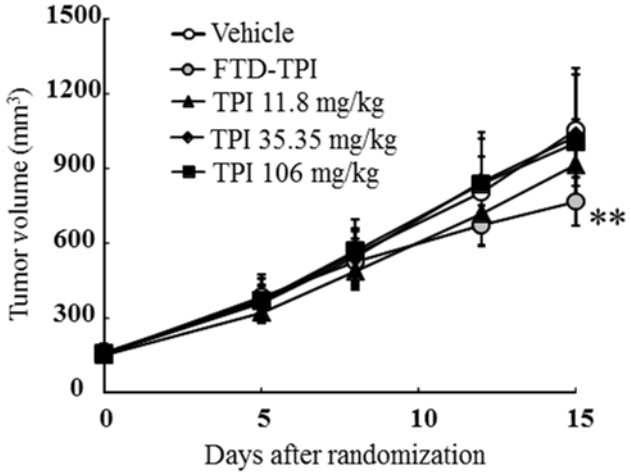
Antiproliferative effects of FTD-TPI on COL-1 and HCT-116 cell lines

Mean ± standard deviation; n = 6
**, Significantly different from the vehicle control with $P < 0.01$ (Student's *t*-test) at 15 days after randomization

The antiproliferative effects of FTD-TPI and TPI were evaluated in nude mice by subcutaneous implantation of the human colon cancer cell line KM20C. The mice were randomized on the day when the tumor volume reached about 100 to 200 mm^3 (15 days after implantation), and started to receive FTD-TPI at a dose of 75 mg/kg BID, or TPI at doses of 11.8, 35.35, or 106 mg/kg BID orally for 14 consecutive days from the day after randomization. The tumor volume was calculated during the

treatment period. Control animals received the vehicle.

At 15 days after randomization, TPI showed no antiproliferative effects at any doses, while FTD-TPI showed a statistically significant antiproliferative effect on the tumor cells as compared with the vehicle control [the following figure].



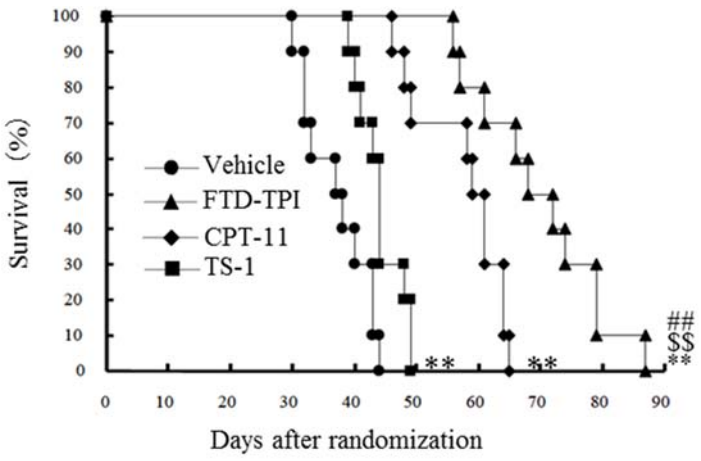
Antiproliferative effect of FTD-TPI on KM20C cell line

Mean ± standard deviation; n = 7
**, Significantly different from the vehicle control with $P < 0.01$ (Student's *t*-test) at 15 days after randomization

ii) Prolonging effect of FTD-TPI on survival of mice implanted with a colon cancer cell line (Report 11TA05)

The prolonging effect of FTD-TPI in terms of the survival time was investigated in nude mice by intraperitoneal implantation of human colon cancer cell line KM20C. From the day after randomization, animals received FTD-TPI at a dose of 75 mg/kg BID orally for 28 consecutive days. Control animals received the vehicle or irinotecan hydrochloride hydrate (CPT-11) at an intravenous dose of 100 mg/kg weekly for 4 weeks, or TS-1 at an oral dose of 8.3 mg/kg once daily (QD) for 28 consecutive days.

Survival time was significantly prolonged in animals receiving FTD-TPI as compared with all the control groups [the following figure].



Prolonging effect of FTD-TPI on survival (Kaplan-Meier curve)

n = 10; **, significantly different from the vehicle control with $P < 0.01$
$$, significantly different from CPT-11 with $P < 0.01$; ##, significantly different from TS-1 with $P < 0.01$ (log-rank test)

3.(i).A.(1).2) Mechanism of action

i) Pharmacological properties of FTD and TPI

- FTD is incorporated into DNA in greater amount than other nucleoside analogs, and is a less potent substrate for DNA glycosylase, a repair enzyme, than 5-FU. Once incorporated into DNA, FTD is not removed from it (*Int J Oncol.* 2011;39:263-70). Most FTD incorporated into DNA of the human gastric cancer cell line NUGC-3 remained at 24 hours after the removal of FTD from cell culture media (*Int J Mol Med.* 2004;13:249-55).
- In cells, FTD is first converted to trifluorothymidine monophosphate (F_3TMP) and then to trifluorothymidine triphosphate (F_3TTP), a substrate for DNA (*Int J Mol Med.* 2004; 13:249-55). F_3TMP inhibits thymidylate synthetase (TS) (*J Med Chem.* 1977;20:1469-73). On the other hand, unlike 5-fluorodeoxyuridine monophosphate (FdUMP), an active metabolite of 5-FU, FTD does not bind covalently to TS (*Biochem Biophys Res Commun.* 1972;48:1565-71) and thus inhibitory effect of FTD on TS did not last long (Report 20111-003).
- TPI inhibits the activity of thymidine phosphorylase (TPase), a metabolic enzyme of FTD that is derived from human placenta (*Biochem Pharmacol.* 2000;59:1227-36).

ii) Bioavailability studies (Report [redacted])

Following a single intravenous (IV) dose of FTD alone at 30 mg/kg, or single oral (PO) dose of FTD or FTD-TPI at 10 mg/kg to male monkeys, plasma FTD concentrations were determined (the table below). The bioavailability (BA) of oral FTD monotherapy was low. The plasma FTD concentration after the single oral dose of FTD-TPI was approximately 100 times that observed after the single oral FTD monotherapy.

Pharmacokinetic parameters of FTD after single intravenous or oral administration of FTD or after a single oral administration of FTD-TPI

	Route	Dose (mg/kg)	C_{max} (ng/mL)	CL (mL/min/kg)	$t_{1/2}$ (min)	t_{max} (h)	AUC_{inf} (ng·min/mL)	BA (%)
FTD	IV	30	122,000 ± 10,000	19.1 ± 3.2	13.4 ± 4.5	-	1,610,000 ± 280,000	-
	PO	10	298 ± 246	740 ± 449*1*2	18.9 ± 1.6*2	0.9 ± 0.8	16,800 ± 8300*2	3.0 ± 1.4
FTD-TPI	PO	10	16,000 ± 2200	—	67.5 ± 14.5	1.5 ± 1.1	1,740,000 ± 300,000	-

Arithmetic mean ± standard deviation, n = 4; *1, CL/BA; *2, n = 3

iii) Evaluation of administration route (oral vs. continuous subcutaneous infusion) and regimen (QD or BID) (Reports 11TA03 and 11TA04)

Following a subcutaneous implantation of cell line MX-1 in nude mice, FTD at an oral dose of 25 mg/kg BID or FTD at a dose of 2 mg/kg/day by continuous subcutaneous infusion using an osmotic pump for 14 consecutive days to the mice in order to investigate the antiproliferative effect of FTD. The daily doses in both groups corresponded to two-thirds their maximum tolerated dose. As a result, compared with the animals in the subcutaneous infusion group, those in the oral administration group were able to

receive a greater amount of FTD and showed a greater amount of FTD incorporated into DNA as well as more substantial antiproliferative effect of FTD.

In a separate study, following a subcutaneous implantation of cell line MX-1 in nude mice, oral doses of FTD-TPI at 150 mg/kg QD or at 75 mg/kg BID (150 mg/kg/day) were administered to the mice for 14 consecutive days to investigate the antiproliferative effect of FTD-TPI. The antiproliferative effect observed in animals in BID group was statistically stronger than that in QD group.

iv) Antiproliferative effect of FTD and FTD-TPI on several types of tumor cell lines *in vitro*: (Report 20061-004)

In vitro studies were conducted to investigate the antiproliferative effects of FTD and 5-FU on the following human cell lines: human gastric cancer cell line NUGC-3, human lung cancer cell line A549, human breast cancer cell line MDA-MB-435, human ovary cancer cell line SK-OV-3, human bladder cancer cell line J82, human prostate cancer cell line DU145, human pancreatic cancer cell line CFPAC-1, human head and neck cancer cell line KB, human leukemia cell line CCRF-CEM, and human cervical cancer cell line HeLa. The IC_{50} values of FTD and 5-FU in these human cell lines ranged from 0.214 to 24.4 μmol/L and from 3.18 to 17.7 μmol/L, respectively (n = 1).

***in vivo*: (Reports 20061-003 and 11TA02)**

- Following a subcutaneous implantation of human gastric cancer cell line SC-2 in nude mice, FTD-TPI at 8, 15.5, 31.5, 62.5, 125, or 250 mg/kg/dose was orally administered BID to the mice for 14 consecutive days to investigate the antiproliferative effect of FTD-TPI. At 14 days after treatment initiation, a significantly stronger antiproliferative effect was observed in animals receiving FTD-TPI at 15.5 to 250 mg/kg/dose than in the vehicle control (Student's *t*-test).
- Following a subcutaneous implantation of cell line MX-1 in nude mice, which has low susceptibility to fluoropyrimidines, FTD-TPI was orally administered at 75 mg/kg/dose BID to the mice for 14 consecutive days in order to investigate the antiproliferative effect of FTD-TPI. On day 14 of treatment, a significantly stronger antiproliferative effect was observed in animals receiving FTD-TPI than in control animals receiving TS-1 at 8.3 mg/kg QD orally for 14 consecutive days (Student's *t*-test).

In experiments using subcutaneous implantation of human breast cancer cell line MC-2 or human lung cancer cell line Lu-134 in nude mice, FTD-TPI exerted significant antiproliferative effects on these cell lines, but there was no significant antiproliferative effect of TPI observed (Report 03-09-008).

v) Study on dose ratios of FTD and TPI (Report 12DA41)

Male monkeys received single oral dose of FTD 10 mg/kg alone (FTD alone), or FTD 10 mg/kg in combination with TPI at molar ratio of 5:1 (Ratio A), 2:1 (Ratio B), or 1:1 (Ratio C), and plasma FTD concentrations were determined (the table below).

In a separate experiment in male monkeys, animals receiving FTD and TPI at molar ratio of 1:1 or 2:1

showed similar C_{max} and AUC_{0-10} (*Int J Oncol*. 2005;27:449-55).

Based on the results above in which both Ratio B and C showed greater values of C_{max} and AUC_{0-10}, the applicant explained that Ratio B was selected for the proposed product because Ratio B contains a smaller amount of TPI than Ratio C and thus is the most appropriate dose ratio.

Pharmacokinetic parameters of FTD in male monkeys receiving single oral dose of FTD alone or FTD in combination with TPI

	Dose ratio FTD : TPI (molar ratio)	C_{max} (ng/mL)	AUC_{0-10} (ng·min/mL)
FTD alone	1:0	277 ± 117	10,900 ± 2900
Ratio A	5:1	13,100 ± 1400***	1,010,000 ± 80,000***
Ratio B	2:1	15,300 ± 2700***	1,400,000 ± 160,000***, #
Ratio C	1:1	18,500 ± 4000***	1,690,000 ± 170,000***, ##

Arithmetic mean ± standard deviation, n = 4; ***, significantly different from FTD alone with $P < 0.001$
#, significantly different from Ratio A with $P < 0.05$; ##, significantly different from Ratio A with $P < 0.01$ (Tukey's test)

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

3.(i).A.(3).1) Effects on the central nervous system (Report [redacted])

Male rats (n = 6/group) received a single oral dose of FTD-TPI (27.2, 108.8, 435 mg/kg), FTD (27.2, 108.8, 435 mg/kg), or TPI (125, 500, 2000 mg/kg), and the effects on clinical signs and behaviors were evaluated. No effects were observed on any parameters in animals receiving FTD-TPI, FTD or TPI.

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

i) Effects on hERG current (Report [redacted])

In human embryonic kidney cell-derived HEK 293 cell line into which human *ether-a-go-go*-related gene (hERG) had been incorporated, effects of FTD (3, 30, 300 μmol/L) and TPI (1, 10, 100 μmol/L) on hERG potassium ion current were evaluated by whole-cell patch clamping. FTD at 300 μmol/L and TPI at 100 μmol/L inhibited hERG current by 4.0 ± 3.3% and 2.5 ± 10.3% (arithmetic mean ± standard deviation, n = 5), respectively, but no statistically significant inhibitions were observed in cells treated with FTD or TPI.

ii) Effects on blood pressure, heart rate, and electrocardiogram (ECG) (Report [redacted])

Male cynomolgus monkeys (n = 4/group) received a single oral dose of FTD-TPI (6.8, 27.2, 108.8 mg/kg), FTD (6.8, 27.2, 108.8 mg/kg), or TPI (62.5, 250, 1000 mg/kg), and effects on blood pressure, heart rate and ECG (e.g. PR interval and QR interval) were investigated. No effects of FTD-TPI, FTD or TPI on these parameters were observed.

3.(i)A.(3).3) Effects on the respiratory system (Report [redacted])

Male rats (n = 8/group) received a single oral dose of FTD-TPI (27.2, 108.8, 435 mg/kg), FTD (27.2, 108.8, 435 mg/kg), or TPI (125, 500, 2000 mg/kg), and effects on respiratory rate, tidal volume, and minute volume were investigated using the whole-body plethysmography. No effects of FTD-TPI, FTD or TPI on these parameters were observed.

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

Based on the submitted data and the following review, PMDA concluded that the efficacy of FTD-TPI in colorectal cancer is expected.

Efficacy of FTD-TPI in colorectal cancer resistant to conventional fluoropyrimidines

PMDA requested the applicant to explain the reason why the applicant expected the efficacy of FTD-TPI in patients with colorectal cancer resistant to conventional fluoropyrimidines (e.g. 5-FU) which are antimetabolites as with FTD-TPI, taking it into account that the pivotal Japanese Phase II study (Study TAS102-J003) was conducted in patients with colorectal cancer who are refractory or intolerant to fluoropyrimidines, CPT-11, and oxaliplatin (L-OHP).

The applicant responded as follows:

The mechanism of action of FTD-TPI is considered as inhibitory effects on various functions of DNA because FTD is incorporated into DNA on the basis of the following reasons.

- The amount of FTD incorporated into DNA correlates with the degree of its antiproliferative effect (Report 03-12-003).
- F_3TTP is not degraded by deoxyuridine triphosphatase (dUTPase), a phosphatase specific to uracil residues (*Biochimie*. 2010;92:178-86). FTD has lower substrate specificity for DNA glycosylase than 5-FU, and once incorporated into DNA, it will not be removed from the DNA [see "3.(i).A.(1).2).i) Pharmacological properties of FTD and TPI"].

Conventional fluoropyrimidines are considered to exert their effects by inhibiting TS, which differs from the mechanism of action of FTD-TPI. It has been reported that 5-FU is degraded by dUTPase (*Biochimie*. 2010;92:178-86) and that 5-FU incorporated into DNA is removed by DNA glycosylase (*Oncogene*. 2002;21:8935-48). These findings suggest that 5-FU is not easily incorporated into DNA.

Although the mechanism of development of resistance to conventional fluoropyrimidines has not been clearly elucidated, it has been reported that the inhibitory effects of fluoropyrimidines on TS is reduced through decreased activity of orotate phosphoribosyltransferase that activates 5-FU (*Int J Oncol*. 2000;17:277-83), increased expression of dihydropyrimidine dehydrogenase, a catabolic enzyme of 5-FU (*Clin Cancer Res*. 2000;6:1322-7), or increased expression of TS (*Biochim Biophys Acta*. 2002;1587:194-205, *Cancer Res*. 1992;52:4:306-12). None of these affects the mechanism of action of FTD-TPI.

The applicant discussed, based on the above, that FTD-TPI is expected to be effective for the treatment of colorectal cancer resistant to conventional fluoropyrimidines.

PMDA considers as follows:

Conventional fluoropyrimidines are also incorporated into DNA (*Int J Oncol*. 2011;39:263-70). Following the oral administration of FTD-TPI, a combination of FTD and TPI, TPI helps maintain a

high FTD concentration in blood and it is possible that, by inhibiting TS, FTD contributes to the antiproliferative effect. Therefore, it cannot be definitely concluded, at present, that FTD-TPI exerts an antiproliferative effect through a mechanism differing from those of conventional fluoropyrimidines. However, PMDA concluded that the applicant's discussion above was understandable to some extent.

3.(ii) Summary of pharmacokinetic studies

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

Pharmacokinetics (PK) of FTD-TPI was investigated in mice, rats, dogs, and monkeys. Plasma protein binding, drug-metabolizing enzymes, and transporters of FTD-TPI were also investigated using biological samples derived from humans or animals.

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

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

Male mice received a single oral dose of FTD-TPI at 15.5 to 150 mg/kg, and plasma concentrations of FTD, FTD metabolite 5-(trifluoromethyl) uracil (trifluorothymine, hereinafter referred to as FTY), and TPI were determined (the table below). The C_{max} of FTD was almost dose-proportional in the range of 15.5 to 62.5 mg/kg, but the C_{max} of FTD at 150 mg/kg was less than dose-proportional. The $AUC_{0\text{-}t}$ and $AUC_{0\text{-}24}$ of FTD were almost dose-proportional in the range of 15.5 to 150 mg/kg. The C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}24}$ of TPI were dose-proportional.

The applicant explained the inconsistency of results among treatment groups as follows: The amount of FTD in the dosing solution for the 150 mg/kg group was greater than the saturation level, and thus FTD was absorbed more slowly in the animals, which resulted in less than dose-proportional C_{max}. $AUC_{0\text{-}t}$ and $AUC_{0\text{-}24}$ were almost dose-proportional because FTD was dissolved in the gastrointestinal fluid and absorbed continuously and extensively through the intestine.

PK parameters of FTD-TPI after a single oral dose to male mice

	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}t}$ (ng·h/mL)	$AUC_{0\text{-}24}$ (ng·h/mL)
FTD	15.5	11,700	0.17	11,558	11,558
	62.5	33,767	0.33	22,880	22,880
	150	45,933	0.33	56,769	56,769
FTY	15.5	3363	0.33	3731	3770
	62.5	9210	0.33	12,360	12,721
	150	14,867	2.0	54,957	55,765
TPI	15.5	85.9	0.33	115	139
	62.5	337	0.33	359	422
	150	704	0.33	895	1062

Arithmetic mean, n = 3/time point (Blood samples were collected from different mice at each time point.)

A single oral or intravenous dose of FTD-TPI containing ^{14}C-labeled FTD (hereinafter referred to as [^{14}C-FTD] FTD-TPI) or FTD-TPI containing ^{14}C-labeled TPI (hereinafter referred to as [^{14}C-TPI] FTD-TPI) at 50 mg/kg was administered to fed or fasted male rats, and plasma concentrations of radioactivity and substances were determined (the table below). The applicant explained the results as follows: in orally administered animals, plasma radioactivity concentration decreased slower than plasma FTD concentration; it was likely attributed to the slower decrease in radioactivity of FTD metabolites

including FTY, which is slow in excretion from the body. The t_{max} of FTD and TPI were delayed in fed animals. Food did not affect the C_{max} and AUC_{inf} of FTD, or the AUC_{inf} of TPI, while the C_{max} of TPI decreased by about 30% in fed animals. The ratios of AUC_{inf} of FTD, FTY, and TPI in fed animals after oral administration of FTD-TPI to those in animals after intravenous administration of the drugs (21,712 ng·h/mL, 26,270 ng·h/mL, 13,095 ng·h/mL, respectively) were 31%, 284%, and 9%, respectively. Taking account of that FTD is partly degraded or metabolized in the gastrointestinal tract before absorption and that the ratio of AUC_{inf} for TPI above was lower than the absorption rate (≥14.7%) for TPI [see "3.(ii).A.(4).1) Excretion in urine, bile and feces"], TPI appears to be susceptible to first-pass effect.

PK parameters of radioactivity etc. after single oral administration of [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI at 50 mg/kg to male rats

Substances administered	Substances assayed	Fed animals				Fasted animals			
		C_{max} (ng eq./mL)	t_{max} (h)	AUC_{inf} (ng eq.·h/mL)	$t_{1/2}$*1 (h)	C_{max} (ng eq./mL)	t_{max} (h)	AUC_{inf} (ng eq.·h/mL)	$t_{1/2}$*1 (h)
[^{14}C-FTD] FTD-TPI	Radioactivity	28,460*2	0.5	171,335*3	2.14	25,135*2	1.0	89,155*3	1.81
	FTD	4562	0.5	6645	0.94	5708	0.25	7415	—
	FTY	22,470	1.0	74,497	1.73	18,057	1.0	50,620	1.47
[^{14}C-TPI] FTD-TPI	Radioactivity	421*4	1.0	3844*5	2.94	607*4	0.5	2911*5	1.99
	TPI	380	1.0	1164	1.52	536	0.5	1188	1.35

Arithmetic mean; n = 4 per time point (Blood samples were collected from different rats at each time point.)
*1, $t_{1/2}$ during the period from t_{max} to 6 hours after administration; *2, ng eq. of FTD/mL; *3, ng eq. of FTD·h/mL; *4, ng eq. of TPI/mL; *5, ng eq. of TPI·h/mL

Male monkeys received a single oral dose of [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI at 10 mg/kg, and radioactivity concentrations in blood and plasma were determined (the table below). Following the administration of [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI, radioactivity concentrations in blood and plasma eliminated in a biphasic manner after reaching C_{max}.

PK parameters of radioactivity after single oral administration of [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI at 10 mg/kg to male monkeys

Substances administered	Samples	C_{max} (ng eq./mL)	t_{max} (h)	AUC_{0-24} (ng eq.·h/mL)	AUC_{inf} (ng eq.·h/mL)	$t_{1/2}$ (h)
[^{14}C-FTD] FTD-TPI	Blood	11,179 ± 5347	2.0 ± 1.0	49,600 ± 19,500	99,400 ± 24,000	38.8 ± 15.6
	Plasma	20,205 ± 10,061	2.0 ± 1.0	83,900 ± 37,300	144,000 ± 37,200	33.7 ± 21.5
[^{14}C-TPI] FTD-TPI	Blood	444 ± 151	3.0 ± 0.0	2470 ± 800	1660 ± 850	7.1 ± 1.7
	Plasma	618 ± 240	3.0 ± 0.0	2950 ± 880	3220 ± 860	9.1 ± 3.2

Arithmetic mean ± standard deviation, n = 3

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

PK parameters after repeated administration of FTD-TPI were determined in rats receiving the drug for 2, 4, or 13 weeks, in dogs for 2 weeks, and in monkeys for 2, 4, or 13 weeks. For rats, the results of 2- and 4-week repeated dose studies were used to evaluate the PK profile of FTD-TPI for the following reasons: changes in mean plasma concentration during the 2-week repeated dose study indicated that the plasma concentration reached steady state after the first dose; and in the 13-week repeated dose study in rats, worsened general conditions affected PK parameters substantially, which would make it difficult to evaluate the effects of repeated administration of FTD-TPI appropriately.

Male rats received oral doses of FTD-TPI ranging from 15 to 450 mg/kg/day for 2 weeks, and plasma concentrations of FTD, FTY, and TPI were determined (the table below). The C_{max} of FTD and TPI after the first dose were generally dose-proportional in the range of 15 to 150 mg/kg but those at 450 mg/kg were less than dose-proportional, while the $AUC_{0\text{-}24}$ values were generally dose-proportional in the range of 15 to 450 mg/kg. No clear effects of repeated doses of FTD-TPI were observed on the C_{max}, t_{max}, or $AUC_{0\text{-}24}$ of FTD, FTY, or TPI.

PK parameters after 2-week repeated oral administration of FTD-TPI to male rats

	Dose (mg/kg)	C_{max} (ng/mL)		t_{max} (h)		$AUC_{0\text{-}24}$ (ng·h/mL)	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
FTD	15	1401	1572	0.25	0.25	980	1575
	50	3717	5646	0.25	0.5	4752	6186
	150	9571	9201	0.5	0.5	16,452	18,601
	450	18,436	15,940	0.5	1.0	49,731	62,410
FTY	15	8202	8917	0.5	0.5	11,107	15,726
	50	19,371	18,256	1.0	1.0	38,951	43,686
	150	29,170	24,303	1.0	2.0	115,139	124,753
	450	46,397	42,730	1.0	4.0	391,687	398,401
TPI	15	109	153	0.5	1.0	453	443
	50	369	535	1.0	1.0	1418	1405
	150	1092	746	1.0	1.0	3425	3028
	450	1877	1694	1.0	1.0	8130	9892

Arithmetic mean; n = 3 animals/time point (Blood samples were collected from different rats at each time point.)

Male and female rats received oral doses of FTD-TPI ranging from 50 to 450 mg/kg/day for 4 weeks, and C_{max} of FTD, FTY, and TPI were determined (table below). In this study, AUC could not be calculated because plasma concentrations were determined only at 0.5 and 1 hours after administration, which were considered near t_{max}. There were no clear differences in the C_{max} of FTD, FTY, or TPI between the male and female rats. The C_{max} values increased with the dose, and no clear effects of repeated administration were observed.

C_{max} (ng/mL) after 4-week repeated oral administration of FTD-TPI to male and female rats

	Dose (mg/kg)	Day 1		Day 14		Day 28	
		Male	Female	Male	Female	Male	Female
FTD	50	5156 ± 934	5244 ± 732	5494 ± 1149	5404 ± 1432	6239 ± 921	7636 ± 1210
	150	11,375 ± 3287	12,324 ± 1230	13,034 ± 4127	16,712 ± 4119	11,345 ± 3341	15,567 ± 1578
	450	23,622 ± 2690	33,222 ± 3756	18,850 ± 3586	37,118 ± 8502	17,830 ± 5515	27,616 ± 4682
FTY	50	19,084 ± 3158	20,808 ± 1592	21,121 ± 3308	17,602 ± 3725	21,331 ± 3761	22,577 ± 2345
	150	31,039 ± 5413	33,316 ± 7704	31,653 ± 13,069	35,139 ± 8112	29,292 ± 11,755	32,722 ± 7615
	450	46,022 ± 8197	49,989 ± 6470	34,796 ± 3623	53,592 ± 3311	33,335 ± 8878	43,951 ± 7401
TPI	50	472 ± 124	431 ± 83	440 ± 51	675 ± 171	449 ± 72	545 ± 59
	150	1021 ± 163	1187 ± 203	956 ± 180	1411 ± 301	833 ± 149	1302 ± 400
	450	2348 ± 516	2871 ± 643	1590 ± 212	2906 ± 1039	1473 ± 236	2134 ± 419

Arithmetic mean ± standard deviation, n = 5

Male dogs received oral doses of FTD-TPI at 17 to 150 mg/kg/day for 2 weeks, and plasma concentrations of FTD, FTY, and TPI were determined (the table below). The C_{max} and $AUC_{0\text{-}24}$ values of FTD, FTY, and TPI after the first dose of FTD-TPI increased with the dose. Although the t_{max} values of FTD, FTY, and TPI tended to increase, no clear effects on the C_{max} or $AUC_{0\text{-}24}$ values were observed after repeated administration.

PK parameters after 2-week repeated oral administration of FTD-TPI to male dogs

	Dose (mg/kg)	C_{max} (ng/mL)		t_{max} (h)		AUC_{0-24} (ng·h/mL)	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
FTD	17	16,379 ± 2642	9155 ± 6914	0.34 ± 0.14	1.17 ± 0.76	14,508 ± 1104	11,528 ± 6038
	50	55,491 ± 11,809	-	0.52 ± 0.03	-	100,203 ± 9498	-
	150	132,762 ± 29,725	-	1.02 ± 0.04	-	388,720 ± 138,393	-
FTY	17	10,896 ± 1134	12,926 ± 1764	1.00 ± 0.00	2.00 ± 1.73	28,235 ± 2900	58,783 ± 21,985
	50	16,381 ± 3232	-	2.33 ± 1.53	-	85,794 ± 21,852	-
	150	34,175 ± 3128	-	5.33 ± 2.31	-	315,115 ± 37,807	-
TPI	17	1351 ± 733	670 ± 328	1.00 ± 0.00	1.67 ± 0.58	4501 ± 2844	3253 ± 1076
	50	4278 ± 1679	-	0.85 ± 0.26	-	14,613 ± 1623	-
	150	11,636 ± 3695	-	1.02 ± 0.04	-	38,784 ± 16,378	-

Arithmetic mean ± standard deviation; n = 3
PK data were not obtained because all animals in the 50 and 150 mg/kg/day groups died after 2 weeks of treatment.

Male and female monkeys received oral doses of FTD-TPI at 1.25 to 20 mg/kg/day for 13 weeks, and plasma concentrations of FTD, FTY, and TPI were determined (the table below). There were no clear differences between the male and female monkeys in the plasma concentrations of FTD, FTY, or TPI. The C_{max} and AUC_{0-24} values increased with dose, and no clear effects of repeated administration were observed.

PK parameters after 13-week repeated oral administration of FTD-TPI to male and female monkeys

	Dose (mg/kg)		C_{max} (ng/mL)	t_{max} (h)		AUC_{0-24} (ng·h/mL)					
			Day 1	Week 6	Week 13	Day 1	Week 6	Week 13	Day 1	Week 6	Week 13
FTD	1.25	Male*1	966 ± 953	2390 ± 450	3390 ± 540	1.2 ± 0.8	0.7 ± 0.3	0.7 ± 0.3	1090 ± 790	2900 ± 540	3200 ± 300
		Female*1	471 ± 143	967 ± 1336	1090 ± 820	1.7 ± 0.6	0.8 ± 0.3	0.5 ± 0.0	866 ± 257	1080 ± 980	1670 ± 1270
	5	Male	6610 ± 920	9940 ± 3360	10,600 ± 3800	1.3 ± 0.7	0.8 ± 0.3	0.8 ± 0.3	12,900 ± 3400	18,600 ± 7900	17,100 ± 5100
		Female	3670 ± 1160	5980 ± 3130	5100 ± 2180	1.3 ± 0.7	1.2 ± 0.4	1.0 ± 0.6	8080 ± 2250	12,900 ± 3100	11,800 ± 2500
	20	Male	14,500 ± 4800	18,700 ± 6800	19,000 ± 6500	2.4 ± 0.9	1.8 ± 0.4	1.4 ± 0.5	50,200 ± 9900	65,100 ± 28,100	59,900 ± 24,100
		Female	25,400 ± 5100	23,600 ± 6300	16,700 ± 8900*2	1.5 ± 0.7	0.9 ± 0.2	0.8 ± 0.3*2	55,900 ± 9500	52,100 ± 5000	45,800 ± 7000*2
FTY	1.25	Male*1 ±	793 ± 694	974 ± 68	1120 ± 220	1.2 ± 0.8	0.8 ± 0.3	0.7 ± 0.3	1660 ± 700	1630 ± 190	1550 ± 370
		Female*1	754 ± 194	725 ± 509	802 ± 260	0.8 ± 0.3	0.7 ± 0.3	0.7 ± 0.3	1600 ± 250	1410 ± 370	1420 ± 450
	5	Male	2630 ± 300	1750 ± 350	1890 ± 420	1.3 ± 0.7	0.9 ± 0.2	1.1 ± 0.5	7680 ± 1240	4230 ± 920	4110 ± 710
		Female	2590 ± 1030	1470 ± 490	1620 ± 350	1.1 ± 0.5	1.2 ± 0.4	0.8 ± 0.3	6850 ± 1380	4090 ± 830	4820 ± 570
	20	Male	4910 ± 1630	2720 ± 580	2380 ± 1060	2.4 ± 0.9	2.4 ± 0.9	1.6 ± 0.5	26,700 ± 5700	19,100 ± 2400	18,100 ± 3900
		Female	6050 ± 2420	3210 ± 810	2500 ± 470*2	1.4 ± 0.5	1.0 ± 0.0	1.8 ± 1.5*2	20,800 ± 8800	14,900 ± 4900	18,200 ± 2700*2
TPI	1.25	Male*1	74.4 ± 90.7	58.5 ± 33.5	87.7 ± 45.4	2.3 ± 1.5	1.7 ± 0.6	1.7 ± 0.6	252 ± 227	202 ± 91	257 ± 70
		Female*1	32.4 ± 17.2	20.7 ± 19.5	28.0 ± 7.9	2.7 ± 1.2	1.7 ± 0.6	2.0 ± 0.0	118 ± 20	107 ± 48	140 ± 32
	5	Male	124 ± 35	154 ± 66	194 ± 83	2.0 ± 0.6	1.8 ± 0.4	1.8 ± 0.4	534 ± 161	596 ± 183	664 ± 236
		Female	166 ± 57	104 ± 35	82.4 ± 39.7	2.0 ± 0.0	2.0 ± 0.0	2.4 ± 0.9	747 ± 367	528 ± 62	525 ± 104
	20	Male	371 ± 208	331 ± 200	441 ± 207	2.8 ± 1.1	1.8 ± 0.4	2.0 ± 0.0	1860 ± 700	2010 ± 730	2220 ± 820
		Female	892 ± 542	345 ± 176	418 ± 251*2	1.6 ± 0.5	1.8 ± 0.4	2.0 ± 1.4*2	3220 ± 1130	1770 ± 510	2090 ± 800*2

Arithmetic mean ± standard deviation, n = 5; *1, n = 3; *2, n = 4

3.(ii).A.(1).3) Gastrointestinal absorption

In order to determine the absorption sites of FTD and TPI, [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI was administered into loops of in stomach; upper, middle, and lower small intestine; and colon of male rats at a dose of 10 mg/body. The plasma radioactivity concentration 120 minutes after the administration of [^{14}C-FTD] FTD-TPI was higher when the radioactivity was administered to loops of the middle and lower small intestine (25.30 ± 4.12 and 21.43 ± 5.09 μg eq./mL, respectively) than when administered to the other loops (2.05 ± 0.87 to 12.70 ± 3.79 μg eq./mL). The plasma radioactivity concentration 120

minutes after the administration of [^{14}C-TPI] FTD-TPI was higher when administered to loops of the upper, middle, and lower small intestine (4.37 ± 1.28, 3.74 ± 0.10, 7.70 ± 1.37 μg eq./mL, respectively) than to loops of the stomach and colon (0.25 ± 0.29 and 0.49 ± 0.24 μg eq./mL, respectively). Based on the above results, the applicant explained that FTD is absorbed mainly in the middle- and lower-small intestine while TPI is absorbed mainly in all areas of the small intestine.

3.(ii).A.(1).4) *In vitro* membrane permeability studies

The permeability of FTD and TPI in the human gastrointestinal tract was evaluated in human colon cancer cell line Caco-2. The apparent permeability coefficient of FTD from the apical to the basolateral surface ($P_{app\ A\rightarrow B}$) was 1.4 ± 0.1, 1.3 ± 0.1, 0.7 ± 0.1, and 0.4 ± 0.0 × 10^{-6} cm/sec (mean ± standard deviation) at concentrations of 2, 5, 50 and 800 μmol/L, respectively, and that from the basolateral to the apical surface ($P_{app\ B\rightarrow A}$) was 3.1 ± 0.1, 2.9 ± 0.2, 2.4 ± 0.2, and 1.1 ± 0.1 × 10^{-6} cm/sec, respectively. The $P_{app\ A\rightarrow B}$ of TPI was 0.2 ± 0.1, 0.2 ± 0.0, 0.2 ± 0.0, and 0.3 ± 0.1 × 10^{-6} cm/sec at concentrations of 2, 5, 50, and 400 μmol/L, respectively, and the $P_{app\ B\rightarrow A}$ was 0.3 ± 0.1, 0.3 ± 0.1, 0.3 ± 0.0, and 0.3 ± 0.1 × 10^{-6} cm/sec, respectively. The applicant explained that FTD and TPI are low in permeability as indicated by a comparison of the $P_{app\ A\rightarrow B}$ values of propranolol and mannitol (24.6 × 10^{-6} cm/sec and 0.3 × 10^{-6} cm/sec, respectively).

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

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

Male albino rats received a single oral dose of [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI at 50 mg/kg, and the tissue distribution of radioactivity was evaluated qualitatively.

At 30 minutes after administration of [^{14}C-FTD] FTD-TPI, high levels of radioactivity were found in gastric and intestinal contents, and radioactivity levels in renal and gastric tissues were higher than those in other tissues. At 72 hours after administration, no radioactivity other than a trace amount in the thymus was found.

At 1 hour after administration of [^{14}C-TPI] FTD-TPI, high levels of radioactivity were found in intestinal contents, urine in the bladder, and gastric contents, and radioactivity levels in the intestine and kidneys were higher than those in other tissues. At 72 hours after administration, no radioactivity was found in any tissues other than a small amount found in intestinal contents.

Male albino rats and male pigmented rats received a single oral dose of [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI at 50 mg/kg, and the tissue distribution of radioactivity was evaluated quantitatively.

In albino rats receiving [^{14}C-FTD] FTD-TPI, the radioactivity level peaked at 15 minutes after administration in the stomach and jejunum, at 6 hours in the colon, and at 1 hour in other tissues. Tissue radioactivity levels at 1 hour after administration were higher in the bladder (135,174 ng eq. of FTD/g tissue), ileum (83,487 ng eq. of FTD/g tissue), and kidneys (59,445 ng eq. of FTD/g tissue) than the plasma radioactivity (27,446 ng eq. of FTD/mL). Although the elimination of radioactivity from the

thymus and spleen tended to be slower than that from the plasma, no accumulation of radioactivity in tissues was observed. In the assessment of safety in repeated dose toxicity studies in rats, decreased organ weights and atrophy of thymus and spleen were observed, but findings in these organs were not serious as compared with those suggestive of toxicity observed in other lymphatic and hematopoietic systems. The effects related to FTD-TPI on the lymphatic and hematopoietic systems do not necessarily appear severely in the thymus or spleen. The applicant explained that, for the clinical use of FTD-TPI, the safety can be assured by investigating effects on the lymphatic and hematopoietic systems in hematological testing.

In albino rats receiving [^{14}C-TPI] FTD-TPI, radioactivity levels peaked at 15 minutes after administration in the stomach, jejunum, and bladder, and at 6 hours after administration in the cerebrum, testes, skeletal muscle, and colon. The radioactivity level in the epididymis peaked at between 15 minutes and 1 hour after administration. In the other tissues, the peak radioactivity level was observed at 1 hour after administration. Tissue radioactivity levels at 1 hour after administration were 50,183 ng eq. of TPI/g tissue in the ileum, 13,863 ng eq. of TPI/g tissue in the jejunum, 6182 ng eq. of TPI/g tissue in the bladder, 4560 ng eq. of TPI/g tissue in the stomach, 2950 ng eq. of TPI/g tissue in the colon, 2533 ng eq. of TPI/g tissue in the kidneys, and 1133 ng eq. of TPI/g tissue in the liver, which were higher than the plasma radioactivity level (421 ng eq. of TPI/mL). The radioactivity levels in all the tissues examined decreased over time in a similar manner to the plasma radioactivity level, and no tissue accumulation was observed.

After a single oral administration of [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI at 50 mg/kg to pigmented rats, the findings of tissue distribution and elimination of radioactivity tended to be similar to those observed in albino rats. Additionally, radioactivity was distributed into melanin-containing tissues, but no residual radioactivity was observed.

The applicant explained that repeated dose tissue distribution studies were not conducted because the differences seen between the two tissues and the plasma were not substantial although the elimination of radioactivity from the thymus and spleen tended to be slower than that from the plasma.

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

^{14}C-labeled FTD (hereinafter referred to as ^{14}C-FTD) at 0.5 to 50 μg/mL and ^{14}C-labeled TPI (hereinafter referred to as ^{14}C-TPI) at 0.05 to 5 μg/mL were incubated with plasma samples derived from mice, rats, dogs, monkeys, and humans, and plasma protein binding of FTD and TPI was evaluated by the ultrafiltration method.

The plasma protein binding rate of FTD in the absence of TPI ranged from 70.0% to 82.5% in mice, 57.1% to 72.3% in rats, 37.8% to 45.4% in dogs, 87.8% to 91.5% in monkeys, and 96.7% to 97.3% in humans. The plasma protein binding rate of FTD in the presence of TPI at 5 μg/mL ranged from 71.4% to 73.1% in rats and 96.4% to 97.0% in humans, and the rate did not differ substantially from that in the absence of TPI.

The plasma protein binding rate of TPI in the absence of FTD ranged from 4.1% to 6.4% in mice, 1.9% to 5.3% in rats, 3.1% to 5.5% in dogs, 3.0% to 6.8% in monkeys, and 1.3% to 7.1% in humans. The plasma protein binding rate of TPI in the presence of FTD at 50 μg/mL ranged from 4.2% to 7.1% in rats and 2.1% to 3.1% in humans, and the rate did not differ substantially from that in the absence of FTD.

Using ^{14}C-FTD, the types of plasma proteins that bind to FTD were investigated by the equilibrium gel filtration method. Human serum albumin (HSA), α1-acid glycoprotein, low-density lipoprotein, high-density lipoprotein, and gamma-globulin were used as ^{14}C-FTD conjugates, and binding of FTD with HSA was confirmed. The result indicates that FTD in blood binds to HSA.

^{14}C-FTD at 0.5 to 50 μg/mL and ^{14}C-TPI at 10 to1000 ng/mL were incubated with blood from rats, monkeys, and humans. As a result, the ratio of blood to plasma radioactivity concentrations of ^{14}C-FTD was 0.701 to 0.788 in rats, 0.628 to 0.678 in monkeys, and 0.596 to 0.619 in humans, and the corresponding ratio of ^{14}C-TPI was 0.776 to 0.865, 0.634 to 0.680, and 0.581 to 0.661, respectively. The applicant explained that FTD and TPI are mainly distributed in plasma regardless of animal species and drug concentrations.

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

A single oral dose of [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI at 50 mg/kg was administered to rats on Gestation Day 18, and the placental transfer and maternal-fetal transfer of these drugs were evaluated. At 0.5 and 1 hours after administration of [^{14}C-FTD] FTD-TPI, the radioactivity level was highest in maternal plasma. Fetal tissue radioactivity levels examined were all lower than maternal plasma radioactivity level. At 48 hours after administration, the radioactivity levels in the placenta, fetal membrane, fetal blood, and tissues were higher than the maternal plasma radioactivity level. At 0.5 and 1 hours after administration of [^{14}C-TPI] FTD-TPI, the radioactivity level was highest in maternal plasma. Fetal tissue radioactivity levels examined were all lower than the maternal plasma radioactivity level. At 48 hours after administration, no radioactivity was found in maternal plasma, blood, or amniotic fluid, while radioactivity was found in the placenta, fetal membrane, and fetal blood and tissues (i.e., the brain, heart, lungs, liver, and kidneys). The applicant explained that these results suggest that FTD-TPI are distributed in fetuses after passing through the placenta.

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

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

^{14}C-FTD and ^{14}C-TPI (5 μg/mL) were separately incubated with human hepatocytes at 37°C for 3 hours to identify metabolites. The main metabolite of FTD was FTY, and 5-carboxyuracil (5-CU) and 5-carboxy-2'-deoxyuridine (5-CdUrd) were also detected. 5-CdUrd was generated also in the absence of human hepatocytes, which suggested 5-CdUrd is generated from FTD without enzymes. When ^{14}C-FTD was incubated with TPI (30, 100 μg/mL) in the presence of human hepatocytes, TPI inhibited the metabolism of FTD by 78.1 ± 15.1% (mean ± standard deviation) at 30 μg/mL and 79.5 ± 14.1% at

100 μg/mL. The applicant explained that since TPI inhibits TPase and it has been reported that TPI inhibits the metabolism of FTD in the liver and small intestine of humans and monkeys (*Biochem Pharmacol*. 2000;59:1227-36), it can be considered that FTD is metabolized into FTY mainly through TPase. As no metabolites of TPI were detected in this experiment, TPI is less likely to be metabolized in human hepatocytes.

On the effect of TPI on FTD being metabolized into FTYit has been reported that TPI inhibits the metabolism of FTD in the liver of mice, rats, monkeys, and humans, small intestine of monkeys and humans, and human tumors, but not in the small intestine of mice and rats, or the liver and small intestine of dogs (*Biochem Pharmacol*. 2000;59:1227-36). Based on the above, the applicant explained that the effect of TPI on the metabolism of FTD differs among species, and the metabolism in humans is most similar to that in monkeys among species tested.

There are no study results or published articles on major metabolizing enzymes of TPI.

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

A single oral dose of [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI at 50 mg/kg was administered to male rats, and metabolites of FTD and TPI in plasma were determined. At 1 hour after administration of [^{14}C-FTD] FTD-TPI, FTD was present in the plasma mainly as FTY, representing 81.9% of the total plasma radioactivity. The unchanged FTD (9.9%) and an unknown metabolite HFP1 (3.7%) were also found. During the 24 hours after administration of [^{14}C-FTD] FTD-TPI, no metabolites other than FTY or HFP1 were detected in plasma. At 2 hours after administration of [^{14}C-TPI] FTD-TPI, TPI was present in the plasma mainly as unchanged TPI (75.5%), and 6-hydroxymethyluracil (6-HMU) (15.8%) was detected as well. During the 8 hours after the administration of [^{14}C-TPI] FTD-TPI, no metabolites other than 6-HMU were detected in plasma.

Male rats received a single oral dose of [^{14}C-FTD] FTD-TPI, and metabolites in urine and feces were determined. In urine collected during the 24 hours after administration, FTY accounted for 36.8% of the radioactivity dose, unchanged FTD (13.8%), and an unknown metabolite HFU1 (6.9%) were detected. At all the time points, FTY accounted for as high percentage as 60.5% to 65.3% of the radioactivity in urine. During the 24 hours after administration, urinary excretion of unchanged FTD decreased over time while that of HFU1 increased over time. In the feces collected during the 24 hours after administration, unknown metabolites HFF1 and HFF2 accounted for 8.8% and 2.9% of the administered radioactivity, respectively. Unknown metabolites HFF3 and HFF5 were also present. The unchanged FTD was not found in the feces.

Male rats received a single oral dose of [^{14}C-TPI] FTD-TPI at 50 mg/kg, and metabolites in urine and feces were determined. In urine up to 24 hours after administration, unchanged TPI and 6-HMU accounted for 9.9% and 3.3%, respectively, of the radioactivity dose. During the 24 hours after administration, urinary excretion of unchanged TPI decreased over time while that of 6-HMU increased over time. In feces up to 24 hours after administration, unchanged TPI and 6-HMU accounted for 59.5%

and 13.8%, respectively, of the radioactivity dose.

A single oral dose of [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI at 10 mg/kg was administered to male monkeys, and metabolites in plasma and urine were determined. In plasma obtained at 1 hour after the administration of [^{14}C-FTD] FTD-TPI, unchanged FTD accounted for 56.2% of the total radioactivity in plasma, FTY (26.1%), a glucuronide conjugate of FTD (5.3%), and trifluoromethyluriedopropionic acid (F_3MUPA), a hydrolysate of FTY, (1.4%) were detected. In plasma samples obtained at 6 and 12 hours after administration, α-trifluoromethyl-β-alanine (F_3MBA), which is a hydrolysate of FTY, was detected. In urine collected at 6 hours after administration of [^{14}C-FTD] FTD-TPI, FTY accounted for 43.0% of the total radioactivity in urine, unchanged FTD (41.4%), F_3MUPA (2.8%), and a glucuronide conjugate of FTD (2.5%) were detected. Moreover, F_3MBA was present in urine samples collected up to 6 and 12 hours after administration. In plasma obtained at 1 hour after administration of [^{14}C-TPI] FTD-TPI, unchanged TPI accounted for 67.9% of the total radioactivity in plasma, and an unknown metabolite T-Peak 5 (3.8%) were detected. Additionally, unknown metabolite T-Peak 3 was present in plasma up to 12 hours after administration. The chemical structures of metabolites T-Peak 3 and T-Peak 5 were not able to be suggested. In urine collected at 6 hours after administration of [^{14}C-TPI] FTD-TPI, unchanged TPI accounted for 85.7% of the total radioactivity in urine, imino-oxidated TPI (1.1%), and an unknown metabolite T-Peak 4 (1.0%) were detected. An unknown T-Peak 2, uracil, and 6-HMU were also present as metabolites in urine sample up to 24 hours. The chemical structures of metabolites T-Peak 2 and T-Peak 4 were not able to be suggested.

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

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

Male rats received a single oral dose of [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI at 50 mg/kg, and excretion in urine, feces, and expired air was determined. During the 168 hours after administration of [^{14}C-FTD] FTD-TPI, 60.6%, 20.6%, and 15.8% of the radioactivity dose were excreted in urine, feces, and expired air, respectively, and 0.6% of the radioactivity dose remained in the body. During the 168 hours after administration of [^{14}C-TPI] FTD-TPI, 14.3%, 83.4%, and 0.4% of the radioactivity dose was excreted in urine, feces, and expired air, respectively, and no residual radioactivity was detected in the body.

Bile duct-cannulated male rats received a single oral dose of [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI at 50 mg/kg, and excretion of FTD and TPI into bile, urine, and feces was determined. During 48 hours after the administration of [^{14}C-FTD] FTD-TPI, 0.4%, 65.8%, and 6.7% of the radioactivity dose were excreted in bile, urine, and feces, respectively. During the 48 hours after administration of [^{14}C-TPI] FTD-TPI, 0.2%, 23.8%, and 67.9% of the radioactivity dosed were excreted in bile, urine, and feces, respectively.

The applicant explained that, on the basis of the fact that radioactivity was hardly excreted in rat bile, excretion in feces seems to be attributable to unabsorbed FTD and TPI, and that the absorption rate of FTD or TPI is considered to be higher than at least the sum of excretion rates in urine and expired air

(76.4% of the administered radioactivity for FTD; 14.7% for TPI). Absorbed FTD and TPI are considered to be mainly excreted in urine.

Female monkeys received a single oral dose of [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI at 10 mg/kg, and excretion in urine and feces was determined. During the 168 hours after administration of [^{14}C-FTD] FTD-TPI, 79.4% and 3.8% of the administered radioactivity were excreted in urine and feces, respectively. During the 168 hours after administration of [^{14}C-TPI] FTD-TPI, 27.3% and 68.1% of the administered radioactivity were excreted in urine and feces, respectively. The applicant explained that absorption rate of FTD or TPI in monkeys is considered to be higher than the corresponding excretion rate in urine (79.4% of the administered radioactivity for FTD; 27.3% for TPI).

The applicant also explained that the results of the above studies as well as non-clinical studies of metabolism of FTD-TPI [see "3.(ii).A.(3) Metabolism"] indicate that FTD is metabolized into FTY and excreted in urine while TPI is hardly metabolized and excreted in urine as unchanged TPI in all the species examined.

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

Lactating female rats on Lactation Day 10 received a single oral dose of [^{14}C-FTD] FTD-TPI or [^{14}C-TPI] FTD-TPI at 50 mg/kg, and excretion of radioactivity in milk was determined. After administration of [^{14}C-FTD] FTD-TPI, the radioactivity-time curve in milk was bimodal, and the radioactivity concentrations peaked at 1 and 6 hours after administration. The ratio of milk to plasma radioactivity concentrations ranged from 0.31 to 1.03 at time points up to 72 hours after administration. After administration of [^{14}C-TPI] FTD-TPI, the radioactivity concentrations in milk peaked at 4 hours after administration, and the ratio of milk to plasma radioactivity concentrations ranged from 0.35 to 4.59 at time points up to 72 hours after administration. The applicant explained that these results suggest that FTD and TPI are excreted in milk.

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

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

In the presence of FTD (0.3-300 μmol/L) or TPI (0.1-100 μmol/L), substrates of human CYPs (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5) were incubated with human liver microsomes to evaluate the inhibitory effects of FTD and TPI on CYPs. The IC_{50} values of FTD and TPI were higher than 300 and 100 μmol/L, respectively, which indicated that FTD and TPI have very weak inhibitory effects on human CYPs, if any.

On the basis of the above results, the applicant explained that FTD up to 300 μmol/L and TPI up to 100 μmol/L do not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4/5.

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

Human hepatocytes were treated with FTD (0.5-50 μg/mL) or TPI (0.01-1 μg/mL) for 3 days, and the enzyme activities of CYP1A2 and 3A4/5 were evaluated. Neither FTD nor TPI enhanced the enzyme

activity of these CYPs.

On the basis of the above results, the applicant explained that FTD up to 50 μg/mL and TPI up to 1 μg/mL do not induce CYP1A2 or 3A4/5.

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

Using MDR1 membrane vesicles isolated from the insect cell line Sf9 transfected to express human p-glycoprotein (P-gp), the transport of ^{14}C-FTD (91 μmol/L) and ^{14}C-TPI (73 μmol/L) by P-gp was investigated. There was almost no ATP-dependent uptake of FTD or TPI in MDR1 membrane vesicles, which suggested that FTD and TPI are not substrates of P-gp.

Using MDR1 membrane vesicles isolated from the insect cell line Sf9 transfected to express P-gp, the inhibitory effects of FTD (5-500 μmol/L) and TPI (2-200 μmol/L) on ATP-dependent uptake of N-methyl-quinidine by P-gp were investigated. The ratio of N-methyl-quinidine uptake without FTD to that with FTD ranged between 97.4% and 107.9%, and the corresponding ratio in TPI ranged from 108.9% to 112.3%, suggesting that FTD up to 500 μmol/L and TPI up to 200 μmol/L do not inhibit P-gp. The applicant explained that the above results indicate that FTD and TPI do not inhibit P-gp, and there is no need for clinical studies on pharmacokinetic interactions of FTD-TPI.

3.(ii).A.(5).4) Interactions through plasma protein binding of FTD

A mixture of warfarin, a drug that binds to HSA, and radiolabeled warfarin at a final warfarin concentration of 5 μg/mL was incubated with FTD and human plasma at 37°C for 8 hours, and the effect of FTD on plasma protein binding of warfarin was evaluated using an equilibrium dialysis method. The plasma protein binding rate of warfarin was 99.0% in the absence of FTD, while those in the presence of FTD were 99.0%, 99.0%, and 98.8% at 0.5, 5, and 50 μg/mL, respectively. The applicant explained that FTD does not appear to affect the plasma protein binding rate of warfarin.

Warfarin, diazepam, or digitoxin, which are drugs that bind to HSA, was incubated with ^{14}C-FTD (5 μg/mL) and human plasma at 37°C for 10 minutes, and the effects of these drugs on the plasma protein binding rate of FTD were evaluated using a ultrafiltration method. The plasma protein binding rate of FTD was 93.1% in the absence of any one of the drugs; 93.0% and 93.0% in the presence of warfarin at 1 and 10 μg/mL, respectively; 93.6% and 93.2% in the presence of diazepam at 0.2 and 2 μg/mL, respectively; and 93.0% and 93.9% in the presence of digitoxin at 0.1 and 1 μg/mL, respectively. The applicant explained that drugs that bind to HSA do not appear to affect the plasma protein binding rate of FTD.

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

Based on the submitted data and the following review, PMDA concluded that the applicant's explanations on the absorption, distribution, metabolism, excretion, and pharmacokinetic interactions of FTD-TPI are acceptable.

Pharmacokinetic interactions of FTD-TPI via transporters other than P-gp

At the time of the regulatory submission, the study results of P-gp only were submitted for pharmacokinetic interactions of FTD-TPI via transporters [see "3.(ii).A.(5).3) Transporters"]. PMDA requested the applicant to explain the results of non-clinical studies on pharmacokinetic interactions of FTD-TPI via transporters other than P-gp, if available. The applicant provided the following results 1) to 3) and discussed as follows.

1) In a study using Xenopus laevis oocytes into which cRNAs of rat concentrative nucleotide transporters 1 (CNT1) and 2 (CNT2) were injected, uptake of ^{14}C-FTD via CNT1 or CNT2 was investigated. In cells injected with the cRNA of CNT1, the K_m value for the uptake of ^{14}C-FTD (3-525 μmol/L) was 27 μmol/L. In cells injected with the cRNA of CNT2, ^{14}C-FTD uptake was observed, but the uptake clearance was substantially lower than that for ^{14}C-labeled inosine, a substrate of CNT2.

   Using an *in situ* single-pass perfusion model in male rats with cannulation in the jejunum, the jejunum was perfused with ^{14}C-FTD at 0.378 μmol/L to determine the uptake of FTD through the intestinal lumen. The mean uptake clearance of FTD was 6.74 μL/cm/min. In the presence of thymidine, an inhibitor of nucleoside transporters such as CNT1, at 1 mmol/L, the mean uptake clearance of FTD decreased to 3.76 μL/cm/min.

   These results indicate that FTD is taken up mainly via CNT1 *in vitro* and *in situ*. Non-clinical studies are underway to investigate the involvement of human CNT1 in the gastrointestinal absorption of FTD.

2) Using human fetal renal cell line HEK293 transfected to express human organic cation transporter 2 (OCT2), the uptake of ^{14}C-TPI (0.000968-10 mmol/L) via OCT2 was investigated. The K_m value was 0.408 mmol/L. On the basis of the fact that (1) the results of a Japanese phase I study (Study TAS102-J001) suggest that in addition to glomerular filtration, renal tubular secretion is involved in urinary excretion of TPI [see "4.(ii).A.(1).6) Japanese phase I study"]; and that (2) human OCT2 are expressed specifically in the kidneys (*J Parm Sci*. 2006;95:25-36), renal tubular secretion via OCT2 contributes to the urinary excretion of TPI.

3) Using the HEK293 cell line transfected to express human OCT2, the inhibitory effect of TPI (0.001-10 mmol/L) on the uptake of ^{3}H-1-methyl-4-phenylpyridinium (^{3}H-MPP^{+}) via OCT2 was investigated. The uptake clearance of ^{3}H-MPP^{+} decreased as TPI concentration increased, and the IC_{50} value of TPI for the uptake via OCT2 was 0.946 mmol/L. On the basis of the fact that the C_{max} of TPI in a Japanese phase I study was ≤1 μmol/L [see "4.(ii).A.(1).6) Japanese phase I study"], it is very unlikely that TPI will cause drug interactions with other drugs by inhibiting human OCT2, when administered to humans.

PMDA considers as follows:
Since the results of the above non-clinical studies to date indicate that FTD is a substrate of CNT1 and TPI is a substrate of OCT2, it is possible that the PK parameters of FTD-TPI are altered by the combination therapy with inhibitors or inducers of CNT1 or OCT2, which may affect the efficacy and safety of FTD-TPI or the concomitant drugs. Therefore, the applicant should provide information appropriately on the fact that FTD is a substrate of CNT1 and TPI is a substrate of OCT2 in the package insert, and should collect further information on possible pharmacokinetic interactions of FTD-TPI including the results of the ongoing study on the involvement of human CNT1 in gastrointestinal absorption of FTD and provide such information to healthcare providers in clinical settings appropriately.

3.(iii) Summary of toxicology studies

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

Single dose toxicity studies, repeat dose toxicity studies, and genotoxicity studies of FTD-TPI, FTD, and TPI, reproduction toxicity studies of FTD-TPI, and photosafety testing of FTD and TPI were conducted.

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

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

Male and female SD rats (n = 5/sex/group) received FTD-TPI at 0 (vehicle), 250, 500, 1000, or 2000 mg/kg orally. One male and 4 female animals in the 2000 mg/kg group died 1 or 2 days after administration. Toxicity findings included diarrhea observed in males in the 250 mg/kg group and animals in the ≥500 mg/kg groups on the day of administration.

The approximate lethal dose of FTD-TPI was determined to be 2000 mg/kg.

3.(iii).A.(1).2) Single oral dose toxicity study in dogs

Male and female beagle dogs (n = 1/sex/group) received a single oral dose of FTD-TPI at 250, 500, 1000, or 2000 mg/kg. At 7 days after administration, 1 male in the 2000 mg/kg group was moribund and euthanized. Toxicity findings included vomiting and soft stools observed in the ≥250 mg/kg groups.

The approximate lethal dose of FTD-TPI was determined to be 2000 mg/kg.

3.(iii).A.(1).3) Single oral dose toxicity study of FTD in rats

Male and female SD rats (n = 5/sex/group) received FTD at 0 (vehicle), 250, 500, 1000, or 2000 mg/kg orally. Two male and 3 female animals in the 2000 mg/kg group died at 1 to 4 days after administration. Toxicity findings included diarrhea observed in males in the 250 mg/kg group and animals in the ≥500 mg/kg groups on the day of administration.

The approximate lethal dose of FTD was determined to be 2000 mg/kg.

3.(iii).A.(1).4) Single oral dose toxicity study of FTD in dogs

Male and female beagle dogs (n = 1/sex/group) received a single oral dose of FTD at 250, 500, 1000, or 2000 mg/kg. Animals in the ≥250 mg/kg groups developed vomiting, soft stools, watery stools, decreased stool volume, or no stool.

The approximate lethal dose of FTD was determined to be not less than 2000 mg/kg.

3.(iii).A.(1).5) Single oral dose toxicity study of TPI in rats

Male and female SD rats (n = 5/sex/group) received a single oral dose of TPI at 0 (vehicle) or 2000 mg/kg. Salivation and pale stools were observed in the 2000 mg/kg group.

The approximate lethal dose of TPI was determined to be ≥2000 mg/kg.

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

3.(iii).A.(2).1) Two-week repeated dose oral toxicity study in rats

Male SD rats (n = 5/group) received FTD-TPI orally at doses of 0 (vehicle), 15, 50, 150, or 450 mg/kg/day for 2 weeks. Observed toxicity findings include necrosis of the small intestinal crypt epithelium, follicular atrophy in the mesenteric and submandibular lymph nodes in the ≥150 mg/kg/day groups, decreased body weight gain, decreased food consumption, decreased white blood cell count, decreased percentage of reticulocytes, decreased spleen and thymus weights, increased adrenal weight, necrosis of the large intestinal crypt epithelium, and thymic atrophy in the 450 mg/kg/day group.

The no observed adverse effect level (NOAEL) of FTD-TPI was determined to be 50 mg/kg/day.

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

Male and female SD rats (n = 12/sex/group) received FTD-TPI orally at doses of 0 (vehicle), 50, 150, or 450 mg/kg/day for 4 weeks, and the toxicity of repeated doses of FTD-TPI was evaluated. Additionally, recovery assessing groups (n = 6/sex/group) were set up in the 0, 150, and 450 mg/kg/day groups and animals were observed during the 4 week recovery period to evaluate whether adverse findings are reversible.

During and at the end of the 4-week treatment period, the following findings were observed.

- Clinical signs: Decreased body weight gain, and decreased food consumption in males in the 450 mg/kg/day group and females in the ≥150 mg/kg/day groups
- Urinalysis: Increased drug-induced crystals in urinary sedimentation in females in the ≥150 mg/kg/day groups, deceased urinary osmolality in the 450 mg/kg/day group, and decreased daily excretion of sodium, potassium, and chlorine ions into the urine in males in the 450 mg/kg/day group
- Hematology: Anemia, decreased white blood cell count in the 450 mg/kg/day group, decreased percentage of reticulocytes, and decreased fibrinogen levels in males in the 450 mg/kg/day group
- Blood chemistry: Decreased total protein and gamma-globulin fraction in the 450 mg/kg/day group,

and increased total cholesterol and total bilirubin levels in females in the 450 mg/kg/day group

- Organ weight: Decreased thymus weight in males in the 450 mg/kg/day group and females in the ≥150 mg/kg/day groups, and increased ovary weight in females in the ≥150 mg/kg/day groups
- Histopathology: Erosions of the glandular stomach, and necrosis of the small intestinal crypt epithelium in the ≥150 mg/kg/day groups, increased extramedullary hemopoiesis in the spleen in males in the ≥150 mg/kg/day groups and females in the 450 mg/kg/day group, splenic atrophy in the 450 mg/kg/day group, atrophy of the thymus, submandibular lymph nodes, and mesenteric lymph nodes in the 450 mg/kg/day group, decreased hematopoietic cells in the bone marrow, atrophy of the large intestinal crypt epithelium in males in the 450 mg/kg/day group, and increased number of small luteal cells in the ovary in females in the ≥150 mg/kg/day groups

In the recovery study, 1 male in the 450 mg/kg/day group died 28 days after the final administration. Findings at the end of the 4-week recovery period included a whitening of the incisors in the ≥150 mg/kg/day groups, and broken incisors in the 450 mg/kg/day group. Histopathological examination revealed the degeneration and disarrangement of ameloblasts, papillary layer cells, and odontoblasts of incisors in the ≥150 mg/kg/day groups. Findings consistent with malnutrition due to a difficulty in chewing solid diet caused by abnormal incisors were observed in the 450 mg/kg/day group. The necrosis of the small and large intestinal crypt epithelium observed at the end of the treatment period was reversible.

Based on these findings, the NOAEL of FTD-TPI was determined to be 50 mg/kg/day.

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

Male and female SD rats (n = 12/sex/group) received FTD-TPI orally at doses of 0 (vehicle), 5, 15, 50, or 150 mg/kg/day for 13 weeks, and the toxicity of repeated doses of FTD-TPI was evaluated. Additionally, recovery assessing groups (n = 6/sex/group) were set up in the 0, 15, 50, and 150 mg/kg/day groups and animals were observed during the 9 week recovery period to evaluate whether adverse findings are reversible.

During and at the end of the 13-week treatment period, the following findings were observed.

- Clinical signs: A whitening and breakage of the incisors in the ≥50 mg/kg/day groups, decreased body weight gain, decreased food consumption, diarrhea, malocclusion of the incisors, and stained fur in the 150 mg/kg/day group
- Hematology: Decreased white blood cell count in the ≥50 mg/kg/day groups, and decreased red blood cell count in the 150 mg/kg/day group
- Organ weight: Decreased thymus weight in the 150 mg/kg/day group
- Histopathology: Increased apoptotic bodies in the small intestinal crypt epithelium, fatty infiltration of the bone marrow, and disarrangement of odontoblasts of the incisors in the ≥50 mg/kg/day groups, thymus atrophy, a thinner dentin layer and decreased odontoblasts, partial loss of dentin, flattened ameloblasts, and flattened papillary layer cells of incisors among others in the 150 mg/kg/day group

At the end of the 9-week recovery period, abnormal incisors were observed in the 150 mg/kg/day group, but other findings were reversible.

Based on these findings, the NOAEL of FTD-TPI was determined to be 15 mg/kg/day. The mean exposure to FTD at the NOAEL ($AUC_{0\text{-}24}$ at the end of the 13-week treatment period) was 1800 ng·h/mL in males and 2550 ng·h/mL in females, which were lower than clinical exposure level.*

* In a Japanese phase I study (Study TAS102-J001), the mean $AUC_{0\text{-}10}$ after the morning dose on Day 12 of treatment in Japanese patients who received FTD-TPI repeatedly at 35 mg/m^2 BID was 20,950 ng·h/mL.

3.(iii).A.(2).4) Two-week repeated dose oral toxicity study of FTD in rats

Male SD rats (n = 5/group) received FTD orally at doses of 0 (vehicle), 15, 50, 150, or 450 mg/kg/day for 2 weeks, and the toxicity of repeated doses of FTD was evaluated. Three animals in the 450 mg/kg/day showed unkempt fur, soft stools or diarrhea, stained fur around the nostrils, emaciation, and decreased locomotor activity, among other findings, and died during the period from Day 11 of treatment to the day of necropsy.

During and at the end of the 2-week treatment period, the following findings were observed.

- Clinical signs: Decreased weight gain or decreased body weight in the ≥150 mg/kg/day group, decreased food consumption, and unkempt fur in the 450 mg/kg/day group
- Urinalysis: Positive for bilirubin and glucose in the 450 mg/kg/day group
- Fecal occult blood: Positive in the 450 mg/kg/day group
- Hematology: Decreased white blood cell count and percentage of reticulocytes in the 450 mg/kg/day group
- Blood chemistry: Decreased triglycerides, potassium level, and total proteins, and increased blood urea nitrogen in the 450 mg/kg/day group
- Organ weight: Decreased thymus and spleen weight in the 450 mg/kg/day group
- Histopathology: Atrophy of the submandibular and mesenteric lymph nodes in the ≥150 mg/kg/day groups, atrophy of the small and large intestinal mucosa, necrosis of the small and large intestinal crypt epithelium, tubular atrophy in the testes, decreased intratubular sperms and increased intratubular debris in the epididymis, and decreased hematopoietic cells in the bone marrow in the 450 mg/kg/day group

Based on these findings, the NOAEL of FTD was determined to be 50 mg/kg/day.

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

Male and female SD rats (n = 12/sex/group) received FTD orally at doses of 0 (vehicle), 15, 50, or 150 mg/kg/day for 4 weeks, and the toxicity of repeated doses of FTD was evaluated. Additionally, recovery assessing groups (n = 6/sex/group) were set up in the 0, 50, and 150 mg/kg/day groups and animals were observed during the 4 week recovery period to evaluate whether adverse findings are reversible.

During and at the end of the 4-week treatment period, the following findings were observed.

- Clinical signs: A whitening of the incisors in the 150 mg/kg/day group, decreased body weight gain,

and decreased food consumption in males in the 150 mg/kg/day group

- Urinalysis: Drug crystals in urinary sediments in the 150 mg/kg/day group, decreased daily excretion of sodium, potassium, and chlorine ions into the urine in males in the 150 mg/kg/day group
- Hematology: Decreased white blood cell count in the 150 mg/kg/day group, and decreased fibrinogen levels in males in the 150 mg/kg/day group
- Blood chemistry: Decreased triglyceride levels, and increased potassium levels in males in the 150 mg/kg/day group
- Organ weight: Decreased thymus weight in males in the 150 mg/kg/day group and increased ovary weight in females in the 150 mg/kg/day group
- Histopathology: Erosion of the glandular stomach, necrosis of the small intestinal crypt epithelium, degeneration and disarrangement of ameloblasts and papillary layer cells of the incisors in the 150 mg/kg/day group, and abnormal dentin in males in the 150 mg/kg/day group

Findings observed during and at the end of the 4-week recovery period included a whitening or breakage of the incisors in the ≥50 mg/kg/day groups, degeneration and disarrangement of ameloblasts and papillary layer cells, abnormal dentin, decreased body weight, decreased food consumption, and unkempt fur and other findings consistent with malnutrition in the 150 mg/kg/day group. Toxicological findings of the small intestinal crypt epithelium were reversible.

Based on the findings above, the NOAEL of FTD was determined to be 15 mg/kg/day (when the findings specific to rats [the whitening and breakage of the incisors] were excluded, the NOAEL was determined to be 50 mg/kg/day).

3.(iii).A.(2).6) Two-week repeated dose oral toxicity study of TPI in rats

Male SD rats (n = 4 or 5/group) received TPI orally at doses of 0 (vehicle), 80, 400, or 2000 mg/kg/day for 2 weeks, and the toxicity of repeated doses of TPI was evaluated.

During and at the end of the 2-week treatment period, changes in clinical signs including pale stools, diarrhea and salivation, and decreased triglycerides in blood chemistry in the ≥400 mg/kg/day groups were observed. The changes observed were considered of little toxicological significance because there were no toxicological findings in body weight, food consumption, or necropsy in this study or the 4-week repeated dose oral toxicity study of TPI in rats.

The NOAEL of TPI was determined to be 2000 mg/kg/day.

3.(iii).A.(2).7) Four-week repeated dose oral toxicity study of TPI in rats

Male and female SD rats (n = 12/sex/group) received TPI orally at doses of 0 (vehicle), 80, 400, or 2000 mg/kg/day for 4 weeks, and the toxicity of repeated doses of TPI was evaluated. Additionally, recovery assessing groups (n = 6/sex/group) were set up in the 0, 400, and 2000 mg/kg/day groups and animals were observed during the 2 week recovery period to evaluate whether adverse findings are reversible.

One male in the 2000 mg/kg/day group died due to misadministration, but no deaths other than that occurred during the treatment and recovery period.

Urinalysis at the end of the 4-week treatment period revealed cloudy urine and drug crystals in the 2000 mg/kg/day group. However, these findings were not considered of toxicological significance as no crystals were found in the urinary tract, or no histopathological changes were found. After the 2-week recovery period, no abnormal findings were observed in urinalysis.

The NOAEL of TPI was determined to be 2000 mg/kg/day.

3.(iii).A.(2).8) Two-week repeated dose oral toxicity study in monkeys

Male and female cynomolgus monkeys (n = 3/sex/group) received FTD-TPI orally at doses of 0 (vehicle), 1.9, 7.5, 30, or 120 mg/kg/day for 2 weeks, and the toxicity of repeated doses of FTD-TPI was evaluated. On Day 8, one male in the 120 mg/kg/day group was moribund and euthanized.

During and at the end of the 2-week treatment period, the following findings were observed.

- Clinical signs: Salivation and watery or soft stools in the ≥30 mg/kg/day groups, and vomiting in the 120 mg/kg/day group
- Hematology: Decreased white blood cell and lymphocyte counts in the ≥7.5 mg/kg/day groups
- Histopathology: Large intestine inflammation and necrosis of the large intestinal crypt epithelium, and atrophy of the germinal center of the spleen in the ≥30 mg/kg/day groups, villus atrophy of small intestinal, atrophy of mesenteric lymph nodes, and decreased hematopoietic cells in the bone marrow in the 120 mg/kg/day group

The NOAEL of FTD-TPI was determined to be 1.9 mg/kg/day.

3.(iii).A.(2).9) Four-week repeated dose oral toxicity study in monkeys

Male and female cynomolgus monkeys (n = 3/sex/group) received FTD-TPI orally at doses of 0 (vehicle), 6.25, 25, or 100 mg/kg/day for 4 weeks, and the toxicity of repeated doses of FTD-TPI was evaluated. Additionally, recovery assessing groups (n = 2/sex/group) were set up in the 0, 25, and 100 mg/kg/day groups and animals were observed during the 4 week recovery period to evaluate whether adverse findings are reversible.

During and at the end of the 4-week treatment period, the following findings were observed.

- Clinical signs: Soft stools, watery stools, vomiting, and dehydration in the ≥25 mg/kg/day groups, anorexia and decreased body weight in the 100 mg/kg/day group
- Urinalysis: Increased urinary creatinine level, and increased potassium and chloride ion levels in females in the 100 mg/kg/day group
- Hematology: Anemia, and decreased white blood cell count in males in the ≥25 mg/kg/day groups and females in the 100 mg/kg/day group, and increased platelet count in the 100 mg/kg/day group
- Blood chemistry: Increased blood urea nitrogen, and increased creatinine and alanine

aminotransferase (ALT) in males in the 100 mg/kg/day group

- Histopathology*: Chronic inflammation of and localized hemorrhage in the gastric body, cecitis and mucosal hemorrhage in the cecum, colitis, atrophy of lymphoid tissues in the spleen, and atrophy of the submandibular lymph nodes, mesenteric lymph nodes, and thymus in the ≥25 mg/kg/day groups, villus atrophy in the small intestine, degeneration or necrosis of the intestinal crypt epithelium, proctitis, decreased hematopoietic cells in the bone marrow, and decreased myeloid/erythroid ratio of bone marrow smears in the 100 mg/kg/day group

After the 4-week recovery period, inflammation in the gastrointestinal tract remained, but decreased in severity and frequency, suggesting the reversibility of these findings.

Based on these findings, the NOAEL of FTD-TPI was determined to be 6.25 mg/kg/day.

*:Histopathological examination of maxillary incisors was performed and no changes were observed.

3.(iii).A.(2).10) Thirteen-week repeated dose oral toxicity study in monkeys

Male and female cynomolgus monkeys (n = 3/sex/group) received FTD-TPI at doses of 0 (vehicle), 1.25, 5, or 20 mg/kg/day, or FTD at 20 mg/kg/day orally for 13 weeks, and the toxicity of repeated doses of FTD-TPI or FTD was evaluated. Additionally, recovery assessing groups (n = 2/sex/group) were set up in the FTD-TPI 0, 5, and 20 mg/kg/day groups and the FTD 20 mg/kg/day group and animals were observed during the 9 week recovery period to evaluate whether adverse findings are reversible. On Day 85, 1 female in the FTD-TPI 20 mg/kg/day group was moribund and euthanized.

During and at the end of the 13-week treatment period, the following findings were observed in animals receiving FTD-TPI, while no toxicological findings related to the treatment with FTD were observed in the FTD 20 mg/kg/day group.

- Clinical signs: Decreased body weight gain or decreased body weight in the FTD-TPI ≥5 mg/kg/day groups, soft stools and watery stools in the FTD-TPI 20 mg/kg/day group, decreased food consumption, bloody or no stools, and decreased locomotor activities in males in the FTD-TPI 20 mg/kg/day group
- Hematology at week 6 of treatment: Anemia and decreased white blood cell count in the FTD-TPI 20 mg/kg/day group
- Hematology at week 13 of treatment: Anemia in the FTD-TPI ≥5 mg/kg/day groups, and decreased lymphocyte count in the FTD-TPI 20 mg/kg/day group
- Histopathology[*1]: Infiltration of inflammatory cells in the rectum, and atrophy of the spleen in the 20 mg/kg/day group

After the 9-week recovery period, no toxicological findings were found in the FTD-TPI groups or in the FTD 20 mg/kg/day group, and findings above were reversible.

Based on these findings, the NOAEL of FTD-TPI was determined to be 1.25 mg/kg/day. The mean

exposure to FTD at the NOAEL (AUC_{0-24} at the end of the 13-week treatment period) was 3200 ng·h/mL in males and 1670 ng·h/mL in females, which were lower than clinical exposure level.*2

*1: Histopathological examination of maxillary incisors was performed and no changes were observed.
*2: In a Japanese phase I study (Study TAS102-J001), the mean AUC_{0-10} on Day 12 of treatment after the morning dose in patients who received FTD-TPI repeatedly at 35 mg/m^2 BID was 20,950 ng·h/mL.

3.(iii).A.(2).11) Two-week repeated dose oral toxicity study in dogs

Male beagle dogs (n = 3/group) received FTD-TPI orally at doses of 0 (vehicle), 17, 50, or 150 mg/kg/day for 2 weeks, and the toxicity of repeated doses of FTD-TPI was evaluated. Animals in the 50 and 150 mg/kg/day groups showed decreased locomotor activities, tremor, decreased skin temperature, vomiting, and abnormal stools (soft, watery, red stools). All animals in the 50 and 150 mg/kg/day groups died, or were moribund and euthanized between Day 5 and Day 8 of treatment.

During and at the end of the 2-week treatment period, the following findings were observed.

- Clinical signs: Vomiting, soft stools, watery stools, decreased stool volume, decreased body weight, and deceased food consumption in the ≥17 mg/kg/day groups.
- Urinalysis: Positive for urinary protein and occult blood in the 17 mg/kg/day group.
- Occult blood in stools: Positive in the 17 mg/kg/day group.
- Hematology: Decreased platelet count in the 17 mg/kg/day group, decreases in white blood cell count, segmented neutrophil count, and lymphocyte count in the ≥17 mg/kg/day groups.
- Blood chemistry: Decreased alkaline phosphatase (ALP) in the 17 mg/kg/day group, decreased potassium level in the ≥17 mg/kg/day groups, increases in blood urea nitrogen, creatinine, glucose, total bilirubin, inorganic phosphorus, cholesterol, triglyceride, total protein, and globulin, and decreased chlorine ion level in the 50 mg/kg/day group, increased ALT, and decreased albumin/bilirubin ratio in the ≥50 mg/kg/day groups, and increased aspartate aminotransferase (AST) in the 150 mg/kg/day group.
- Histopathology: Necrosis of the small and large intestinal crypt epithelium, decreased hematopoietic cells in the bone marrow, atrophy of the submandibular lymph nodes, atrophy of lymphoid tissues in the thymus, ileum, and spleen in the ≥17 mg/kg/day groups, hemorrhagic pneumonia in the 50 mg/kg/day group, atrophy of the esophageal squamous epithelium, and atrophy of the mesenteric lymph nodes in the ≥50 mg/kg/day groups.

Based on these findings, the NOAEL of FTD-TPI was determined to be less than 17 mg/kg/day.

3.(iii).A.(2).12) Four-week repeated dose oral toxicity study of FTD in monkeys

Male and female cynomolgus monkeys (n = 3/sex/group) received FTD orally at doses of 0 (vehicle), 1.56, 6.25, or 25 mg/kg/day for 4 weeks, and the toxicity of repeated doses of FTD was evaluated. Additionally, recovery assessing groups (n = 2/sex/group) were set up in the 0, 6.25, and 25 mg/kg/day groups and animals were observed during the 4 week recovery period to evaluate whether adverse findings are reversible.

At the end of the 4-week treatment period, atrophy of the mucosa and villi of the gastrointestinal tract that were possibly related to the pharmacological effect of FTD were observed at 1.56 and 25 mg/kg/day. However, these findings were not observed at the end of the recovery period. These findings were not accompanied by degenerative lesions, nor did they occur dose-dependently. The NOAEL of FTD was determined to be 25 mg/kg/day.

Male cynomolgus monkeys (n = 2/group) received FTD orally at doses of 50, 100, or 150 mg/kg/day for 4 weeks, and the toxicity of repeated doses of FTD was evaluated. All animals in the ≥100 mg/kg/day groups were moribund and euthanized between Day 13 and Day 23 of treatment.

During and at the end of the 4-week treatment period, the following findings were observed.

- Clinical signs: Reduced body weight, decreased food consumption, and diarrhea in the ≥50 mg/kg/day groups, and bloody stools in the ≥100 mg/kg/day group.
- Occult blood in stool: Positive in the ≥100 mg/kg/day groups.
- Hematology: Decreased white blood cell and reticulocyte counts in the ≥50 mg/kg/day groups.
- Blood chemistry: Increases in glucose, blood urea nitrogen, creatinine, inorganic phosphorus, and potassium, and decreases in total cholesterol, phospholipids, sodium ions and chloride ions in the ≥100 mg/kg/day groups.
- Necropsy: Absence of clearly visible Peyer's patches in the ileum in the ≥100 mg/kg/day group, among other findings.
- Histopathology: Decreased lymphocyte in the thymus, atrophy of white pulps in the spleen, decreased or increased hematopoietic cells in the bone marrow, infiltration of inflammatory cells in the gastrointestinal tract, and increased apoptotic bodies and atrophy in the gastrointestinal mucus in the ≥50 mg/kg/day groups, decreased glycogen areas of hepatocytes in the liver, enlarged renal tubules in the kidneys, decreased cytoplasmic vacuolation and swollen cortex in the adrenal glands, degeneration and necrosis of the seminiferous tubular epithelium, presence of multinucleated giant cells, increased cell debris in the epididymis, thickening and ulceration of the epidermis, and infiltration of inflammatory cells in the subcutaneous tissues in the ≥100 mg/kg/day groups.

Since toxicological findings were observed even in the lowest dose group, the NOAEL of FTD was not able to be determined in this study.

3.(iii).A.(2).13) Two-week repeated dose oral toxicity study of FTD in dogs

Male beagle dogs (n = 3/group) received FTD orally at doses of 0 (vehicle), 2, 6, or 17 mg/kg/day for 2 weeks, and the toxicity of repeated doses of FTD was evaluated. Animals in the 17 mg/kg/day group showed decreases in body weight and food consumption, vomiting, soft stools, watery stools, decreased stool volume, decreased locomotor activities, dehydration, decreased skin temperature, debilitation, tremor, hunchback position, and labored breathing. All animals in the 17 mg/kg/day group died, or were moribund and euthanized on Day 12 or Day 13 of treatment.

During and at the end of the 2-week treatment period, the following findings were observed.

- Clinical signs: Decreased food consumption in the ≥6 mg/kg/day groups
- Urinalysis: Positive for bilirubin and bacteria in the ≥6 mg/kg/day groups, positive for glucose, occult blood, and protein in the 17 mg/kg/day group
- Hematology: Decreases in white blood cells, segmented neutrophil, monocyte, and eosinophil counts at 6 mg/kg/day, and decreased platelet count in the 17 mg/kg/day group
- Blood chemistry: Increases in total bilirubin, ALP, cholesterol, triglycerides, and globulin, and decreases in albumin/globulin ratio, sodium, potassium, and chlorine ion in the 17 mg/kg/day group
- Histopathology: Necrosis of the small and large intestinal crypt epithelium, and decreased hematopoietic cells in the bone marrow in the ≥2 mg/kg/day groups, atrophy of the lymphoid tissues in the ileum, spleen, thymus, submandibular lymph nodes and mesenteric lymph nodes in the 17 mg/kg/day group

The necrosis of the small and large intestinal crypt epithelium and decreased hematopoietic cells in the bone marrow observed in the 2 mg/kg/day group were mild in severity, and thus the NOAEL of FTD was determined to be 2 mg/kg/day.

3.(iii).A.(2).14) Four-week repeated dose oral toxicity study of TPI in monkeys

Male and female cynomolgus monkeys (n = 3/sex/group) received TPI orally at doses of 0 (vehicle), 100, 300, or 1000 mg/kg/day for 4 weeks, and the toxicity of repeated doses of TPI was evaluated. Additionally, recovery assessing groups (n = 2/sex/group) were set up in the 0, 300, and 1000 mg/kg/day groups and animals were observed during the 4 week recovery period to evaluate whether adverse findings are reversible.

During and at the end of the 4-week treatment period, the following findings were observed.

- Clinical signs: Soft stools in males in the ≥300 mg/kg/day groups and in females in the 1000 mg/kg/day group, and watery stools in animals in the 1000 mg/kg/day group
- Histopathology: Colitis including mucosal hyperplasia, and atrophy of lymphoid tissues in the thymus in the ≥300 mg/kg/day groups, and gastritis, hemorrhage of gastric mucosa, infiltration of foamy mononuclear cells in the spleen, atrophy of lymphoid tissues of the spleen, and lymphoid hyperplasia in mesenteric lymph nodes in the 1000 mg/kg/day group

After the 4-week recovery period, soft stools, watery stools, and inflammation of the gastrointestinal tract were still present, but they were mild in severity and their incidences were low, which indicates that these findings are reversible.

Based on the above, the NOAEL of TPI was determined to be 100 mg/kg/day.

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

Bacterial reverse mutation assays were conducted to assess the genotoxicity of FTD-TPI, FTD, and TPI using the following strains: *Salmonella typhimurium* TA100, TA1535, TA98, and TA1537; and

Escherichia coli WP2*uvrA*. FTD-TPI and FTD increased the number of revertants in *S. typhimurium* TA100 and TA1535, and *E. coli* WP2*uvrA* in the presence or absence of exogenous metabolic activation (rat liver S9 homogenate [S9 mix]), which indicated that FTD-TPI and FTD are capable to induce base-pair substitutions. TPI did not increase the number of revertants, and TPI was not considered capable to induce mutations.

A chromosome aberration assay in the Chinese hamster lung derived cells (CHL/IU) was conducted to investigate the effect of FTD-TPI, FTD, and TPI with an exposure time of 6 hours (a short-term test). FTD-TPI and FTD increased the incidence of cells with structural chromosomal aberrations in the presence or absence of metabolic activation, which suggested that FTD-TPI and FTD are capable to induce chromosomal aberration. TPI did not induce the incidence of cells with structural chromosomal aberrations, and was not considered capable to induce chromosomal aberration.

In a bone marrow micronucleus test to investigate the effect of FTD-TPI, FTD, or TPI, mice received these substances orally. FTD-TPI and FTD increased the incidence of polychromatic erythrocytes with micronuclei, which suggested that FTD-TPI is capable to induce micronuclei. TPI did not increase the incidence of polychromatic erythrocytes with micronuclei, and TPI was not considered capable to induce micronuclei.

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

No carcinogenicity studies have been conducted with FTD-TPI as the product will be indicated for the treatment of unresectable advanced or recurrent colorectal cancer.

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

3.(iii).A.(5).1) Fertility and early embryonic development to implantation

Male SD rats (n = 20/group) received FTD-TPI orally at doses of 0 (vehicle), 50, 150, or 450 mg/kg/day from 14 days prior to mating through to the day before necropsy including mating period in between. The male rats were mated with untreated female rats. Although reduced body weight gain and food consumption were observed in the ≥150 mg/kg/day groups and dark red spots in the glandular stomach in the 450 mg/kg/day group, no toxicological findings were observed in fertility or early embryonic development.

The NOAEL for paternal general toxicity was determined to be 50 mg/kg/day, and those for paternal fertility and early embryonic development were determined to be 450 mg/kg/day.

Female SD rats (n = 20/group) received FTD-TPI orally at doses of 0 (vehicle), 15, 50, or 150 mg/kg/day from14 days prior to mating through to gestation day 7 including mating period in between. The female rats were mated with untreated male rats. Reduced body weight gain and food consumption were observed in the ≥50 mg/kg/day groups, and the numbers of corpora lutea and implantations and the rate of postimplantation loss increased in the 150 mg/kg/day group.

The NOAEL for maternal general toxicity was determined to be 15 mg/kg/day, and those for maternal fertility and early embryonic development were determined to be 50 mg/kg/day.

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

In a dose-finding study, pregnant SD rats (n = 8-10/group) received FTD-TPI orally at doses of 0 (vehicle), 50, 150, 300, or 600 mg/kg/day from gestation day 7 to 17, and were subjected to caesarean section on gestation day 21. Two females at 600 mg/kg/day died or were sacrificed moribund. General toxicological findings observed in female animals were decreased body weight gain in the ≥150 mg/kg/day groups, and decreased food consumption in the ≥300 mg/kg/day groups. Toxicological findings observed in embryos and fetuses were increased mortality, low body weight, and increased incidence of external anomalies in the ≥150 mg/kg/day groups. No live fetuses were observed in the ≥300 mg/kg/day groups.

Pregnant SD rats (n = 20-21/group) received FTD-TPI orally at doses of 0 (vehicle), 15, 50, or 150 mg/kg/day from gestation day 7 to 17, and were subjected to caesarean section on gestation day 21.

General toxicological findings observed in maternal animals were reduced body weight gain in the ≥50 mg/kg/day groups, and decreased food consumption, abortion, and total resorption of litter in the 150 mg/kg/day group. Toxicological findings observed in embryos and fetuses were low fetal body weight and delayed ossification in the ≥50 mg/kg/day groups, high postimplantation loss rate, high incidence of external anomaly (kinked tail), visceral anomalies (aberrant subclavian artery, left-sided umbilical arteries, subclavian artery running behind the esophagus), and skeletal anomalies (e.g., malformation and abnormal arrangement of vertebrae, bifid sternebrae, supernumerary ribs) in the 150 mg/kg/day group. These results indicated that FTD-TPI inhibits fetal development at ≥50 mg/kg/day, and kills embryos and induces teratogenic effects at 150 mg/kg/day.

On the basis of these results, the NOAEL for dams and that for embryo-fetal development were determined to be 15 mg/kg/day.

3.(iii).A.(6) Local tolerance

In repeated dose oral toxicity studies of FTD-TPI, the effect of FTD-TPI on the gastrointestinal tract was evaluated. There were no findings that indicate the risk concerning local tolerance in the gastrointestinal tract in clinical use. No other routes than oral administration were investigated for local tolerance of FTD-TPI.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Immunotoxicity

No immunotoxicity studies have been conducted for FTD-TPI since toxicological findings in the lymphatic and hematopoietic systems were observed in the repeated dose toxicity studies of FTD-TPI, and FTD-TPI is considered to affect the immune system.

3.(iii).A.(7).2) Photosafety testing

Using 3T3 mouse fibroblasts, the photosafety of FTD and TPI was evaluated *in vitro* by the neutral red uptake assay. No differences in the cytotoxicity between UVA irradiation and non-irradiation groups were found, and therefore FTD and TPI are not phototoxic.

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

Based on the submitted data and the following review, PMDA concluded that FTD-TPI has no safety margins, but may be used in clinical settings considering the severity of the disease for which FTD-TPI will be indicated.

3.(iii).B.(1) Effects on teeth

Abnormalities of incisors were observed in the 4-week repeated dose oral toxicity study of FTD-TPI in rats [see "3.(iii).A.(2).2) 4-week repeated dose oral toxicity study in rats"], and the 13-week repeated dose oral toxicity study of FTD-TPI in rats [see "3.(iii).A.(2).3) 13-week repeated dose oral toxicity study in rats"], and the 4-week repeated dose oral toxicity study of FTD in rats [see "3.(iii).A.(2).5) 4-week repeated dose oral toxicity study of FTD in rats"]. PMDA requested the applicant to explain its mechanism of development, possible effects on human teeth, and whether a caution about the effects should be included in the package insert.

The applicant responded as follows.

It has been reported that fluorouracil analogs cause histopathological changes of ameloblasts at the stage of matrix formation (*J Toxicol Pathol*. 1990;3:245-56). On the basis of the fact FTD-TPI and FTD exert cytotoxicity similar to those of fluorouracil analogs, the abnormality of the incisors appears to be caused by a histopathological change in ameoblasts at the stage of matrix formation.

An effect of FTD-TPI on children's teeth cannot be ruled out because amelogenesis occurs in children's teeth. The package insert will contain a caution regarding the effect of FTD-TPI on children's teeth.

In 4- and 13-week repeated dose oral toxicity studies of FTD-TPI in monkeys of which incisors have roots [see "3.(iii).A.(2).9) 4-week repeated dose oral toxicity study in monkeys" and "3.(iii).A.(2).10) 13-week repeated dose oral toxicity study in monkeys"], no histopathological changes were observed in the incisors. These findings indicate that the histopathological change in rat incisors are specific to rootless teeth, and that FTD-TPI does not affect human adult teeth. The applicant explained that no particular cautions concerning the effect on adult teeth are necessary.

PMDA accepted the applicant's explanation.

3.(iii).B.(2) Effects on the ovary

In the 4-week repeated dose oral toxicity study of FTD-TPI in rats, increases in ovary weight and small luteal cells were observed [see "3.(iii).A.(2).2) 4-week repeated dose oral toxicity study in rats"]. Increased ovary weight was also observed in the 4-week repeated dose oral toxicity study of FTD in rats

[see "3.(iii).A.(2).5) 4-week repeated dose oral toxicity study of FTD in rats"], and increases in the numbers of corpora lutea and implantations were observed in the study of the effect of FTD-TPI on female fertility and early embryonic development to implantation in female rats [see "3.(iii).A.(5).1). Fertility and early embryonic development to implantation"]. PMDA requested the applicant to explain the mechanisms of development of these findings and whether they are relevant to humans. The applicant explained as follows.

There is a possibility that the increased numbers of corpora lutea and implantations in the study on female fertility and early embryonic development to implantation were attributed to some effect of FTD-TPI on the ovary that increased the number of ovulations, but the detailed mechanism of action is unclear.

Considering the fact that these findings were observed in rats receiving FTD-DTP at 150 mg/kg/day or higher doses, and the exposure to FTD in rats at 150 mg/kg/day is similar to or lower than clinical exposure, a relevance to humans cannot be ruled out. The applicant will provide a precaution on the possible effect of FTD-DTP on gonad glands in patients in reproductive age.

PMDA accepted the applicant's explanation. PMDA considers that the applicant should continuously collect information on the mechanism of how FTD-DTP affects the ovary and the relevance of these findings to humans, and should provide information to healthcare providers in clinical settings when new evidence becomes available.

4. Clinical data

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

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

The applicant developed three different formulations of rapid-release film-coated tablets containing trifluridine (FTD) and tipiracil hydrochloride (TPI) at a molar ratio of 2:1 as follows: formulation A and B tablets used in clinical studies; and the commercial formulation tablet. Formulation A tablets was used in foreign phase I clinical studies (Studies TAS102-9801, TAS102-9802, TAS102-9803, TAS102-9804, and TAS102-9805) and a foreign phase II clinical study (Study TAS102-9806), and formulation B tablets was used in Japanese phase I studies (Studies TAS102-J001, TAS102-J002, and TAS102-J004) and the Japanese phase II study (Study TAS102-J003). Dissolution tests have demonstrated the bioequivalence between (1) formulation B 15 mg tablets and formulation B 20 mg tablets; (2) the commercial formulation 15 mg tablets and the commercial formulation 20 mg tablets; (3) formulation B 15 mg tablets and the commercial formulation 15 mg tablets; and (4) formulation B 20 mg tablets and the commercial formulation 20 mg tablets.

4.(i).A.(1) Assays

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to quantify FTD, FTY (a metabolite of FTD), 5-carboxyuracil (5-CU) (a metabolite of FTD), TPI, 6-HMU (a metabolite of TPI), and thymidine in human plasma samples. The lower limit of quantification was 5 ng/mL for FTD, 5 ng/mL for FTY, 1 ng/mL for 5-CU, 50 ng/mL for TPI, 0.2 ng/mL for 6-HMU, and 0.4 ng/mL for

thymidine.

LC-MS/MS was used to quantify FTD, FTY, TPI, and 6-HUM in human urine samples. The lower limit of quantification was 200 ng/mL for FTD, 200 ng/mL for FTY, 200 ng/mL for TPI, and 50 ng/mL for 6-HMU.

4.(i).A.(2) Effects of food on PK of FTD-TPI

Japanese phase I study (5.3.1.1.1: Study TAS102-J004, PK evaluation period, [redacted] to [redacted], multiple administration period, ongoing)

A crossover study was conducted to investigate the effects of food on PK of FTD, FTY, 5-CU, and TPI in 16 patients with advanced solid tumor except those with gastric cancer or those after gastrectomy. (Evaluation was conducted in 14 patients excluding 2 patients who deviated from the protocol in food intake.) Patients were to receive, in a crossover manner, the following two treatments: For one treatment, single oral doses of FTD-TPI at a dose of 35 mg/m^2 were administered to patients under fasted conditions and the patients were kept fasted for 10 hours before and 4 hours after the dose; and for the other treatment, the same dose of FTD-TPI was administered to patients under postprandial conditions after consuming food containing 110 kcal of protein, 180 kcal of carbohydrates, and 360-430 kcal of fat (the table below).

The ratios of geometric means of C_{max}, AUC_{0-t}, AUC_{0-12}, and AUC_{inf} of FTD in the postprandial state to those in the fasted state were 0.6074 [90% confidence interval (CI), 0.5037-0.7323], 0.9561 [0.8566-1.0671], 0.9560 [0.8566-1.6070], and 0.9559 [0.8556-1.0680], respectively; and the corresponding figures for TPI were 0.5578 [0.4732-0.6576], 0.5526 [0.4802-0.6358], 0.5526 [0.4802-0.6358], and 0.5581 [0.4872-0.6392], respectively. The AUC values of FTD were not affected by food, while the C_{max} of FTD and the C_{max} and AUC values of TPI decreased after a meal. Wilcoxon's signed rank test revealed no significant differences in t_{max} values of FTD and TPI between the fasted and postprandial states. On the basis of the above findings, the applicant explained that food consumption decreases the absorption rate of FTD and the bioavailability of TPI.

The C_{max} of FTY, a metabolite of FTD, was 860 ± 207 ng/mL (mean ± standard deviation) in the fasted state and 728 ± 186 ng/mL in postprandial state, and the AUC_{inf} of FTY was 2972 ± 868 ng·h/mL in the fasted state and 3121 ± 941 ng·h/mL in postprandial state. The C_{max} of 5-CU, another metabolite of FTD, was 2.93 ± 1.69 ng/mL in the fasted state and 2.32 ± 0.57 ng/mL in the postprandial state, and the AUC_{inf} was 32 ± 8 ng·h/mL in the fasted state and 29 ± 10 ng·h/mL in the postprandial state. The C_{max} of FTY in the postprandial state tended to be lower than that in the fasted state, but the AUC_{inf} of FTY and the C_{max} and AUC_{inf} of 5-CU did not differ between the fasted and postprandial states.

An analysis of metabolites of FTD in plasma revealed trace amounts of 5-CU and 5-carboxy-2'-deoxyuridene (5-CdUrd) other than FTY.

PK parameters of FTD and TPI in the fasted and postprandial states

Substance		C_{max} (ng/mL)	t_{max} (h)	AUC(ng·h/mL)			$t_{1/2}$ (h)	CL/F* (L/h/kg)	Vd (L/kg)
				AUC_{0-t}	AUC_{0-12}	AUC_{inf}			
FTD	Fasted	5630 ± 1840	0.88 ±0.42	10,647 ±5012	10,648 ±5011	10,943 ±5581	2.13 ±0.76	0.106 ±0.056	0.310 ±0.181
	Postprandial	3510 ±1380	1.32 ±0.93	9840 ±4247	9840 ±4247	10,082 ±4593	1.72 ±0.58	0.115 ±0.060	0.260 ±0.102
TPI	Fasted	135 ±39	2.07 ±0.92	647 ±281	647 ±281	677 ±309	2.19 ±0.66	0.775 ±0.320	2.42 ±1.25
	Postprandial	76.8 ±26.3	2.79 ±1.37	361 ±160	361 ±160	384 ±189	2.22 ±0.45	1.34 ±0.45	4.10 ±1.24

Arithmetic mean ± standard deviation; n = 14; *, Oral clearance

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

4.(i).B.(1) Effects of food

The applicant explained that postprandial administration was adopted as the dosage regimen for FTD-TPI, although food consumption decreased the C_{max} of FTD and the C_{max} and AUC of TPI while it did not affect the AUC of FTD [see "4.(i).A.(2) Effects of food on PK of FTD-TPI"], for the following reasons:

Since food consumption did not affect the AUC of FTD, it is unlikely to affect the efficacy and safety of FTD-TPI, although it decreased the C_{max} of FTD and the C_{max} and AUC of TPI. However, there was a significant correlation observed between the C_{max} of FTD and decreased neutrophil count in the Japanese phase I study (Study TAS102-J001) [see "4.(ii).A.(3).2) Relationship between exposure and safety"]. It is thus preferable that FTD-TPI is given after a meal to ensure the safety of treatment since the C_{max} of FTD in the postprandial state is lower than that in the fasted state. Based on the above, postprandial administration of FTD-TPI was decided.

PMDA considers as follows:

The applicant should have considered the effect of food on the efficacy of FTD-TPI in addition to the safety, as there is a possibility that the exposure to FTD relates to the efficacy of treatment [see "4.(i).A.(3).1) Relationship between exposure and efficacy"]. However, it is acceptable to select the postprandial administration of FTD-TPI as the dosage regimen because the clinical usefulness of FTD-TPI was indicated in a Japanese phase II study (Study TAS102-J003) where FTD-TPI was given after a meal [see "4.(iii).B.(1) Efficacy" and "4.(iii).B.(2) Safety"]. Since the administration of FTD-TPI in the fasted state may increase the C_{max} of FTD and induce bone marrow suppression, the applicant should provide information on this matter appropriately in the package insert.

4.(i).B.(2) The effects of gastrointestinal pH level on PK of FTD-TPI

PMDA requested the applicant to explain the effects of gastric pH level on the PK of FTD-TPI.

The applicant responded as follows:

Considering the fact that (1) in the dissolution testing of FTD-TPI using the paddle method at 50 rpm, almost 100% of FTD and TPI contained in the product are dissolved within 15 minutes in solutions with a pH level between 1.2 and 6.8, and (2) the solubilities of FTD and TPI drug substances are high and do not depend on pH level, it is unlikely that a change in gastric pH level within the physiological pH range (pH 1.2-6.8) affects the dissolution of FTD and TPI in FTD-TPI. Accordingly, a change in gastric pH level will not affect the PK of FTD-TPI.

PMDA accepted the applicant's explanation.

4.(ii) Summary of clinical pharmacology studies

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

The PK of FTD-TPI in patients with cancer was evaluated following FTD-TPI monotherapy.

4.(ii).A.(1) Patients with cancer

4.(ii).A.(1).1) Foreign phase I study (5.3.3.2.2: Study TAS102-9801, from [redacted] to [redacted]

In an open-label study to evaluate PK profiles of FTD, FTY, and TPI, 14 patients with advanced solid tumor received FTD-TPI orally at a dose of 50 to 100 mg/m^2 QD before breakfast in 21-day cycles, each consisting of a 14-day treatment period followed by a 7-day rest period. A total of 12 patients were included in the PK analysis.

In 6 patients receiving FTD-TPI at a dose of 50 mg/m^2 QD, which was selected as the recommended dose, the C_{max} values of FTD on Days 1 and 14 were 9068 and 8938 ng/mL, respectively, and the AUC_{0-24} values were 15,938 and 30,248 ng·h/mL, respectively.

4.(ii).A.(1).2) Foreign phase I study (5.3.3.2.3: Study TAS102-9802, from [redacted] to [redacted]

In an open-label study to evaluate PK profiles of FTD, FTY, and TPI, 24 patients with advanced solid tumor received FTD-TPI orally at a dose of 50 to 110 mg/m^2 QD before breakfast in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period. A total of 21 patients were included in the PK analysis.

In 5 patients receiving FTD-TPI at 100 mg/m^2, which was selected as the recommended dose, the C_{max} values of FTD on Days 1 and 12 were 12,174 and 15,413 ng/mL, respectively, and AUC_{0-24} values on Days 1 and 12 were 40,726 and 83,240 ng·h/mL, respectively.

4.(ii).A.(1).3) Foreign phase I study (5.3.3.2.4 : Study TAS102-9803, from [redacted] to [redacted]

In an open-label study to evaluate PK profiles of FTD, FTY, and TPI, 39 patients with advanced solid tumor received FTD-TPI orally at a dose of 100 to 180 mg/m^2 QD before breakfast in 21-day cycles, each consisting of a 5-day treatment period followed by a 16-day rest period. A total of 27 patients were included in the PK analysis.

In 4 patients receiving FTD-TPI at 160 mg/m^2, which was selected as the recommended dose, the C_{max} values of FTD on Days 1 and 5 were 19,250 and 23,400 ng/mL, respectively, and the AUC_{0-24} values on Days 1 and 5 were and 69,584 and 143,505 ng·h/mL, respectively.

4.(ii).A.(1).4) Foreign phase I study (5.3.3.2.5 : Study TAS102-9804, from [redacted] to [redacted]

In an open-label study to evaluate PK profiles of FTD, FTY, and TPI, 19 patients with advanced solid tumor received FTD-TPI orally at a dose of 25 to 40 mg/m^2/dose BID after breakfast and supper in 28-

day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period. A total of 12 patients were included in the PK analysis (the table below).

As the dose of FTD-TPI increased, the C_{max} and AUC_{0-12} values of FTD, FTY, and TPI increased. A comparison of AUC_{0-12} values on Days 1 and 12 revealed that multiple administration of FTD-TPI caused an accumulation of FTD but did not cause accumulation of FTY or TPI.

PK parameters of FTD, FTY, and TPI after single and multiple administration

Dose (mg/m^2/dose)		Day of measurement	n	C_{max} (ng/mL)	t_{max} (h)	AUC(ng·h/mL)			$t_{1/2}$ (h)	CL/F (L/h/kg)	Vd/F*1 (L/kg)
						AUC_{0-t}	AUC_{0-12}	AUC_{inf}			
FTD	25	Day 1	7	2321 ± 1067	1.21 ± 0.57	4442 ± 1127	4659 ± 1161	4660 ± 1165	1.10 ± 0.27	0.132 ± 0.031	0.202 ± 0.029
		Day 12	7	4673 ± 1368	1.02 ± 0.50	14,660 ± 3924	14,761 ± 3892	-	1.62 ± 0.49	0.041 ± 0.008	0.093 ± 0.021
	30*2	Day 1	2	3520	1.25	5985	6004	6022	1.49	0.108	0.223
		Day 12	2	4605	1.50	20,066	21,391	-	2.02	0.030	0.086
	30*3	Day 1	1	6160	0.500	7720	7759	7754	1.21	0.102	0.179
		Day 12	1	3670	2.00	19,954	19,954	-	1.37	0.040	0.079
	30*4	Day 1	3	4400 ± 2090	1.00 ± 0.87	6563 ± 1330	6589 ± 1327	6599 ± 1337	1.40 ± 0.57	0.106 ± 0.012	0.208 ± 0.065
		Day 12	3	4293 ± 880	1.67 ± 0.58	20,029 ± 530	20,912 ± 2028	-	1.80 ± 0.81	0.033 ± 0.006	0.084 ± 0.027
	40	Day 1	2	7855	0.775	11,853	11,885	11,914	1.34	0.096	0.182
		Day 12	2	6830	0.742	23,882	24,850	-	2.09	0.042	0.127
FTY	25	Day 1	7	691 ± 225	1.43 ± 0.53	2161 ± 406	2264 ± 418	2263 ± 420	1.20 ± 0.17	-	-
		Day 12	7	495 ± 52	1.45 ± 0.55	2829 ± 512	2820 ± 562	-	3.25 ± 0.86	1.22 ± 0.29	-
	30*2	Day 1	2	908	1.25	2757	2822	2817	1.22	-	-
		Day 12	2	585	1.50	3683	4284	-	6.40	1.54	-
	30*3	Day 1	1	1120	1.00	3369	3407	3398	1.06	—	-
		Day 12	1	411	2.00	3035	3035	-	3.24	0.90	-
	30*4	Day 1	3	978 ± 237	1.17 ± 0.76	2961 ±551	3017 ± 554	3011 ± 560	1.17 ± 0.25	-	-
		Day 12	3	527 ± 110	1.67 ± 0.58	3467 ± 447	3867 ± 804	-	5.34 ± 3.52	1.32 ± 0.39	-
	40	Day 1	2	1088	1.03	3124	3154	3181	1.41	-	-
		Day 12	2	454	0.992	2593	2975	-	6.40	0.98	-
TPI	25	Day 1	7	71.8 ± 39.4	2.72 ± 1.25	272 ± 156	273 ± 170	277 ± 174	1.57 ± 0.33	1.35 ± 0.77	2.83 ± 1.35
		Day 12	7	69.1 ± 31.4	2.02 ± 0.99	254 ± 118	266 ± 134	-	3.30 ± 0.98	1.22 ± 0.47	5.81 ± 2.58
	30*2	Day 1	2	86.4	2.00	317	317	324	1.92	1.01	2.74
		Day 12	2	60.0	2.00	271	285	-	2.61	1.06	3.95
	30*3	Day 1	1	77.2	1.00	279	279	284	1.86	1.31	3.53
		Day 12	1	42.0	2.00	202	202	—	2.68	1.84	7.13
	30*4	Day 1	3	83.3 ± 22.3	1.67 ± 0.58	304 ± 98	304 ± 98	310 ± 102	1.90 ± 0.18	1.11 ± 0.32	3.00 ± 0.68
		Day 12	3	54.0 ± 14.2	2.00 ± 0	248 ± 44	258 ± 48	-	2.63 ± 0.27	1.32 ± 0.46	5.01 ± 1.84
	40	Day 1	2	109	1.54	307	310	314	2.00	1.76	4.64
		Day 12	2	77.1	1.48	344	348	-	1.63	1.35	3.10

Arithmetic mean ± standard deviation; *1, Apparent volume of distribution; *2, Patients who received FTD-TPI before protocol amendment; *3, Patients who received FTD-TPI after protocol amendment except patients with impaired bone marrow reserve judged by investigators; *4, Patients combining those of *2 and *3

4.(ii).A.(1).5) Foreign phase I study (5.3.3.2.6: Study TAS102-9805, from [redacted] to [redacted]

In an open-label study to evaluate PK profiles of FTD, FTY, and TPI, 15 patients with advanced solid tumor received FTD-TPI orally at a dose of 60 to 80 mg/m^2/day 3 times a day (TID) after breakfast,

lunch, and supper in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period. A total of 2 patients were included in the PK analysis.

In 1 patient in the group of 70 mg/m^2/day which was selected as the recommended dose, the C_{max} of FTD after breakfast was 2140 ng/mL on Day 1, and 5460 ng/mL on Day 12. The applicant explained that no conclusion was reached in terms of PK of FTD-TPI because the number of patients was small.

4.(ii).A.(1).6) Japanese phase I study (5.3.3.2.1：Study TAS102-J001, from [redacted] to [redacted]

In an open-label study, 21 patients with advanced solid tumor received FTD-TPI orally at a dose of 15 to 35 mg/m^2/dose BID after breakfast and supper in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period. As a result, PK profiles of FTD, FTY, TPI, and thymidine were determined (the table below).

The C_{max}, $AUC_{0\text{-}10}$, and AUC_{inf} values of FTD and TPI after single administration of FTD-TPI tended to increase as the dose level of FTD-TPI increased. A regression analysis using the power model did not confirm linearity of these PK parameters of FTD, but significant nonlinearity was not found. On the other hand, linearity was observed for TPI in this analysis. PK parameters at Day 12 compared with those at Day 1 revealed that C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}10}$, and $t_{1/2}$ of FTD tended to be higher, and CL/F and Vd/F of FTD lower while C_{max} of FTY tended to be lower, and $t_{1/2}$ of FTY higher. However, no effects of multiple administration were observed for TPI. The urinary excretion rates (Ae) of FTD, FTY, and TPI up to 10 hours after administration of FTD-TPI at Day 1 were generally constant regardless of the dose. FTD was mainly excreted as FTY in urine. About 20% of TPI administered was excreted in urine.

An analysis of metabolites of TPI in the plasma and urine revealed trace amounts of 6-HMU, which indicates that TPI administered to humans is hardly metabolized before excretion into urine. The applicant also described that the renal clearance of TPI on Day 1 of treatment with FTD-TPI at a dose of 35 mg/m^2 BID was 0.331 L/h/kg and the protein binding rate of TPI was ≤8%, and thus the renal clearance of free TPI is considered to be higher than the glomerular filtration rate when this rate is assumed to be 0.125 L/h/kg according to a published article (*Pharm Res*. 1993;10:1093-5). These findings suggest that tubular secretion in addition to glomerular filtration plays an important role in the urinary excretion of TPI.

Mean plasma thymidine concentration was approximately 2 ng/mL before treatment and reached to the C_{max}, 8.2 to 32 ng/mL, at 4.3 to 8.0 hours after a single administration of FTD-TPI. The C_{max} of thymidine on Day 12 ranged between 68 and 128 ng/mL. The applicant explained that the increased plasma thymidine concentration after the administration of FTD-TPI was caused by the inhibition of TPase by TPI.

PK parameters of FTD, FTY, and TPI after single and multiple administration

Dose (mg/m^2/dose)		Day of measurement	n	Cmax (ng/mL)	tmax (h)	AUC(ng·h/mL)			t1/2 (h)	CL/F (L/h/kg)	Vd/F (L/kg)	Ae (%)
						AUC_{0-t}	AUC_{0-10}	$AUC_{0-\infty}$				
FTD	15	Day 1	6	1009 ± 491	1.7 ± 1.3	2032 ± 777	2037 ± 773	2163 ± 836	1.39 ± 0.38[*1]	0.164 ± 0.036	0.324 ± 0.095	3.59 ± 3.82
		Day 12	6	1205 ± 421	1.6 ± 0.7	5478 ± 2849	5478 ± 2849	—	2.44 ± 1.57	0.067 ± 0.020	0.205 ± 0.078	—
	20	Day 1	3	1840 ± 737	1.2 ± 0.8	4343 ± 538	4347 ± 535	4373 ± 568	1.17 ± 0.15	0.124 ± 0.035	0.204 ± 0.030	4.85 ± 5.61
		Day 12	3	2747 ± 610	1.7 ± 0.6	9994 ± 2109	9994 ± 2109	—	1.52 ± 0.34	0.057 ± 0.025	0.121 ± 0.046	—
	25	Day 1	3	2450 ± 1,021	1.5 ± 0.9	4278 ± 1384	4281 ± 1380	4297 ± 1387	1.49 ± 0.59	0.178 ± 0.055	0.384 ± 0.175	7.64 ± 4.49
		Day 12	3	2757 ± 1173	1.3 ± 0.6	9876 ± 3740	8656[*2]	—	1.96 ± 0.10	0.096[*2]	0.266[*2]	—
	30	Day 1	3	3677 ± 1459	1.2 ± 0.8	8229 ± 1441	8229 ± 1441	8435 ± 1645	1.88 ± 0.73	0.103 ± 0.014	0.273 ± 0.089	0.96[*2]
		Day 12	3	5437 ± 1685	1.3 ± 0.6	23,672 ± 7844	23,672 ± 7844	—	2.33 ± 1.26	0.038 ± 0.010	0.120 ± 0.043	—
	35	Day 1	6	3338 ± 767	1.3 ± 0.5	8555 ± 1626	8678 ± 1786[*1]	8672 ± 1710	1.41 ± 0.38	0.118 ± 0.018	0.234 ± 0.054	3.69 ± 3.42[*1]
		Day 12	6	4752 ± 1697	1.9 ± 1.6	20,950 ± 2237	20,950 ± 2237	—	1.97 ± 0.51	0.047 ± 0.003	0.136 ± 0.038	—
FTY	15	Day 1	6	248 ± 83	2.1 ± 1.6	990 ± 394	993 ± 392	1016 ± 407	1.34 ± 0.30	—	—	21.2 ± 9.6
		Day 12	6	198 ± 49	2.3 ± 0.8	1301 ± 524	1301 ± 524	—	4.57 ± 2.74	—	—	—
	20	Day 1	3	453 ± 91	1.7 ± 0.6	1735 ± 172	1740 ± 172	1776 ± 216	1.32 ± 0.40	—	—	25.3 ± 3.4
		Day 12	3	398 ± 4	2.0 ± 0.0	2259 ± 411	2259 ± 411	—	4.55 ± 2.90	—	—	—
	25	Day 1	3	645 ± 23	1.5 ± 0.9	1899 ± 319	1901 ± 316	1915 ± 327	1.18 ± 0.18	—	—	25.3 ± 4.2
		Day 12	3	470 ± 174	1.7 ± 0.6	2248 ± 492	2401[*2]	—	4.79 ± 2.50	—	—	—
	30	Day 1	3	753 ± 293	1.5 ± 0.9	2653 ± 537	2653 ± 537	2710 ± 559	1.62 ± 0.32	—	—	11.9[*2]
		Day 12	3	512 ± 41	1.2 ± 0.8	3095 ± 538	3095 ± 538	—	9.60 ± 5.31	—	—	—
	35	Day 1	6	878 ± 228	2.0 ± 0.0	3376 ± 599	3165 ± 341[*1]	3492 ± 693	1.57 ± 0.38	—	—	27.2 ± 7.0[*1]
		Day 12	6	560 ± 92	2.3 ± 1.4	3622 ± 1094	3622 ± 1094	—	7.27 ± 2.95	—	—	—
TPI	15	Day 1	6	25.8 ± 14.7	2.6 ± 1.6	117 ± 84	117 ± 84	129 ± 96	2.27 ± 0.74	1.52 ± 0.67	4.90 ± 2.37	19.4 ± 12.2
		Day 12	6	44.1 ± 51.8	2.8 ± 1.5	234 ± 283	234 ± 283	—	2.89 ± 0.83	1.26 ± 0.73	4.70 ± 2.21	—
	20	Day 1	3	43.1 ± 6.5	1.7 ± 0.6	166 ± 29	166 ± 29	170 ± 29	1.53 ± 0.17	1.52 ± 0.50	3.30 ± 0.93	22.9 ± 5.1
		Day 12	3	41.8 ± 14.7	2.7 ± 1.2	161 ± 41	161 ± 41	—	1.82 ± 0.18	1.69 ± 0.82	4.53 ± 2.57	—
	25	Day 1	3	54.2 ± 28.5	1.7 ± 0.6	214 ± 79	214 ± 79	222 ± 79	1.78 ± 0.27	1.66 ± 0.56	4.31 ± 1.85	20.0 ± 9.6
		Day 12	3	50.2 ± 13.1	2.7 ± 1.2	309 ± 28	300[*2]	—	4.01 ± 3.57	1.13[*2]	7.91[*2]	—
	30	Day 1	3	136 ± 77	2.7 ± 1.2	521 ± 338	521 ± 338	542 ± 360	1.66 ± 0.37	0.91 ± 0.40	2.06 ± 0.62	20.0[*2]
		Day 12	3	99.6 ± 43.8	2.7 ± 1.2	447 ± 278	447 ± 278	—	2.21 ± 0.62	1.10 ± 0.51	3.55 ± 2.31	—
	35	Day 1	6	76.6 ± 32.1	2.3 ± 0.8	289 ± 91	281 ± 99[*1]	302 ± 96	1.67 ± 0.22	1.83 ± 1.06	4.42 ± 2.68	19.0 ± 7.5[*1]
		Day 12	6	70.0 ± 43.4	2.3 ± 0.8	317 ± 182	317 ± 182	—	2.37 ± 0.93	1.89 ± 0.94	7.16 ± 6.73	—

Arithmetic mean ± standard deviation; *1, n = 5; *2, n = 2

4.(ii).A.(2) PK parameters of FTD-TPI in Japanese and non-Japanese patients

Taking into account the points below, there is no clear difference in the PK profiles of FTD-TPI between Japanese and non-Japanese patients. The applicant also stated that although different formulations of FTD-TPI were used in the clinical studies in and outside Japan [see "4.(i).A. Summary of the submitted data"], the results of the studies may be used to investigate possible ethnic differences in the PK profiles of FTD-TPI when considering the compositions and dissolution profiles of the formulations used in and outside Japan, as well as the results of studies of permeability of FTD and TPI through biological membranes.

- Studies TAS102-J001 and TAS102-9804 showed no differences in the PK profiles of FTD and TPI between Japanese and non-Japanese patients in terms of the following points:
  - Mean C_{max}, t_{max}, and AUC* values following single dose (Day 1) or multiple doses (Day 12) of FTD-TPI at 25 or 30 mg/m^2/dose BID
  - The distributions of C_{max} and AUC* following single dose (Day 1) or multiple doses (Day 12) of FTD-TPI
- The table below shows the Ae of FTD, FTY, and TPI on Day 1 in Studies TAS102-J001, TAS102-9801, and TAS102-9802. Although the duration of urine collection differed between these studies, i.e, 10 hours after administration in Study TAS102-J001 and 24 hours after administration in Study TAS102-9802, no clear differences in Ae were seen between Japanese and American patients.

  *: AUC_{inf} was used as the data on Day 1, while AUC_{0-10} in Study TAS102-J001 and AUC_{0-12} in Study TAS102-9804 were used as the data on Day 12.

Ae of FTD, FTY, and TPI after single dose of FTD-TPI

Country	Study	Dose (mg/m^2/dose)	n	FTD (%)	FTY (%)	TPI (%)
Japan	TAS102-J001	15	6	3.59±3.82	21.2±9.6	19.4±12.2
		20	3	4.85±5.61	25.3±3.4	22.9±5.1
		25	3	7.64±4.49	25.3±4.2	20.0±9.6
		30	2	0.963	11.9	20.0
		35	5	3.69±3.42	27.2±7.0	19.0±7.5
US	TAS102-9801	25	6	5.72±4.64	17.7±5.3	19.2±11.4
		30	4	5.24±6.92	33.4±29.9	50.4±30.3
		50	1	1.00	8.17	2.30
	TAS102-9802	25	2	2.18	24.2	32.6
		35	6	2.23±1.40	30.6±10.7	21.0±8.4
		40	2	3.01	25.2	29.5
		45	3	3.46±3.29	18.5±7.6	31.4±13.8
		50	4	6.90±5.60	19.3±10.5	16.3±7.3
		55	2	2.80	14.6	24.0

Arithmetic mean ± standard deviation

4.(ii).A.(3) Relationships between exposure to FTD-TPI and efficacy and safety of treatment

4.(ii).A.(3).1) Relationship between exposure and efficacy

The results of Study TAS102-J001, a Japanese phase I study, in patients with advanced solid tumor were used to assess the relationship between exposure to FTD, FTY, and TPI and the efficacy of FTD-TPI.

Patients were stratified by levels of C_{max} and AUC_{0-10} of FTD, FTY, and TPI on Day 12 into 2 subgroups,

namely patients with median or higher exposure (high exposure subgroup) and patients with lower-than-median exposure (low exposure subgroup). As a result, a subgroup analysis by C_{max} and AUC_{0-10} of FTD and FTY revealed that patients in the high exposure subgroup tended to show longer progression-free survival (PFS) and overall survival (OS) as compared with those in the low exposure subgroup. However, a subgroup analysis by C_{max} and AUC_{0-10} of TPI revealed that there were no significant differences in PFS or OS between patients in the high and low exposure subgroups.

The applicant explained that, based on the relationship between exposure (C_{max}, AUC_{0-10}) to FTD, FTY, and TPI and efficacy parameters (PFS, OS), the findings above suggest a possible relationship between exposure to FTD and clinical efficacy of FTD-TPI, although the number of patients in Study TAS102-J001 was limited.

4.(ii).A.(3).2) Relationship between exposure and safety

The results of Study TAS102-J001, a Japanese phase I study, were used to assess the relationship of exposure to FTD, FTY, and TPI with the safety of FTD-TPI.

A linear regression analysis and Spearman's rank correlation were used to examine relationships between PK parameters (C_{max}, AUC_{0-10}) of FTD, FTY, and TPI on Day 12 and reductions in hematological parameters (white blood cells, neutrophil, platelet counts, hemoglobin), which were defined as the maximum percentage reduction of each parameter during the course of treatment relative to baseline value. Significant correlations were observed between decreases in white blood cell and neutrophil counts and the C_{max} and AUC_{0-10} values of FTD, FTY, and TPI.

The applicant explained that these findings suggest a possible relationship between exposure to FTD, FTY, and TPI and the occurrence of bone marrow suppression as an adverse reaction of FTD-TPI.

4.(ii).A.(4) Effects of renal function on PK of FTD-TPI

No clinical studies have been conducted to investigate the PK of FTD-TPI in patients with renal impairment. The applicant explained that a precaution on the use of FTD-TPI for patients with renal impairment will be provided in the package insert because the drug should be carefully administered to such patients for the following reasons:

- As TPI appears to be hardly metabolized before excretion in urine in humans [see "4.(ii).A.(1).6) Japanese phase I study"], renal impairment may increase exposure to TPI and inhibit the metabolism of FTD to affect the PK of FTD.
- A total of 119 patients (combined FTD-TPI group) to whom treatment with FTD-TPI in accordance with the dosage and administration proposed in the application was given in Study TAS102-J003, a Japanese phase II study (113 patients), and in Study TAS102-J001, a Japanese phase I study (6 patients), were stratified by creatinine clearance (CrCL) calculated using the Cockcroft-Gault equation.* As a result, the incidence of adverse drug reactions related to bone marrow suppression (e.g., platelet count decreased and red blood cell count decreased, Grade 3 or higher haemoglobin decreased, Grade 4 neutrophil count decreased) tended to be higher in patients with mild to

moderate renal function as compared with patients with normal renal function (the table below). In addition, FTD-TPI was not administered to patients with severe renal impairment or those with end-stage renal disease.

*: Normal renal function was defined as a CrCL of ≥90 mL/min; mild renal impairment as 60 to 89 mL/min; moderate renal impairment as 30 to 59 mL/min; severe renal impairment as 15 to 29 mL/min; and end-stage renal disease as <15 mL/min.

Incidence of adverse drug reactions related to bone marrow suppression by renal function

Renal function	n (%)			
	Platelet count decreased (Grade 4 or lower)	Red blood cell count decreased (Grade 4 or lower)	Haemoglobin decreased (Grade 3 or 4)	Neutrophil count decreased (Grade 4)
Normal	17/49 (34.7)	8/49 (16.3)	3/49 (6.1)	7/49 (14.3)
Mild impairment	24/50 (48.0)	24/50 (48.0)	14/50 (28.0)	12/50 (24.0)
Moderate impairment	8/20 (40.0)	6/20 (30.0)	5/20 (25.0)	4/20 (20.0)

A foreign phase I clinical study in patients with renal impairment will be conducted from the [redacted] quarter in [redacted] to investigate the PK profile of FTD-TPI in this patient population.

4.(ii).A.(5) Effects of hepatic function on the PK of FTD-TPI

No clinical studies have been conducted to investigate the PK of FTD-TPI in patients with hepatic impairment.

The applicant explained that, taking into account the points below, the Precautions for Dosage and Administration section of the package insert will include the criteria used for the treatment in clinical studies of FTD-TPI, and that physicians and healthcare providers will be provided a caution that treatment should be given to the patients who meet the criteria. The applicant explained that no additional precautions on the use for patients with hepatic impairment are necessary.

- As findings suggest that FTD is eliminated mainly through metabolism and that TPase in the liver plays a major role in the metabolism of FTD [see "3.(ii).A.(3).1) *In vitro* metabolism"], hepatic impairment may affect the PK of FTD.
- The above-mentioned 119 patients (combined FTD-TPI group) were stratified by hepatic function (i.e. normal hepatic function, mild, moderate, severe hepatic impairment) using the NCI classification of hepatic impairment.* As a result, there was no substantial difference in the incidence of adverse drug reactions between patients with normal hepatic function (96.3%, 77 of 80 patients) and those with mild hepatic impairment (97.4%, 38 of 39 patients). FTD-TPI has not been administered to patients with moderate or severe hepatic impairment.

*: Patients were stratified according to the following criteria

Hepatic function	Normal	Mild impairment	Moderate impairment	Severe impairment
Total bilirubin	≤ ULN	Mild 1:≤ ULN Mild 2: >1.0-1.5 × ULN	>1.5-3.0 × ULN	>3.0 × ULN
AST and ALT	≤ ULN	Mild 1: > ULN Mild 2: N/A	N/A	N/A

ULN, upper limit of normal

A foreign phase I clinical study in patients with hepatic impairment will be conducted from the [redacted]

quarter in [redacted] to investigate the PK profile of FTD-TPI in this patient population.

4.(ii).A.(6) Mass balance of FTD-TPI

In Study TAS102-J001, a Japanese phase I study, Ae of FTD, FTY, and TPI up to 10 hours after administration on Day 1 were constant regardless the dose level. FTD was metabolized mainly into FTY and excreted in urine. TPI was excreted in urine almost entirely as unchanged substance [see "4.(ii).A.(1).6) Japanese phase I study"].

The applicant described currently available data on the mass balance of FTD, TPI, and their metabolites in humans as follows:

In a study on the mass balance of FTD after a single intravenous administration of ^{14}C-FTD, the sum of 48-hour cumulative urinary excretion rates of FTD, FTY, and 5-CU was 99% (10, 76, and 13%, respectively), and ≤1% of the administered radioactivity was excreted in the expired air (*Cancer Res*. 1972;32:247-53). No reports have been published on the mass balance of TPI administered alone.

In Study TAS102-9801, a foreign phase I study, the Ae of FTD, FTY, and TPI up to 24 hours after the first oral dose of FTD-TPI at 50 to 180 mg/m^2/day ranged from about 1.00% to 5.72%, 6.46% to 33.4%, and 2.46% to 50.4%, respectively. The results of Studies TAS102-9802 and TAS102-9803 were consistent with those of Study TAS102-9801.

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

4.(ii).B.(1) Effects of FTD-TPI on QT/QTc intervals

No clinical data on the relationship between exposure to FTD-TPI and QT/QTc intervals were included in the application. PMDA requested the applicant to explain the effects of FTD-TPI on QT/QTc intervals.

The applicant responded as follows:

Based on the findings below, it is unlikely that FTD-TPI affects QT/QTc intervals. A foreign phase I study (Study TPU-TAS-102-103) is underway to investigate whether FTD-TPI is cardiotoxic or not, and the results are expected to be available in [redacted].

- An analysis of ECG findings and adverse events related to prolonged QT intervals observed in completed or ongoing clinical studies revealed no tendency toward increased risk of prolonged QT/QTc intervals in association with FTD-TPI therapy [see "4.(iii).B.(2).5) Cardiac disorders"].
- In non-clinical safety pharmacology studies, FTD-TPI did not affect the cardiovascular system [see "3.(i).A.(3).2) Effects on the cardiovascular system"].

PMDA considers as follows:

Although no firm conclusion can be made on whether FTD-TPI affects QT/QTc intervals with the limited clinical data available to date, PMDA can accept the applicant's explanation that no tendency toward clearly prolonged QT/QTc intervals was observed in association with FTD-TPI treatment during clinical studies. However, the applicant will have to provide information on this matter promptly when

the results of the ongoing foreign phase I clinical study TPU-TAS-102-103 are obtained, and take appropriate measures whenever necessary.

4.(ii).B.(2) Administration of FTD-TPI to patients with hepatic impairment

The applicant explained that there is currently no need to provide precautions on the use of FTD-TPI in patients with hepatic impairment [see "4.(ii).A.(5) Effects of hepatic function on the PK of FTD-TPI"].

PMDA considers as follows:

Considering the fact that (1) the applicant explained that hepatic impairment may affect the PK of FTD, and (2) FTD-TPI has not been administered to patients with moderate or severe hepatic impairment, FTD-TPI should be administered with caution to this patient population. PMDA concluded that appropriate precautions should be provided on the use of FTD-TPI in patients with moderate or severe hepatic impairment.

4.(ii).B.(3) Dosage regimen

PMDA requested the applicant to explain the appropriateness of the dosage regimen used in the clinical studies in Japan, in which FTD-TPI was administered twice daily in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period.

The applicant responded as follows:

On the basis of the following findings obtained in 3 foreign phase I studies (Studies TAS102-9801, TAS102-9802, and TAS102-9803), the applicant selected the dosage regimen of FTD-TPI being administered once daily continuously in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period.

- Dose-limiting toxicity was bone marrow suppression in these 3 studies, and managing bone marrow suppression is important to continue FTD-TPI therapy.
- Following multiple administration at the recommended doses (50 mg/m^2/day QD; 100 mg/m^2/day QD; and 160 mg/m^2/day QD in the respective studies above), the $AUC_{0\text{-}24}$ values of FTD (on Days 14, 12, and 5 in the respective studies above) indicated higher exposure to FTD can be tolerable in 5-consecutive-day treatment than in 14-consecutive-day treatment [see "4.(ii).A.(1).1)" to "4.(ii).A.(1).3) Foreign phase I study"].
- The total dose per cycle at each recommended dose was 700, 1000, and 800 mg/m^2 in the respective studies above, and the total dose in Study TAS102-9802 was the highest. Thus, the dosage regimen in this study which was 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period was considered optimal, when FTD-TPI is given once daily continuously.

Additionally, 2 foreign phase I studies (TAS102-9804, TAS102-9805) were conducted to investigate the optimal number of doses per day using the dosage regimen of 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period. On the basis of findings below

obtained in these studies, the applicant considered that it is appropriate to administer FTD-TPI twice daily in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period in clinical studies in Japan.

- The percentage of patients who continued treatment in Study TAS102-9804 in which the recommended dose of 50 mg/m^2/day BID was given was greater than that in Study TAS102-9805 in which recommended dose was 70 mg/m^2/day TID.
- The C_{max} and AUC values of FTD after multiple administration correlated significantly with the incidence of bone marrow toxicity, a dose-limiting toxicity, in Studies TAS102-9801, TAS102-9802, TAS102-9803, and TAS102-9804. Thus, it was considered important to maintain the exposure to FTD at the lowest possible level from the safety point of view.
- The C_{max} value in patients receiving FTD-TPI at 50 mg/m^2/day BID in Study TAS102-9804 (4673 ng/mL on Day 12) was lower than C_{max} values at the recommended doses of 50, 100, and 160 mg/m^2/day QD in three foreign phase I studies, TAS102-9801, TAS102-9802, and TAS102-9803, respectively [see "4.(ii).A.(1).1)" to "4.(ii).A.(1).3) Foreign phase I study"].

PMDA considers as follows:

Taking into account the points below, it is unclear whether or not the dosage regimen of FTD-TPI of “twice daily in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period” used in Japanese clinical studies was optimal. However, considering that the clinical usefulness of FTD-TPI was demonstrated in the Japanese phase II study (TAS102-J003) in which this dosage regimen was used [see "4.(iii).B.(1) Efficacy" and "4.(iii).B.(2) Safety"], it is acceptable to select this regimen as the dosage and administration.

- As Studies TAS102-9804 and TAS102-9805 investigated the continuity of treatment with FTD-TPI at different doses of 50 mg/m^2/day and 70 mg/m^2/day, it is inappropriate to simply compare the results of the two studies to assess the effect of dosing intervals.
- The applicant should have assessed the efficacy of FTD-TPI in addition to its safety, since the results of a Japanese phase I study (TAS102-J001) suggested a relationship of exposure to FTD with the efficacy of the treatment [see "4.(i).A.(3).1) Relationship between exposure and efficacy"].

4.(iii) Summary of clinical efficacy and safety

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

As evaluation data for the efficacy and safety, the results of 3 clinical studies in Japan, i.e., 2 phase I studies and 1 phase II study, were submitted. As reference data, the results of 6 foreign clinical studies consisting of 5 phase I studies and 1 phase II study were submitted.

List of clinical studies on the efficacy and safety of FTD-TPI

Category of data	Site	Study title	Phase	Patients	No. of enrolled patients	Outline of dosage regimens*	Primary endpoints
Evaluation	Japan	TAS102-J004	I	Patients with solid tumor	16	PK evaluation period: A single oral dose of FTD-TPI at 35 mg/m^2 was administered to Group A after a meal and Group B under fasted conditions. After a ≥3-day washout, the same dose of FTD-TPI was administered to Group A under fasted conditions and Group B after a meal. Multiple administration period: Multiple administration was initiated after the second single administration of FTD-TPI followed by a ≥3-day washout of the PK evaluation period. FTD-TPI at 35 mg/m^2 BID given orally after breakfast and supper in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period	Safety PK
		TAS102-J001	I	Patients with solid tumor	21	FTD-TPI at 15, 20, 25, 30, or 35 mg/m^2 BID given orally after breakfast and supper in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period	Safety PK
		TAS102-J003	II	Patients with unresectable advanced or recurrent colorectal cancer	172 (1) 114 (2) 58	(1) FTD-TPI 35 mg/m^2/dose BID or (2) placebo given orally after breakfast and supper in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period	Efficacy Safety
Reference	Foreign	TAS102-9801	I	Patients with solid tumor	14	FTD-TPI at 50, 60, or 100 mg/m^2 QD given orally before breakfast in 21-day cycles, each consisting of 14-day treatment and 7-day rest period	Safety PK
		TAS102-9802	I	Patients with solid tumor	24	FTD-TPI at 50, 70, 80, 90, 100, or 110 mg/m^2 QD given orally before breakfast in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period	Safety PK
		TAS102-9803	I	Patients with solid tumor	39	FTD-TPI at 100, 110, 120, 130, 140, 150, 160, 170, or 180 mg/m^2 QD given orally before breakfast in 21-day cycles, each consisting of 5-day treatment and 16-day rest period	Safety PK
		TAS102-9804	I	Patients with solid tumor	19	FTD-TPI at 25, 30, or 40 mg/m^2/dose BID given orally after breakfast and supper in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period	Safety PK
		TAS102-9805	I	Patients with solid tumor	15	FTD-TPI at 60, 70, or 80 mg/m^2/day TID given orally after breakfast, lunch, and supper in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period	Safety PK
		TAS102-9806	II	Patients with unresectable advanced or recurrent gastric cancer	18	FTD-TPI at 25 mg/m^2/dose BID given orally after breakfast and supper in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period	Efficacy Safety

PK, pharmacokinetics; *, The doses of FTD-TPI were expressed in the dose of trifluridine (FTD).

The results of the clinical studies were as summarized below.

Main adverse events other than deaths observed in the clinical studies are described in the section "4.(iv) Adverse events observed in clinical studies," and the results of PK evaluation are described in the sections "4.(i) Summary of biopharmaceutical studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies."

4.(iii).A-1 Evaluation data

Clinical studies in Japan

4.(iii).A-1.1) Japanese phase I study (5.3.1.1-1: Study TAS102-J004, PK evaluation period, [redacted] to [redacted]; multiple administration period, ongoing)

An open-label uncontrolled study in patients with advanced solid tumor except those with gastric cancer or those after gastrectomy (target sample size, 16) was conducted in order to assess the safety and PK profile of FTD-TPI at 1 medical institution in Japan.

In the PK evaluation period, a single oral dose of FTD-TPI at 35 mg/m^2 (the doses of FTD-TPI are expressed in the dose of FTD) was administered to one group (Group A) after a meal and the other group (Group B) under fasted conditions. After a washout period of ≥3 days, the same dose of FTD-TPI was administered to Group A under fasted conditions and Group B after a meal. After another washout period of ≥3 days, the multiple administration period initiated and FTD-TPI was administered at 35 mg/m^2 BID after breakfast and supper in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period. In the multiple administration period, treatment was to be continued until disease progression or occurrence of intolerable adverse events.

All of the 16 patients enrolled in the study received FTD-TPI and were included in the safety analysis.

No deaths occurred during the PK evaluation period.

4.(iii).A-1.2) Japanese phase I study (5.3.3.2-1: Study TAS102-J001, from [redacted] to [redacted]

An open-label uncontrolled study in patients with advanced solid tumor (target sample size, 24-48 patients) was conducted at 3 medical institutions in Japan to assess the maximum tolerated dose (MTD), safety, and PK of FTD-TPI.

FTD-TPI was given at a dose of 15, 20, 25, 30, or 35 mg/m^2, BID after breakfast and supper in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period.

All of the 21 patients enrolled in the study received FTD-TPI and were included in the safety analysis.

During the first cycle, patients were observed for dose-limiting toxicity (DLT) to determine whether treatment is tolerable or not. DLT was found in 1 of the 6 patients in the 15 mg/m^2 group as decreased neutrophil, white blood cell, and platelet counts, and in 1 of the 6 patients in the 35 mg/m^2 group as decreased neutrophil and white blood cell counts. The MTD was not achieved in this study.

A total of 2 patients died during the study period or until 30 days after the final administration of FTD-TPI. The 2 patients died due to disease progression, and a causal relationship to FTD-TPI was ruled out for both deaths.

4.(iii).A-1.3) Japanese phase II study (5.3.5.1-1: Study TAS102-J003, from [redacted], ongoing; safety data cut off on [redacted]

A double-blind, randomized, placebo-controlled study (Study TAS102-J003) was conducted at 20 medical institutions in Japan in order to investigate the efficacy and safety of FTD-TPI in patients with unresectable or recurrent colorectal cancer[*1] who had a history of ≥2 chemotherapies and were refractory or intolerant to fluoropyrimidines, irinotecan hydrochloride (CPT-11), and oxaliplatin (L-OHP). This patient population is referred to as "patients with unresectable or recurrent colorectal cancer who are refractory or intolerant to standard chemotherapy" hereinafter. The target sample size was 162 patients.[*2]

*1 The study protocol requirements were as follows: (1) patients with no history of treatment with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies had to undergo KRAS testing before enrollment; (2) if the test result was wild-type KRAS, patients with wild type KRAS were asked about whether they would receive a treatment using anti-EGFR monoclonal antibodies; (3) if patients with wild type KRAS had received the treatment with anti-EGFR monoclonal antibodies, they were to be asked again, after the treatment, whether they will be enrolled in this study.

*2 Based on the results of a Japanese phase I study (TAS102-J001) and other studies, the median OS was assumed to be 9.0 months in the FTD-TPI group and 6.0 months in the placebo group. When patients are randomized in a ratio of 2:1 to the FTD-TPI and placebo groups, the one-sided level of significance is set at 10%, and the power is set at 80%, a total of 121 events should be required. Considering possible exclusions from the analysis set, the target sample size was set at 162 patients.

Patients received FTD-TPI at a dose of 35 mg/m^2 BID or placebo after breakfast and supper in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period. Treatment with FTD-TPI or placebo was continued until disease progression or occurrence of intolerable adverse events.

Of 172 patients (114 patients in the FTD-TPI group, 58 patients in the placebo group) enrolled in the study, 3 patients were excluded from analysis because of (1) ineligibility for the study found after the administration of study drug in 1 patient[*1] in the FTD-TPI group and (2) no administration of study drug in 2 patients[*2] (1 patient each in the FTD-TPI and placebo groups). The remaining 169 patients (112 patients in the FTD-TPI group, 57 patients in the placebo group) were assessed as the full analysis set (FAS) for the efficacy of treatment. A total of 170 patients (113 patients in the FTD-TPI group, 57 patients in the placebo group) after excluding the 2 patients who did not receive study drug (1 patient each in the 2 groups) were assessed as the safety analysis set.

*1 After the initiation of treatment with FTD-TPI, the patient reported that he or she was on thermal therapy at another medical institution since before the enrollment in the study.

*2 In the patient in the FTD-TPI group, Grade 1 rash observed at the time of enrollment aggravated to Grade 3 before the administration of investigational drug. This patient discontinued the study. The patient in the placebo group developed pulmonary thrombosis after the enrollment. The investigator decided to withdraw this patient from the study.

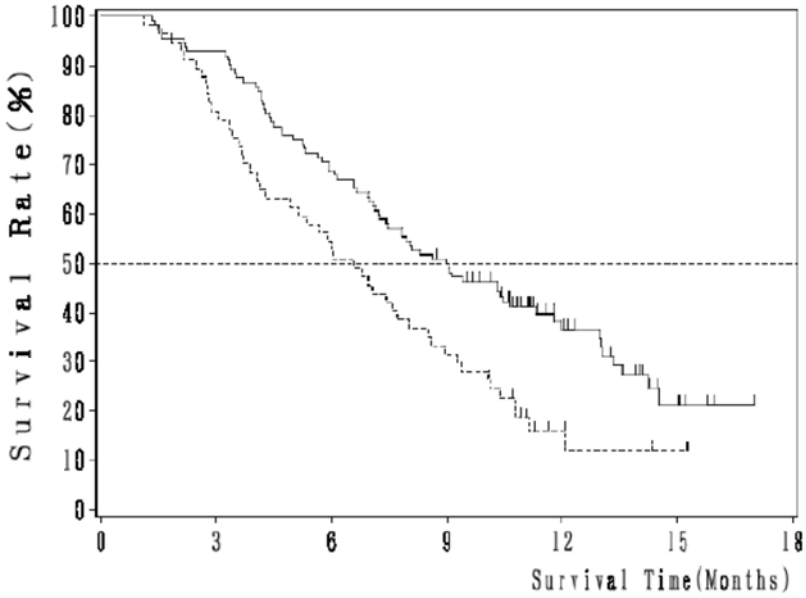
The primary efficacy endpoint was OS.

The results of the analysis of the primary endpoint, OS, and Kaplan-Meier curve are as follows.

Results of primary analysis of OS (FAS, data cut off on [redacted])

	FTD-TPI	Placebo
No. of patients	112	57
No. of deaths (%)	75 (67.0)	48 (84.2)
Medium*1 [95% CI] (months)	9.0 [7.3-11.3]	6.6 [4.9-8.0]
Hazard ratio *2 [95% CI]	0.56 [0.39-0.81]	
P value (one-sided)*3	0.0005	

*1, Estimated using the Kaplan-Meier method; *2, A Cox-proportional hazard model using treatment and the Eastern Cooperative Oncology Group performance status (ECOG PS) as covariates; *3, Stratified log-rank test (stratified by ECOG PG) with a one-sided level of significance of 0.10



Patients at risk

FTD-TPI	112	104	77	55	23	6
Placebo	57	46	31	18	4	1

Kaplan-Meier curve of OS (FAS, data cut off on [redacted])

One patient in the FTD-TPI group died during the period from the beginning of the study to 30 days after the last dose of FTD-TPI. The patient died due to interstitial lung disease, and a causal relationship between the death and FTD-TPI was ruled out.

4.(iii).A-2 Reference data

Foreign clinical studies

4.(iii).A-2.1) Foreign phase I study (5.3.3.2-2: Study TAS102-9801, from [redacted] to [redacted])

An open-label uncontrolled clinical study in patients with advanced solid tumor was conducted with a target sample size of 30 patients at 1 medical institution in the United States to assess the safety and PK of FTD-TPI.

All of the 14 enrolled patients received FTD-TPI. No deaths occurred during the period from the

beginning of the study to 30 days after the last dose of FTD-TPI.

4.(iii).A-2.2) Foreign phase I study (5.3.3.2-3: Study TAS102-9802, from [redacted] to [redacted]
An open-label uncontrolled clinical study in patients with advanced solid tumor was conducted with a target sample size of 30 patients at 1 medical institution in the United States to assess the safety and PK of FTD-TPI.

All of the 24 enrolled patients received FTD-TPI. No deaths occurred during the period from the beginning of the study to 30 days after the last dose of FTD-TPI.

4.(iii).A-2.3) Foreign phase I study (5.3.3.2-4: Study TAS102-9803, from [redacted] to [redacted]
An open-label uncontrolled clinical study in patients with advanced solid tumor was conducted with a target sample size of 45 patients in 1 medical institution in the United States to assess the safety and PK of FTD-TPI.

All of the 39 enrolled patients received FTD-TPI. One patient died during the period from the beginning of the study to 30 days after the last dose of FTD-TPI. The patient died due to disease progression, and a causal relationship between the death and FTD-TPI was ruled out.

4.(iii).A-2.4) Foreign phase I study (5.3.3.2-5: Study TAS102-9804, from [redacted] to [redacted]
An open-label uncontrolled clinical study in patients with advanced solid tumor was conducted with a target sample size of 24 patients in 1 medical institution in the United States to assess the safety and PK of FTD-TPI.

All of the 19 enrolled patients received FTD-TPI. No patients died during the period from the beginning of the study to 30 days after the last dose of FTD-TPI.

4.(iii).A-2.5) Foreign phase I study (5.3.3.2-6: Study TAS102-9805, from [redacted] to [redacted]
An open-label uncontrolled clinical study in patients with advanced solid tumor was conducted with a target sample size of 24 patients in 1 medical institution in the United States to assess the safety and PK of FTD-TPI.

All of the 15 enrolled patients received FTD-TPI. One patient died during the period from the beginning of the study to 30 days after the last dose of FTD-TPI. The patient died due to disease progression, and a causal relationship between the death and FTD-TPI was ruled out.

4.(iii).A-2.6) Foreign phase II study (5.3.5.2-1: Study TAS102-9806, from [redacted] to [redacted]
An open-label uncontrolled clinical study in patients with unresectable, advanced or recurrent gastric cancer was conducted with a target sample size of 61 patients in 1 medical institution in the United States to assess the efficacy and safety of FTD-TPI.

All of the 18 enrolled patients received FTD-TPI. Two patients died during the period from the beginning of the study to 30 days after the last dose of FTD-TPI. The cause of death was aspiration pneumonia in 1 patient, and hepatic encephalopathy in 1 patient. A causal relationship between the death and FTD-TPI was ruled out in both patients.

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

4.(iii).B.(1) Efficacy

PMDA reviewed the efficacy data as follows, and concluded that the efficacy of FTD-TPI is expected for the treatment of patients with unresectable or recurrent colorectal cancer who are refractory or intolerant to standard chemotherapy.

4.(iii).B.(1).1) Appropriateness of control group

The applicant provided the following explanation on the appropriateness of including placebo group as the control in Study TAS102-J003 in which patients enrolled were those with unresectable or recurrent colorectal cancer and were refractory or intolerant to standard chemotherapy, and, if with KRAS wild-type, had received treatment with anti-EGFR antibodies or declined to receive anti-EGFR therapy.

At the initiation of Study TAS102-J003, antitumor drugs available for patients with unresectable advanced or recurrent colorectal cancer were fluoropyrimidines such as fluorouracil, L-OHP, CPT-11, bevacizumab (recombinant) (BEV), anti-EGFR monoclonal antibody cetuximab (recombinant) (cetuximab), and panitumumab (recombinant) according to *the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Colon Cancer v.2.2009* (hereinafter referred to as the NCCN Guidelines) and *the Guidelines for the treatment of colon cancer in 2009* by the Japanese Society for Cancer of the Colon and Rectum (Kanehara & Co., Ltd., 2009). Panitumumab was not listed in the guidelines in Japan.

When the study was initiated, first-line therapy for unresectable advanced or recurrent colorectal cancer commonly consisted of a combination of (1) fluorouracil, folinate calcium (or levofolinate calcium), and L-OHP (FOLFOX) plus BEV or (2) fluorouracil, folinate calcium, and CPT-11 (FOLFIRI) plus BEV. Second-line therapy consisted of either FOLFOX or FOLFIRI, whichever was not used in the first-line therapy, plus BEV or, for patients with KRAS wild type, plus cetuximab. In patients with KRAS wild type tumors, cetuximab or panitumumab was used in third-line therapy if not used in first- or second-line therapy.

Since no other treatment options were available for this patient population, the applicant considers it appropriate that a placebo group was included as the control group in Study TAS102-J003.

PMDA accepted the applicant's explanation.

4.(iii).B.(1).2) Efficacy endpoints and the results of efficacy evaluation

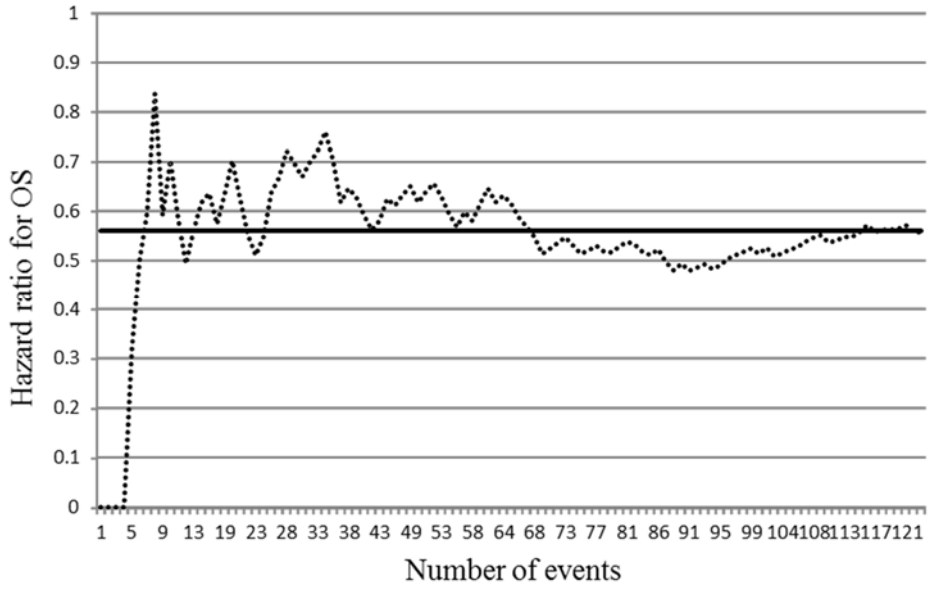
PMDA considers it acceptable that OS was selected as the primary endpoint in Study TAS102-J003.

The applicant explained the efficacy of FTD-TPI based on the results of Study TAS102-J003 as follows: Compared with the study results of other antitumor agents as third-line or later therapy in patients with unresectable or recurrent colorectal cancer, the OS obtained in Study TAS102-J003 [see the Evaluation data "4.(iii).A-1.3) Japanese Phase II clinical study"] demonstrated clinical significance of FTD-TPI therapy.

- In the NCIC CTG CO.17/CA225-025 Study, a foreign phase III study of cetuximab in patients with EGFR-positive unresectable or recurrent colorectal cancer who have been treated with fluoropyrimidines and are resistant or not indicated for regimens containing CPT-11 or L-OHP, the efficacy and safety of cetuximab with best supportive care (BSC) was investigated as compared with BSC alone. As a result, the hazard ratio of OS [95% CI] was 0.766 [0.637-0.921] ($P = 0.0046$), and the median OS was 6.1 months in the cetuximab group and 4.6 months in the BSC alone group (cf. the Review Report of Erbitux Injection 100 mg , dated May 7, 2008).
- In a foreign phase III study (20020408 Study) in patients with EGFR-positive unresectable or recurrent colorectal cancer who experienced disease progression during or after a second or third regimen containing fluoropyrimidines, CPT-11 or L-OHP, the efficacy and safety of panitumumab with BSC was investigated as compared with BSC alone. As a result, the hazard ratio of OS [95% CI] was 1.000 [0.816-1.224] ($P = 0.8061$), and the median OS was 6.4 months in the panitumumab group and 6.3 months in the BSC alone group (cf. the Review Report of Vectibix Intravenous Infusion 100 mg and Vectibix Intravenous Infusion 100 mg Takeda Bio dated February 10, 2010).

PMDA requested the applicant to explain the robustness of the results of efficacy evaluation in Study TAS102-J003, which achieved the prespecified efficacy endpoint as compared with the placebo group [see the Evaluation data "4.(iii).A-1.3) Japanese Phase II clinical study"] but was originally designed as an exploratory study to investigate the efficacy of FTD-TPI.

The applicant answered as follows:
The figure below shows changes in hazard ratio over time until the primary analysis. As the number of events increased, the hazard ratio became closer to the results of the primary analysis. The results of OS appear consistent.



Change in the hazard ratio for OS over time

Treatment effect of FTD-TPI was investigated in Study TAS102-J003 considering the impacts of patient characteristics that may possibly affect OS statistically or clinically. The results were similar to those found in the primary analysis. In a separate analysis treating 46 patients (37 in the FTD-TPI group and 9 in the placebo group) who were alive and censored in the primary analysis of OS as events, the hazard ratio of OS was 0.62 [95% CI, 0.45-0.85] (P = 0.0007) and the median OS was longer in the FTD-TPI group (8.9 months) than that in the placebo group (6.6 months).

The above findings indicate the robustness of the results on OS in Study TAS102-J003.

PMDA considers as follows:
Since the efficacy of FTD-TPI was explored in Study TAS102-J003 in which the significance level was larger than that commonly used in confirmatory studies, PMDA cannot conclude that the study has confirmed the efficacy of FTD-TPI. However, the study provided a certain degree of robustness because (1) Study TAS102-J003 is a double-blind, randomized, comparative study using an appropriate control group; (2) the results of an analysis considering prognostic factors indicate that it is not likely that patient characteristics affect OS; and (3) as the number of events increased, the hazard ratio became converged to the results of the primary analysis. In Study TAS102-J003 using OS as the primary endpoint, the difference in median OS between the FTD-TPI and placebo groups and the hazard ratio for OS demonstrated an improvement of OS and indicated an excellent clinical usefulness of FTD-TPI, therefore, PMDA concluded that the efficacy of FTD-TPI is expected for the treatment of patients with unresectable or recurrent colorectal cancer who are refractory or intolerant to standard chemotherapy.

Moreover, a global phase III study (TPU-TAS-102-301) is ongoing to confirm the superiority of FTD-TPI to placebo in terms of OS in patients with colorectal cancer refractory to standard chemotherapies with a target sample size of 800 patients including [redacted] Japanese patients. PMDA considers that the

applicant should provide the study results to healthcare providers in clinical settings appropriately without delay and take other measures whenever necessary.

4.(iii).B.(2) Safety [see "4.(iv) Adverse events observed in clinical studies" for adverse events]

PMDA reviewed safety data as follows and concluded that adverse events for which careful observation is required are bone marrow suppression, infections, gastrointestinal symptoms (e.g., diarrhoea, nausea, vomiting, and decreased appetite), peripheral neuropathy, cardiac disorders, ileus, interstitial lung disease, and hepatic impairment. The physician should observe the patient carefully for these adverse events during the treatment with FTD-TPI.

However, PMDA considers that FTD-TPI is tolerable in Japanese patients with colorectal cancer if physicians with sufficient knowledge and experience in cancer chemotherapy observe their patients carefully for adverse events, manage adverse events if they occur, and take appropriate measures such as dose reduction, treatment interruption or discontinuation.

4.(iii).B.(2).1) Safety profile of FTD-TPI

The applicant explained the safety profile of FTD-TPI on the basis of the results of Study TAS102-J003 as follows:

The safety findings in the FTD-TPI and placebo groups in Study TAS102-J003 are summarized below.

Summary of safety findings in Study TAS102-J003

	No. of patients (%)	
	FTD-TPI group n = 113	Placebo group n = 57
All adverse events	111 (98.2)	52 (91.2)
Grade 3 or 4 adverse events	77 (68.1)	9 (15.8)
Grade 5 adverse events	1 (0.9)	0
Serious adverse events	21 (18.6)	5 (8.8)
Adverse events resulting in discontinuation of treatment	3 (2.7)	1 (1.8)
Adverse events requiring dose reduction	22 (19.5)	0
Adverse events requiring interruption of treatment	75 (66.4)	5 (8.8)

Adverse events of any grade that occurred ≥10 % more frequently in the FTD-TPI group than in the placebo group were diarrhoea, nausea, fatigue, influenza like illness, blood bilirubin increased, haematocrit decreased, haemoglobin decreased, lymphocyte count decreased, neutrophil count decreased, platelet count decreased, red blood cell count decreased, weight decreased, white blood cell count decreased, and decreased appetite. Of them, adverse events of Grade ≥3 were haemoglobin decreased, neutrophil count decreased, and white blood cell count decreased (table below).

Serious adverse events that occurred ≥3% more frequently in the FTD-TPI group than in the placebo group were febrile neutropenia. Adverse events that occurred ≥3% more frequently in the FTD-TPI group than in the placebo group and that required dose reduction were febrile neutropenia and neutrophil count decreased. Adverse events that occurred ≥5% more frequently in the FTD-TPI group than in the

placebo group and that required interruption of treatment were nausea, fatigue and neutrophil count decreased. Adverse events that resulted in discontinuation of treatment were myocardial ischaemia (Grade 4), small intestinal obstruction, disseminated intravascular coagulation, hepatic failure, renal failure and colonic obstruction (Grade 3 for all events other than disseminated intravascular coagulation which was Grade 2), and anal fistula (Grade 2). A causal relationship between FTD-TPI and these events other than anal fistula could not be ruled out.

Adverse events that occurred in ≥10% of patients in either treatment group (Study TAS102-J003)

System organ class (SOC) Preferred term (PT) (MedDRA ver.13.1)	No. of patients (%)			
	FTD-TPI group n = 113		Placebo group n = 57	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	111 (98.2)	78 (69.0)	52 (91.2)	9 (15.8)
Gastrointestinal disorders				
Abdominal distension	2 (1.8)	0	6 (10.5)	0
Abdominal pain	22 (19.5)	1 (0.9)	10 (17.5)	0
Diarrhoea	43 (38.1)	7 (6.2)	12 (21.1)	0
Nausea	73 (64.6)	5 (4.4)	16 (28.1)	0
Stomatitis	17 (15.0)	0	6 (10.5)	0
Vomiting	38 (33.6)	4 (3.5)	14 (24.6)	0
General disorders and administration site conditions				
Fatigue	66 (58.4)	7 (6.2)	24 (42.1)	2 (3.5)
Influenza like illness	17 (15.0)	0	1 (1.8)	0
Oedema peripheral	14 (12.4)	1 (0.9)	4 (7.0)	1 (1.8)
Pyrexia	16 (14.2)	0	7 (12.3)	1 (1.8)
Investigation				
ALT increased	10 (8.8)	0	6 (10.5)	0
AST increased	23 (20.4)	2 (1.8)	12 (21.1)	1 (1.8)
Blood albumin decreased	29 (25.7)	1 (0.9)	11 (19.3)	2 (3.5)
Blood bilirubin increased	33 (29.2)	3 (2.7)	7 (12.3)	1 (1.8)
Blood lactate dehydrogenase increased	14 (12.4)	0	13 (22.8)	0
Blood sodium decreased	16 (14.2)	2 (1.8)	4 (7.0)	1 (1.8)
Haematocrit decreased	34 (30.1)	0	4 (7.0)	0
Haemoglobin decreased	82 (72.6)	19 (16.8)	9 (15.8)	3 (5.3)
Lymphocyte count decreased	39 (34.5)	11 (9.7)	7 (12.3)	2 (3.5)
Neutrophil count decreased	81 (71.7)	57 (50.4)	1 (1.8)	0
Platelet count decreased	44 (38.9)	5 (4.4)	1 (1.8)	0
Red blood cell count decreased	37 (32.7)	0	2 (3.5)	0
Weight decreased	23 (20.4)	0	1 (1.8)	0
White blood cell count decreased	86 (76.1)	32 (28.3)	2 (3.5)	0
White blood cell count increased	4 (3.5)	0	7 (12.3)	0
Protein urine present	20 (17.7)	0	6 (10.5)	0
Blood ALP increased	17 (15.0)	3 (2.7)	15 (26.3)	1 (1.8)
Metabolism and nutrition disorders				
Decreased appetite	70 (61.9)	5 (4.4)	19 (33.3)	2 (3.5)
Musculoskeletal and connective tissue disorders				
Back pain	12 (10.6)	0	3 (5.3)	0
Skin and subcutaneous tissue disorders				
Exfoliative rash	12 (10.6)	0	5 (8.8)	0

PMDA considers as follows:

Adverse events that occurred more frequently in the FTD-TPI group than in the placebo group should be carefully monitored. However, considering the fact that there were no substantial differences in the incidence of adverse events resulting in discontinuation of treatment or death between the 2 groups,

these adverse events are tolerable and manageable with appropriate measures such as dose reduction, treatment interruption or discontinuation of treatment. When FTD-TPI is administered, the physician should observe the patient carefully for the adverse events that occurred more frequently in the FTD-TPI group than in the placebo group in the clinical studies. The applicant should raise caution especially about the occurrence of adverse events that were reported ≥10% more frequently in the FTD-TPI group, e.g., diarrhoea, nausea, fatigue, influenza like illness, blood bilirubin increased, haematocrit decreased, haemoglobin decreased, lymphocyte count decreased, neutrophil count decreased, platelet count decreased, red blood cell count decreased, weight decreased, white blood cell count decreased, and decreased appetite.

In the following sections, the review focused on the adverse events and serious adverse events that occurred more frequently in the FTD-TPI group than in the placebo group in TAS102-J003.

4.(iii).B.(2).2) Bone marrow suppression and infections

The applicant explained the occurrence of bone marrow suppression (white blood cell count decreased, neutrophil count decreased, lymphocyte count decreased, platelet count decreased, haemoglobin decreased, and febrile neutropenia) and infections associated with FTD-TPI therapy as follows:

In the FTD-TPI group in Study TAS102-J003, the incidences of bone marrow suppression related events were as follows: 86 of 113 patients (76.1%) for white blood cell count decreased; 81 of 113 patients (71.7%) for neutrophil count decreased; 39 of 113 patients (34.5%) for lymphocyte count decreased; 44 of 113 patients (38.9%) for platelet count decreased; 82 of 113 patients (72.6%) for haemoglobin decreased; and 5 of 113 patients (4.4%) for febrile neutropenia. Of them, the numbers of patients whose adverse event was Grade 3 or higher in severity were 32 (28.3%), 57 (50.4%), 11 (9.7%), 5 (4.4%), 19 (16.8%), and 5 (4.4%) in the respective adverse events above. In the placebo group, the incidences of the adverse events listed above were as follows: 2 of 57 patients (3.5%) for white blood cell count decreased; 1 of 57 patients (1.8%) for neutrophil count decreased; 7 of 57 patients (12.3%) for lymphocyte count decreased; 1 of 57 patients (1.8%) for platelet count decreased; 9 of 57 patients (15.8%) for haemoglobin decreased; and 0 of 57 patients (0%) for febrile neutropenia. Of them, the numbers of patients whose adverse event was Grade 3 or higher in severity were 0, 0, 2 (3.5%), 0, 3 (5.3%), and 0 in the respective adverse events above.

In the patients who developed Grade 3 or higher bone marrow suppression during FTD-TPI therapy, the median number of days from Day 1 of the cycle in which the adverse event occurred to the days on which the lowest levels of blood test parameters were reported was as follows: white blood cell count, 23.0 days; neutrophil count, 27.0 days; platelet count, 19.5 days; and hemoglobin level, 22.0 days. The median number of days from the days on which the lowest levels were reported to the days on which the adverse event improved to Grade 2 or lower was 7.0 days for all these events. Bone marrow suppression was reduced or subsided in all patients after appropriate measures including interruption of treatment. No patients discontinued FTD-TPI therapy due to bone marrow suppression.

The number of patients who experienced adverse events related to infections (i.e., events classified into MedDRA SOC category of infections and infestations or PT of influenza like illness or pyrexia) during Study TAS102-J003 was 49 of 113 patients (43.4%) in the FTD-TPI group and 11 of 57 patients (19.3%) in the placebo group. Of them, the number of patients with Grade 3 or higher adverse events related to infections was 9 of 113 (8.0%) in the FTD-TPI group and 2 of 57 (3.5%) in the placebo group. Serious infections associated with FTD-TPI therapy were pneumonia in 3 patients, pelvic infection in 2 patients, eye infection, infection, and sepsis in 1 patient each. No patients discontinued FTD-TPI therapy due to adverse events associated with infections. Serious infections observed in the placebo group were biliary tract infection and device related infection in 1 patient each. The patient who experienced device related infection discontinued the study treatment.

In order to clarify the relationship between bone marrow suppression and infections, the number of patients who developed infections after white blood cell or neutrophil count decreased was evaluated. Among patients with white blood cell or neutrophil count decreased (90 patients in the FTD-TPI group and 2 patients in the placebo group), infection-related adverse events followed in 27 of 90 (30.0%) in the FTD-TPI group and 1 of 2 (50.0%) in the placebo group. Grade 3 or higher infection-related adverse events were reported in 5 of 90 patients (5.6%) in the FTD-TPI group and 0 patients in the placebo group. These findings indicate that FTD-TPI may cause bone marrow suppression and thereby increase susceptibility to infection.

PMDA considers as follows:
In Study TAS102-J003, no patients discontinued FTD-TPI therapy due to bone marrow suppression or infections, and these adverse events were manageable with treatment interruption or other measures. PMDA thus considers that FTD-TPI may be tolerable provided that appropriate measures such as dose reduction, treatment interruption or discontinuation are made if adverse events occur. However, since (1) bone marrow suppression was commonly observed during FTD-TPI therapy, and (2) the incidence of Grade 3 or higher neutrophil count decreased was higher in the FTD-TPI group than in the placebo group, PMDA considers that physicians should be instructed to conduct blood tests periodically and monitor the patient's condition carefully. Moreover, because infections often occurred in association with bone marrow suppression, the physicians must observe the patient carefully for infections.

PMDA concluded accordingly that it is necessary to provide information on the occurrence of bone marrow suppression and infections in the package insert and other appropriate materials, and instruct physicians to monitor patients carefully through periodic clinical and laboratory tests in the package insert.

4.(iii).B.(2).3) Gastrointestinal symptoms (diarrhoea, nausea, vomiting, and decreased appetite)
The applicant described the occurrence of gastrointestinal symptoms (diarrhoea, nausea, vomiting, decreased appetite) associated with FTD-TPI therapy in Study TAS102-J003 as follows:
Diarrhoea developed in 43 of 113 patients (38.1%) in the FTD-TPI group and 12 of 57 patients (21.1%) in the placebo group. Of them, Grade 3 diarrhoea developed in 7 patients (6.2%) in the FTD-TPI group

and in 0 patients in the placebo group. Grade 4 diarrhoea was not observed. Grade 3 diarrhoea developed during the first 3 cycles of treatment with FTD-TPI. Four events of Grade 3 diarrhea in 3 patients required treatment, but 6 events in 5 patients improved or resolved with no particular treatment. One patient required dose reduction of FTD-TPI, but no patients discontinued the therapy due to diarrhoea.

The number of patients who experienced nausea was 73 of 113 patients (64.6%) in the FTD-TPI group and 16 of 57 patients (28.1%) in the placebo group. The number of patients who experienced vomiting was 38 (33.6%) and 14 (24.6%), in the respective groups above, and the number of patients who experienced decreased appetite was 70 (61.9%) and 19 (33.3%), in the respective groups above. The numbers of patients with Grade 3 or higher event in the FTD-TPI and placebo groups were 5 (4.4%) and 0 for nausea, 4 (3.5%) and 0 for vomiting, and 5 (4.4%) and 2 (3.5%) for decreased appetite, respectively. These events were all Grade 3 in severity except 1 event of decreased appetite in the placebo group. Many of Grade 3 or higher nausea, vomiting, and decreased appetite developed during the first 3 cycles of treatment. No patients discontinued treatment due to these adverse events.

PMDA considers as follows:
Although caution should be exercised for gastrointestinal symptoms (diarrhoea, nausea, vomiting, decreased appetite) as their incidences were higher in the FTD-TPI group, most of the gastrointestinal adverse events were Grade 2 or lower in severity and were manageable with appropriate measures such as dose reduction and treatment interruption. FTD-TPI may be tolerable provided that appropriate measures such as dose reduction, treatment interruption or discontinuation are made if adverse events occur. However, the occurrence of gastrointestinal adverse events should be provided appropriately in the package insert.

4.(iii).B.(2).4) Peripheral neuropathy (peripheral motor neuropathy, peripheral sensory neuropathy)

The applicant explained the occurrence of peripheral neuropathy (peripheral motor neuropathy, peripheral sensory neuropathy) associated with FTD-TPI therapy in Study TAS102-J003 as follows:

Peripheral motor neuropathy developed in 1 of 113 patients (0.9%) in the FTD-TPI group and in 0 patients in the placebo group. The adverse event reported in the 1 patient in the FTD-TPI group was Grade 3 or higher and a causal relationship between the adverse event and FTD-TPI was ruled out.

Peripheral sensory neuropathy developed in 7 of 113 patients (6.2%) in the FTD-TPI group and in 1 of 57 patients (1.8%) in the placebo group. Of those, Grade 3 or higher adverse event was observed in 1 of 113 patients (0.9%) and 0 patients in the placebo group. A causal relationship between the adverse event and treatment with FTD-TPI could not be ruled out in 3 patients in FTD-TPI group. The severity was Grade 2 or lower in all 3 patients, and the outcome was recovery in 2 patients and no change in 1 patient.

Median days to onset of peripheral neuropathy (peripheral motor neuropathy, peripheral sensory neuropathy) and its median duration were 27.0 days and 11.0 days, respectively.

PMDA considers as follows:

Precautions for peripheral neuropathy should be made since these adverse events developed more commonly in the FTD-TPI group than in the placebo group and persisted in some patients in the FTD-TPI group. On the other hand, in the 8 patients who experienced peripheral motor neuropathy or peripheral sensory neuropathy, the adverse events were Grade 2 or lower in 6 patients (75.0%), and no adverse events required discontinuation of treatment. Thus, FTD-TPI may be tolerable provided that the adverse event is managed with appropriate measures such as dose reduction, treatment interruption or discontinuation, although the occurrence of peripheral neuropathy associated with FTD-TPI should be provided appropriately in the package insert.

4.(iii).B.(2).5) Cardiac disorders

The applicant explained the occurrence of cardiac disorders and QT/QTc interval prolongation associated with FTD-TPI therapy, based on the results from Studies TAS102-J001, TAS102-J002, TAS102-J003, and TAS102-J004 as follows:

- In Study TAS102-J003, cardiac disorders were observed in 5 of 113 patients (4.4%) in the FTD-TPI group and in 0 patients in the placebo group. Of them, Grade 3 or higher cardiac disorder was observed in 1 of 113 patients (0.9%)[*1] in the FTD-TPI group. A causal relationship between cardiac disorders and FTD-TPI could not be ruled out in 3 patients in the FTD-TPI group (1 patient each with Grade 1 atrial fibrillation, Grade 2 atrial flutter, and Grade 4 myocardial ischaemia).
- In Studies TAS102-J001, J002, J003, and J004, 2 patients showed QT/QTc interval prolongation[*2] after initiation of treatment with FTD-TPI, but neither case was likely to be attributable to FTD-TPI.
- In Studies TAS102-J001 to TAS102-J004, 10 patients experienced adverse events related to QT/QTc interval prolongation.[*3] Of them, no patients other than 1 patient[*4] underwent ECG recording at the occurrence of adverse event, but the nature of the adverse events related to QT/QTc interval prolongation was blood potassium decreased in all patients with a severity of Grade 4 in 1 patient, Grade 3 in 2 patients, and Grade 1 in 7 patients. No other events related to QT/QTc interval prolongation were observed. Grade 4 and Grade 3 blood potassium decreased observed were considered due to tumor progression.

*1: The averse event was Grade 4 myocardial ischaemia and considered serious. It occurred on Day 2 of treatment and the outcome was reported as improved.

*2: The causes of QT/QTc interval prolongation were both considered due to the patients' predisposition: ECG at baseline showed QT/QTc interval prolongation in 1 patient; small intestinal obstruction and colonic obstruction were seen in the other patient at the occurrence of QT/QTc interval prolongation and no QT/QTc interval prolongation was observed thereafter.

*3: Adverse events related to QT/QTc interval prolongation were defined as cardiac arrest, cardio-respiratory arrest, blood potassium decreased, loss of consciousness in addition to events defined in the ICH E14 Guidelines i.e., torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, syncope, and seizures.

*4: The patient experienced Grade 1 blood potassium decreased on Day 48, and ECG on that day showed atrial fibrillation. The patient was complicated with atrial fibrillation, which was also noted in ECG before FTD-TPI was administered (Day 15).

PMDA considers as follows:

Considering the fact that 3 patients experienced cardiac disorders, including Grade 4 adverse event, for which a causal relationship with FTD-TPI could not be ruled out, the occurrence of cardiac disorders should be provided appropriately in the package insert. The applicant should collect data on cardiac disorders continuously through routine pharmacovigilance practices after the market launch, and should take appropriate measures including providing additional alerts when safety information such as occurrence of serious cardiac disorders are newly obtained during post-marketing surveillance.

4.(iii).B.(2).6) Ileus

The applicant explained the occurrence of ileus associated with FTD-TPI therapy, based on the results from Study TAS102-J003, as follows:

Adverse events related to ileus* were observed in 5 of 113 patients (4.4%) in the FTD-TPI group and 1 of 57 patients (1.8%) in the placebo group. All these events were serious and Grade 3 or higher in severity. Of the patients who experienced serious ileus, 1 patient who had small intestinal obstruction and colonic obstruction discontinued FTD-TPI therapy. A causal relationship between ileus in this patient and FTD-TPI could not be ruled out.

*: Defined as colonic obstruction, small intestinal obstruction, small intestinal stenosis, rectal obstruction, ileus, and subileus in MedDRA PT

PMDA considers as follows:

Although ileus may be associated with colorectal cancer, the primary disease, the incidence of ileus tended to be higher in the FTD-TPI group than in the placebo group, and 1 patient experienced serious ileus for which a causal relationship with FTD-TPI could not be ruled out. The occurrence of ileus should be provided in the package insert and other relevant materials.

4.(iii).B.(2).7) Interstitial lung disease

The applicant explained the occurrence of interstitial lung disease associated with FTD-TPI therapy as follows:

In Study TAS102-J003, interstitial lung disease developed in 1 of 113 patients (0.9%), which was Grade 5 in severity, in the FTD-TPI group, and in 0 patients in the placebo group. A respiratory physician independent of the study concluded that the imaging findings in the patient who developed Grade 5 adverse event were not inconsistent with imaging findings in patients with interstitial lung disease, and the adverse event observed was attributed to exacerbation of colorectal cancer, or administration of FTD-TPI or concomitant drugs. Pathological examination of biopsy samples revealed that findings were not inconsistent with those of interstitial lung disease and diffuse alveolar damage due to viral infection, but drugs and fungal infection could also cause diffuse alveolar damage. Taking into account of the results of pathological examination, the investigator diagnosed the condition found as interstitial pneumonia caused by immunodeficiency due to end-stage cancer, and a causal relationship between the adverse event and FTD-TPI was ruled out.

No cases of interstitial lung disease have been reported in any clinical studies of FTD-TPI in or outside Japan other than Study TAS102-J003.

PMDA considers as follows:
Although a causal relationship with FTD-TPI was ruled out, death due to interstitial lung disease occurred in 1 patient in the FTD-TPI group, and this case was the only death reported in Study TAS102-J003. It is necessary to provide appropriate cautions on this matter. The applicant should continue to carefully monitor occurrence of interstitial lung disease after the market launch, and must take appropriate measures including providing additional cautions when obtaining safety information such as occurrence of serious interstitial lung disease.

4.(iii).B.(2).8) Hepatic impairment
The applicant explained the occurrence of hepatic impairment associated with FTD-TPI therapy, based on the results from Study TAS102-J003, as follows:

The following table summarizes adverse events and abnormal laboratory findings related to hepatic function. There were no cases of hepatic impairment that meet the criteria of Hy's Law (defined on the basis of Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, U.S. Department of Health and Human Services, Food and Drug Administration, July 2009).

Hepatic f impairment (Study TAS102-J003)

Events	No. of patients (%)			
	FTD-TPI group n = 113		Placebo group n = 57	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Adverse events related to hepatic impairment	71 (62.8)	11 (9.7)	31 (54.4)	3 (5.3)
Hepatic failure	2 (1.8)	2 (1.8)	0	0
ALT increased	10 (8.8)	0	6 (10.5)	0
AST increased	23 (20.4)	2 (1.8)	12 (21.1)	1 (1.8)
Bilirubin conjugated increased	1 (0.9)	0	0	0
Blood albumin decreased	29 (25.7)	1 (0.9)	11 (19.3)	2 (3.5)
Blood bilirubin increased	33 (29.2)	3 (2.7)	7 (12.3)	1 (1.8)
Blood cholinesterase decreased	1 (0.9)	0	0	0
Blood lactate dehydrogenase increased	14 (12.4)	0	13 (22.8)	0
Gamma-glutamyltransferase increased	4 (3.5)	3 (2.7)	1 (1.8)	0
Blood ALP increased	17 (15.0)	3 (2.7)	15 (26.3)	1 (1.8)

Serious adverse events related to hepatic impairment were observed in 2 of 113 patients (1.8%) in the FTD-TPI group and in 0 patients in the placebo group. Of those, adverse event resulting in treatment discontinuation was hepatic failure observed in 1 of 113 patients (0.9%) in the FTD-TPI group, and a causal relationship with FTD-TPI could not be ruled out for the adverse event.

PMDA considers as follows:
The incidences of adverse events related to hepatic impairment other than blood albumin decreased and blood bilirubin increased were lower in the FTD-TPI group than in the placebo group, or similar between

the groups. However, 1 patient receiving FTD-TPI discontinued treatment due to hepatic failure, for which a causal relationship with FTD-TPI could not be ruled out. It is thus necessary to continue to carefully monitor occurrence of hepatic impairment after the market launch.

4.(iii).B.(3) Clinical positioning

PMDA reviewed current treatment policies for patients with unresectable advanced or recurrent colorectal cancer described in treatment guidelines and textbooks in and outside Japan, and confirmed the accuracy of the following explanation by the applicant. PMDA also confirmed that no descriptions on FTD-TPI are found to date in international textbooks of oncology such as "*DeVita, Hellman, and Rosenverg's Cancer: principles & practices of oncology 9th ed.*" (Lippincott Williams & Wilkins. 2011, PA, USA).

The applicant explained the clinical positioning of FTD-TPI as follows:

Since the results of Study TAS102-J003 showed that OS was improved to a degree suggestive of the excellent clinical usefulness of FTD-TPI in the treatment of patients with unresectable or recurrent colorectal cancer who are refractory or intolerant to standard chemotherapy, and that FTD-TPI has a tolerable safety profile, FTD-TPI may be positioned as a new treatment option for patients with unresectable or recurrent colorectal cancer who have been treated with 2 or more regimens and have no other standard regimens available. It is recommended that, for patients with KRAS-wild type colorectal cancer, FTD-TPI should be used after they become refractory or intolerant to anti-EGFR monoclonal antibodies (e.g., cetuximab or panitumumab) for the following reasons.

- Japanese and foreign guidelines for the treatment of colorectal cancer, i.e., the NCCN guidelines v.3.2013 and *Japanese Society for Cancer of the Colon and Rectum guidelines 2010 for the treatment of colorectal cancer* (Kanehara & Co., Ltd.; 2010) (hereinafter referred to as JSCCR Guidelines for the Treatment of Colorectal Cancer 2010 ed.) recommend the use of anti-EGFR monoclonal antibodies for patients with KRAS wild type in the first-, second-, or third-line therapy.
- Among the patients enrolled in Study TAS102-J003, ≥90% of patients with KRAS wild type (49 patients in the FTD-TPI group and 23 patients in the placebo group) had received anti-EGFR monoclonal antibodies before the study, and only a small number of patients (5 patients in the FTD-TPI group and 1 patient in the placebo group) had no history of anti-EGFR therapy. A subgroup analysis of patients with KRAS wild type with prior treatment with anti-EGFR monoclonal antibodies revealed a hazard ratio for OS of 0.77 [95% CI, 0.44-1.32] (P = 0.337) (median OS: 7.1 months in the FTD-TPI group; 7.4 months in the placebo group), which indicates a tendency towards prolonged OS in the FTD-TPI group as compared with the placebo group.

The NCCN guidelines v.3.2013 list regorafenib hydrate (hereinafter referred to as regorafenib) as a treatment option for the third-line or subsequent therapy for patients with unresectable or recurrent colorectal cancer. As FTD-TPI and regorafenib differ in terms of safety profile, these drugs should be chosen for each patient individually by taking into account multidisciplinary treatment strategy, patient characteristics (e.g., performance status, complications, bone marrow function) and information on the

efficacy and safety of FTD-TPI.

PMDA considers as follows:
Considering the patient population enrolled in Study TAS102-J003 and its study results, the applicant's explanation is generally understandable in terms that FTD-TPI is positioned as a treatment option for patients with unresectable or recurrent colorectal cancer who have undergone ≥2 regimens and have no other treatment options available including anti-EGFR monoclonal antibodies. However, the sample size was small in the subgroup analysis of patients with KRAS wild type who had prior history of treatment with anti-EGFR monoclonal antibodies and the efficacy in the subgroup was not able to be fully assessed. It is thus necessary to provide the relevant information appropriately. Additionally, although the physician might select FTD-TPI based on the patient's condition and the safety profile of FTD-TPI among other factors, based on the points below, FTD-TPI should be used only for patients for whom regorafenib is not indicated because treatment with FTD-TPI will not be recommended over regorafenib until the results of the global phase III study of FTD-TPI (TPU-TAS-102-301) are obtained. The clinical positioning of FTD-TPI will be further clarified when the results of ongoing Study TPU-TAS-102-301 become available.

- Study TAS102-J003 is an exploratory study, and there is no results of confirmatory studies that provide evidence of the efficacy and safety of FTD-TPI to date.
- The efficacy and safety of regorafenib has been demonstrated in a confirmatory study in a patient population similar to that enrolled in Study TAS102-J003, with a hazard ratio for OS of 0.774 [95% CI, 0.636-0.942] (one-sided *P* value = 0.005178), and a median OS of 196 days for the regorafenib group and 151 days for the placebo group (see the Review Report on Stivarga 40 mg tablets, dated March 4, 2013). Also regorafenib has been approved in Japan.

4.(iii).B.(4) Indications
The proposed indication was "unresectable advanced or recurrent colorectal cancer." At the time of filing of the application, the applicant explained that the Precautions for Indications section will include the following statements: (1) The efficacy and safety of FTD-TPI in first-line chemotherapy, or neoadjuvant or adjuvant chemotherapy have not been established; and (2) FTD-TPI should be indicated for patients who have undergone chemotherapies containing fluorouracil, CPT-11, and L-OHP, or have developed recurrent cancers.

On the basis of the review in "4.(iii).B.(1) Efficacy," "4.(iii).B.(2) Safety," and "4.(iii).B.(3) Clinical positioning," as well as the following reviews in this section, PMDA concluded that it is appropriate to indicate FTD-TPI for "unresectable advanced or recurrent colorectal cancer" as proposed by the applicant, and include the following descriptions in the Precautions for Indications section.

- The efficacy and safety of FTD-TPI as first-line or second-line chemotherapy have not been established.
- The efficacy and safety of FTD-TPI in adjuvant chemotherapy have not been established.
- Physicians should be acquainted with the prior treatment history of the patients enrolled in the

clinical studies of FTD-TPI via information in the Clinical Studies section in order to fully understand the efficacy and safety of FTD-TPI, and consider carefully for other treatment options before prescribing FTD-TPI for the patient.

4.(iii).B.(4).1) Intended patient population

PMDA considers the intended patient population as follows:

FTD-TPI is currently recommended for patients with unresectable or recurrent colorectal cancer refractory to other antitumor agents including regorafenib for whom no standard therapies including anti-EGFR monoclonal antibodies are available [see "4.(iii).B.(1) Efficacy," "4.(iii).B.(2) Safety," "4.(iii).B.(3) Clinical positioning"], and it is appropriate to provide the following alerts in the Precautions for Indications section in the package insert.

- The efficacy and safety of FTD-TPI as first-line or second-line chemotherapy have not been established.
- Physicians should be acquainted with the prior treatment history of the patients enrolled in the clinical studies of FTD-TPI via information in the Clinical Studies section in order to fully understand the efficacy and safety of FTD-TPI, and consider carefully for other treatment options before prescribing FTD-TPI for the patient.

4.(iii).B.(4).2) Efficacy and safety in neoadjuvant or adjuvant chemotherapy

On the basis of the fact that no clinical study results have been obtained in terms of the efficacy and safety of FTD-TPI in neoadjuvant or adjuvant chemotherapy, the applicant explained that the Precautions for Indications will include alerts on this matter.

PMDA considers as follows:

PMDA largely accepted the applicant's explanation. However, there is little need to provide an alert on the lack of established efficacy and safety of FTD-TPI in neoadjuvant chemotherapy because (1) the clinical positioning of neoadjuvant chemotherapy for treatment of colorectal cancer has not been established in Japan as described in the JSCCR Guidelines for the Treatment of Colorectal Cancer 2010 ed., and (2) neoadjuvant chemotherapy is not recommended for patients awaiting radical surgery for the treatment of non-metastatic resectable colorectal cancer in the NCCN Guidelines v.3.2013 or the JSCCR Guidelines for the Treatment of Colorectal Cancer 2010 ed., although neoadjuvant chemotherapy may be considered for patients with colorectal cancer and resectable liver metastases as described in the NCCN Guidelines v.3.2013.

4.(iii).B.(5) Dosage and administration

The proposed dosage and administration is as follows: “the usual initial adult dose of the combination product of trifluridine and tipiracil tydrochloride (FTD-TPI) is determined based on body surface area (BSA) and shown in the dosing table below, which presents predefined ranges of BSA and the corresponding initial doses (on the basis of trifluridine at approximately 35 mg/m^2/dose). FTD-TPI is orally administered twice daily, after breakfast and after supper in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period. The dose may be reduced

according to the patient's condition." The applicant proposed the following contents in the Precautions for Dosage and Administration section of the draft package insert. The applicant proposed the following contents in the Precautions for Dosage and Administration section of the draft package insert.

- The efficacy and safety of FTD-TPI in combination with other antitumor drugs have not been established.
- The dose of FTD-TPI should be reduced by 10 mg/day, and the lowest dose should be 30 mg/day. When FTD-TPI is administered at a dose of 50 mg/day, the patient should take 20 mg after breakfast and 30 mg after supper.
- FTD-TPI should be administered on the basis of the criteria used in Study TAS102-J003, and the dose should be reduced or the treatment should be interrupted whenever necessary.

On the basis of the following review, PMDA has concluded that the dosage and administration may be specified as follows as proposed by the applicant: "the usual initial adult dose of the combination product of trifluridine and tipiracil tydrochloride (FTD-TPI) is determined based on body surface area (BSA) and shown in the dosing table below, which presents predefined ranges of BSA and the corresponding initial doses (on the basis of trifluridine at approximately 35 mg/m^2/dose). FTD-TPI is orally administered twice daily, after breakfast and after supper, in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period. The dose may be reduced according to the patient's condition." The applicant proposed the following contents in the Precautions for Dosage and Administration section of the draft package insert. PMDA has also concluded that the Precautions for Dosage and Administration section should include descriptions as proposed by the applicant to provide alerts and information.

4.(iii).B.(5).1) Dosage and administration

The applicant explained the dosage and administration of FTD-TPI as follows:

When FTD-TPI was administered at a dose of 35 mg/m^2/dose BID in Study TAS102-J003, the clinical usefulness of FTD-TPI was demonstrated. Thus, taking account of the results of the clinical studies described below, the dosage regimen employed in Study TAS102-J003 was adopted as the dosage and administration.

- The results of 3 foreign phase I studies in patients with advanced solid tumors (Studies TAS102-9801, TAS102-9802, and TAS102-9803) indicated that higher exposure to FTD is tolerable in 5-consecutive-day treatment than in 14-consecutive-day treatment [see "4.(ii).A.(1) Patients with cancer"].
- In Japanese phase I study in patients with advanced solid tumors (Study TAS102-J001) in which the safety of FTD-TPI at 15 to 35 mg/m^2/dose BID was investigated, the MTD was not achieved at any dose levels, which demonstrated the tolerability of FTD-TPI at all doses investigated [see "4.(iii).A-1.2) Japanese phase I study"].
- In 2 foreign phase I studies in patients with advanced solid tumors (Studies TAS102-9804 and TAS102-9805), 3 patients each receiving FTD-TPI at 80 mg/m^2/day in these 2 studies experienced neutrophil count decreased, which was Grade 3 in 1 patient each in the 2 studies, and Grade 4 in 2 patients in Study TAS102-9804 and 1 patient in Study TAS102-9805. These findings suggested that

80 mg/m^2/day is likely to be the MTD [see Reference data "4.(iii).A-2.4) Foreign phase I study" and "4.(iii).A-2.5) Foreign phase I study"].

- A comparison of results of a Japanese phase I clinical study in patients with advanced solid tumors (Study TAS102-J001) with those of a foreign phase I study in patients with advanced solid tumors (Study TAS102-9804) revealed no clear differences in PK parameters (t_{max}, $C_{max,}$ and AUC of FTD and TPI) between Japanese and foreign patients [see Evaluation data "4.(iii).A-1.2) Japanese phase I study" and Reference data "4.(iii).A-2.4) Foreign phase I study"].

PMDA accepted the applicant's explanation.

4.(iii).B.(5).2) Dose adjustment and other matters

The applicant explained the criteria for starting/restarting or interruption of treatment, or dose reduction as follows.

In Study TAS102-J003, the criteria for starting/restarting, or interruption of treatment, or dose reduction of FTD-TPI were clearly specified and followed, and as a result, FTD-TPI was found tolerable. Thus, the criteria used in Study TAS102-J003 will be included in the Precautions for Dosage and Administration section. Additionally, the different dose levels to be given in the morning and evening for the treatment with FTD-TPI at a dose of 50 mg/day will also be described in the Precautions for Dosage and Administration section.

PMDA accepted the applicant's explanation.

4.(iii).B.(5).3) Use of FTD-TPI in combination with other antitumor drugs

PMDA requested the applicant to explain a possibility of using FTD-TPI in combination with other antitumor drugs including fluoropyrimidines, and the efficacy and safety of the combination regimens.

The applicant answered as follows:

No study results have been obtained in terms of the efficacy of FTD-TPI in combination with other antitumor drugs. On the other hand, the safety of FTD-TPI in combination with CPT-11 is being assessed in a Japanese phase I clinical study (Study TAS102-J002)* in patients with unresectable advanced or recurrent colorectal cancer who have received 1 chemotherapy and do not respond to fluoropyrimidines or L-OHP. In Study TAS102-J002, serious adverse events developed in 2 of the 10 patients receiving FTD-TPI and CTP-11 (ascites and hyperbilirubinaemia in 1 patient, and febrile neutropenia and diarrhoea in the other patient). A causal relationship between adverse events and treatment could not be ruled out in the patient with febrile neutropenia and diarrhoea. A comparison of patients receiving the combination of FTD-TPI and CTP-11 with those receiving FTD-TPI alone in Study TAS102-J003 indicated that patients receiving the combination therapy have a higher risk of severe adverse events related to bone marrow suppression.

It also appears that serious adverse drug reactions such as haematotoxicity may develop and efficacy

may be reduced when FTD-TPI is used in combination with the following drugs/therapies: fluoropyrimidines; fluoropyrimidine therapies including folinate/tegafur/uracil therapy; antifungal drug flucytosine; or antifolate drugs including methotrexate and pemetrexed sodium hydrate (hereinafter referred collectively to as "fluoropyrimidines and other related anti-tumor agents") on the basis of the following points.

- FTD has a pyrimidine skeleton, and has a structure similar to those of fluoropyrimidines.
- The inhibitory effect of TPI on TPase may affect the nucleic acid metabolism through which "fluoropyrimidines and other related anti-tumor agents" exert their antitumor effects.
- Concomitant therapy of FTD-TPI with fluoropyrimidines and other related anti-tumor agents that inhibit TS may affect the uptake of FTD into DNA.

Since no results have been obtained in comparative studies to investigate the efficacy and safety of FTD-TPI in combination with other antitumor drugs in a sufficient number of patients, the package insert will include in the Precautions for Dosage and Administration section an alert that the efficacy and safety of FTD-TPI in combination with other antitumor agents have not been established, as well as additional alerts on the use of FTD-TPI with fluoropyrimidines and other related anti-tumor agents.

*: FTD-TPI at doses from 20 to 35 mg/m^2 BID is given orally after breakfast and after supper in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period. In order to evaluate the PK of CPT-11 monotherapy, the dosage regimen on the second cycle was modified so that FTD-TPI was orally administered BID (after breakfast and supper) in a 28-day cycle consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period. CPT-11 at 150 mg/m^2/dose was infused intravenously over 90 minutes on Days 1 and 15 of all cycles.

PMDA accepted the applicant's explanation.

4.(iii).B.(6) Post-marketing investigations

The applicant explained the post-marketing investigations as follows:

In order to assess the safety of FTD-TPI in routine clinical use after the market launch, a use-results survey using a central registration system will be conducted in patients with unresectable advanced or recurrent colorectal cancer.

The survey will investigate (1) bone marrow suppression,[*1] (2) infections,[*2] and (3) presence/absence and severity of renal or hepatic impairment at baseline[*3] as priority investigation items. In an analysis of 119 patients consisting of 113 patients enrolled in the Japanese phase II study (TAS102-J003) and 6 patients in the Japanese phase I study (TAS102-J001) who received FTD-TPI according to the dosage and administration proposed in the application, the incidence of bone marrow suppression tended to be higher in patients with renal impairment than in those without it. Risk factors for bone marrow suppression will be investigated in the survey.

*1: Bone marrow suppression is a major adverse event associated with FTD-TPI and a dose-limiting toxicity.
*2: Infections are commonly associated with bone marrow suppression and should be monitored carefully.
*3: During clinical studies, only limited data have been obtained in terms of the effects of baseline renal or hepatic impairment on the safety of FTD-TPI.

The target number of patients was calculated based on the following results of analysis of 119 patients consisting of 113 patients in Study TAS102-J003 and 6 patients in Study TAS102-J001 who received FTD-TPI according to the dosage and administration proposed in the application in order to capture at least 5 cases each (the same number of cases reported in clinical studies) of Grade ≥3 platelet count decreased and febrile neutropenia in patients with hepatic impairment. In order to capture at least 5 cases each of the two types of adverse drug reactions that occurred at an incidence of 4.2% in clinical studies at a probability of 98%, 249 patients need to be assessed. Assuming patients with hepatic impairment accounts for 32.8% of all registered patients, 760 patients need to be assessed in the post-marketing surveillance. Therefore, considering the number of dropouts, the target number of patients will be set as 800 patients. About 2 years is anticipated for the enrollment of the patients.

- The least frequently reported Grade 3 or severer adverse drug reactions related to bone marrow suppression were platelet count decreased and febrile neutropenia (both of which occurred in 4.2% of patients).
- Patients with hepatic impairment accounted for 32.8%, which was lower than the percentage of patients with renal impairment (58.8%).

The mean and median treatment durations in Study TAS102-J003 covered 3.6 and 3 cycles, respectively, and thus, patients will be followed for 4 cycles in the survey. There were some adverse drug reactions first reported in Cycle 5 or later, namely atrial fibrillation, dry mouth, hypothermia, arthralgia, and cough, but all of the adverse drug reactions occurred in ≤2 patients each. It is unlikely that these adverse drug reactions are specifically occur in Cycle 5 or later. Therefore, the applicant claims that it is appropriate to observe patients for 4 cycles.

PMDA considers as follows:
Most common adverse events associated with FTD-TPI therapy were generally similar to those observed in the treatment with approved antimetabolites that inhibit DNA synthesis, but no sufficient safety data of FTD-TPI in Japanese patients have been accumulated. A post-marketing surveillance should be conducted to investigate the safety of FTD-TPI in routine clinical use in Japan. At present, the priority investigation items, target number of patients, and observation period proposed by the applicant are acceptable.

The global phase III study (TPU-TAS-102-301) is currently underway. The applicant should investigate the efficacy and safety of FTD-TPI in detail without delay when the study results are available, investigate whether the use-results survey plan should be modified or not and whether additional pharmacovigilance activities and risk minimization actions are needed or not, and provide the study results to healthcare providers in clinical settings without delay.

4.(iv) Adverse events observed in clinical studies

This section describes common non-fatal adverse events described in the submitted document for safety review. Fatal adverse events are described in the section of "4.(iii) Summary of clinical efficacy and

safety."

4.(iv).(1) Japanese phase I study (Study TAS102-J004)

Adverse events developed in 6 of the 16 patients (37.5%), and 2 of the 16 patients (12.5%) experienced adverse events for which a causal relationship with FTD-TPI could not be ruled out. There were no adverse events experienced by ≥20% of the patients. No serious adverse events were observed, or no adverse events resulted in discontinuation of treatment.

4.(iv).(2) Japanese phase I study (Study TAS102-J001)

Adverse events developed in all patients (100%) in the 30, 40, 50, 60, and 70 mg/m^2/day groups. All patients experienced adverse events for which a causal relationship with FTD-TPI could not be ruled out. Adverse events observed in ≥40% of patients in any group are listed in the following table.

Adverse events observed in ≥40% of patients in any group

System organ class Preferred term (MedDRA ver.10.0)	No. of patients (%)									
	30 mg/m^2/day group (n = 6)		40 mg/m^2/day group (n = 3)		50 mg/m^2/day group (n = 3)		60 mg/m^2/day group (n = 3)		70 mg/m^2/day group (n = 6)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	6 (100)	3 (50.0)	3 (100)	1 (33.3)	3 (100)	3 (100)	3 (100)	3 (100)	6 (100)	5 (83.3)
Gastrointestinal disorders										
Abdominal distension	5 (83.3)	0	0	0	1 (33.3)	0	1 (33.3)	0	0	0
Abdominal pain	2 (33.3)	1 (16.7)	1 (33.3)	0	1 (33.3)	0	2 (66.7)	0	1 (16.7)	0
Constipation	4 (66.7)	0	0	0	1 (33.3)	0	1 (33.3)	0	2 (33.3)	0
Diarrhoea	2 (33.3)	0	0	0	2 (66.7)	1 (33.3)	2 (66.7)	0	1 (16.7)	0
Nausea	4 (66.7)	0	0	0	2 (66.7)	0	3 (100)	0	5 (83.3)	0
Vomiting	2 (33.3)	0	0	0	2 (66.7)	0	2 (66.7)	0	2 (33.3)	0
General disorders and administration site conditions										
Malaise	4 (66.7)	2 (33.3)	1 (33.3)	0	2 (66.7)	0	2 (66.7)	0	2 (33.3)	0
Pyrexia	1 (16.7)	0	0	0	1 (33.3)	0	0	0	3 (50.0)	0
Investigation										
Blood albumin decreased	2 (33.3)	0	1 (33.3)	0	2 (66.7)	0	2 (66.7)	0	2 (33.3)	0
Blood bilirubin increased	5 (83.3)	3 (50.0)	1 (33.3)	0	0	0	2 (66.7)	0	3 (50.0)	1 (16.7)
Blood chloride decreased	1 (16.7)	0	1 (33.3)	0	2 (66.7)	0	1 (33.3)	0	0	0
Blood lactate dehydrogenase increased	2 (33.3)	0	1 (33.3)	0	1 (33.3)	0	2 (66.7)	0	2 (33.3)	0
Blood potassium increased	2 (33.3)	0	0	0	2 (66.7)	0	0	0	0	0
Blood urea increased	2 (33.3)	0	1 (33.3)	0	2 (66.7)	0	1 (33.3)	0	2 (33.3)	0
Haematocrit decreased	3 (50.0)	2 (33.3)	2 (66.7)	0	3 (100)	1 (33.3)	3 (100)	1 (33.3)	4 (66.7)	1 (16.7)
Blood urine present	4 (66.7)	0	0	0	1 (33.3)	0	0	0	0	0
Haemoglobin decreased	4 (66.7)	2 (33.3)	1 (33.3)	0	2 (66.7)	2 (66.7)	3 (100)	1 (33.3)	4 (66.7)	4 (66.7)
Lymphocyte count decreased	3 (50.0)	2 (33.3)	2 (66.7)	0	3 (100)	0	2 (66.7)	0	4 (66.7)	3 (50.0)
Neutrophil count decreased	2 (33.3)	1 (16.7)	2 (66.7)	0	2 (66.7)	1 (33.3)	3 (100)	3 (100)	6 (100)	4 (66.7)
Platelet count decreased	2 (33.3)	2 (33.3)	0	0	1 (33.3)	0	1 (33.3)	0	5 (83.3)	0
Red blood cell count decreased	2 (33.3)	2 (33.3)	2 (66.7)	0	3 (100)	0	3 (100)	1 (33.3)	5 (83.3)	1 (16.7)
Weight decreased	2 (33.3)	0	0	0	1 (33.3)	0	2 (66.7)	0	4 (66.7)	1 (16.7)
White blood cell count decreased	4 (66.7)	1 (16.7)	2 (66.7)	0	2 (66.7)	1 (33.3)	3 (100)	1 (33.3)	6 (100)	4 (66.7)
Protein urine present	4 (66.7)	0	1 (33.3)	0	2 (66.7)	0	3 (100)	0	2 (33.3)	0
Blood ALP increased	3 (50.0)	0	1 (33.3)	0	0	0	2 (66.7)	0	3 (50.0)	1 (16.7)
Metabolism and nutrition disorders										
Anorexia	5 (83.3)	1 (16.7)	1 (33.3)	0	2 (66.7)	0	3 (100)	0	5 (83.3)	0
Dehydration	0	0	0	0	2 (66.7)	1 (33.3)	0	0	0	0

Serious adverse events developed in 2 of 6 patients (33.3%) in the 30 mg/m^2/day group, 1 of 3 patients (33.3%) in the 60 mg/m^2/day group, and 1 of 6 patients (16.7%) in the 70 mg/m^2/day group. No serious adverse events were observed in patients in the 40 or 50 mg/m^2/day groups. Serious adverse events observed in the 30 mg/m^2/day group were condition aggravated and pneumonia in 2 patients each (33.3%), hyperglycaemia, hypoglycaemia, neutrophil count decreased, platelet count decreased, white blood cell count decreased, sepsis, and urinary tract infection in 1 patient each (16.7%). Serious adverse events in other dose groups were hydronephrosis in 1 patient (33.3%) in the 60 mg/m^2/day group and atelectasis in 1 patient (16.7%) in the 70 mg/m^2/day group. A causal relationship with FTD-TPI could not be ruled out for neutrophil count decreased, platelet count decreased, white blood cell count decreased, or pneumonia in 1 patient each in the 30 mg/m^2/day group.

No adverse events resulted in discontinuation of FTD-TPI therapy.

4.(iv).(3) Japanese phase II study (Study TAS102-J003)

Adverse events developed in 111 of 113 patients (98.2%) in the FTD-TPI group and 52 of 57 patients (91.2%) in the placebo group, and adverse events for which a causal relationship with study treatment could not be ruled out developed in 109 of 113 patients (96.5%) and 40 of 57 patients (70.2%), respectively. Adverse events observed in ≥10% of patients in any group are listed in the following table.

Adverse events observed in ≥10% of patients in any group

System organ class Preferred term (MedDRA ver.13.1)	No. of patients (%)			
	FTD-TPI group (n = 113)		Placebo group (n = 57)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	111 (98.2)	78 (69.0)	52 (91.2)	9 (15.8)
Gastrointestinal disorders				
Abdominal distension	2 (1.8)	0	6 (10.5)	0
Abdominal pain	22 (19.5)	1 (0.9)	10 (17.5)	0
Diarrhoea	43 (38.1)	7 (6.2)	12 (21.1)	0
Nausea	73 (64.6)	5 (4.4)	16 (28.1)	0
Stomatitis	17 (15.0)	0	6 (10.5)	0
Vomiting	38 (33.6)	4 (3.5)	14 (24.6)	0
General disorders and administration site conditions				
Fatigue	66 (58.4)	7 (6.2)	24 (42.1)	2 (3.5)
Influenza like illness	17 (15.0)	0	1 (1.8)	0
Oedema peripheral	14 (12.4)	1 (0.9)	4 (7.0)	1 (1.8)
Pyrexia	16 (14.2)	0	7 (12.3)	1 (1.8)
Investigation				
ALT increased	10 (8.8)	0	6 (10.5)	0
AST increased	23 (20.4)	2 (1.8)	12 (21.1)	1 (1.8)
Blood albumin decreased	29 (25.7)	1 (0.9)	11 (19.3)	2 (3.5)
Blood bilirubin increased	33 (29.2)	3 (2.7)	7 (12.3)	1 (1.8)
Blood lactate dehydrogenase increased	14 (12.4)	0	13 (22.8)	0
Blood sodium decreased	16 (14.2)	2 (1.8)	4 (7.0)	1 (1.8)
Haematocrit decreased	34 (30.1)	0	4 (7.0)	0
Haemoglobin decreased	82 (72.6)	19 (16.8)	9 (15.8)	3 (5.3)
Lymphocyte count decreased	39 (34.5)	11 (9.7)	7 (12.3)	2 (3.5)
Neutrophil count decreased	81 (71.7)	57 (50.4)	1 (1.8)	0
Platelet count decreased	44 (38.9)	5 (4.4)	1 (1.8)	0
Red blood cell count decreased	37 (32.7)	0	2 (3.5)	0
Weight decreased	23 (20.4)	0	1 (1.8)	0
White blood cell count decreased	86 (76.1)	32 (28.3)	2 (3.5)	0
White blood cell count increased	4 (3.5)	0	7 (12.3)	0
Protein urine present	20 (17.7)	0	6 (10.5)	0
Blood ALP increased	17 (15.0)	3 (2.7)	15 (26.3)	1 (1.8)
Metabolism and nutrition disorders				
Decreased appetite	70 (61.9)	5 (4.4)	19 (33.3)	2 (3.5)
Musculoskeletal and connective tissue disorders				
Back pain	12 (10.6)	0	3 (5.3)	0
Skin and subcutaneous tissue disorders				
Exfoliative rash	12 (10.6)	0	5 (8.8)	0

Serious adverse events developed in 21 of 113 patients (18.6%) in the FTD-TPI group and 5 of 57 patients (8.8%) in the placebo group. Serious adverse events observed in the FTD-TPI group were febrile neutropenia in 4 patients (3.5%), pneumonia, haemoglobin decreased, and decreased appetite in 3 patients each (2.7%), pelvic infection, ileus, small intestinal obstruction, neutrophil count decreased, hepatic failure, and fatigue in 2 patients each (1.8%), sepsis, eye infection, musculoskeletal pain, aspiration, infection, colonic obstruction, small intestinal stenosis, abdominal pain, bone pain, anal fistula, myocardial ischaemia, pneumonitis, white blood cell count decreased, platelet count decreased, disseminated intravascular coagulation, and renal failure in 1 patient each (0.9%). Serious adverse events observed in the placebo group were blood creatinine increased, device related infection, ureteric obstruction, fatigue, rectal obstruction, biliary tract infection, and hypersensitivity in 1 patient each (1.8%). Among these events observed in the FTD-TPI group, a causal relationship with FTD-TPI

therapy could not be ruled out for the following cases: febrile neutropenia in 4 patients; haemoglobin decreased, pneumonia in 3 patients each; pelvic infection, neutrophil count decreased in 2 patients each; or sepsis, eye infection, anal fistula, myocardial ischaemia, fatigue, pneumonia, small intestinal obstruction, colonic obstruction, renal failure, hepatic failure, white blood cell count decreased, platelet count decreased, disseminated intravascular coagulation in 1 patient each. In the placebo group, a causal relationship between the event and study treatment could not be ruled out for 1 patient with rectal obstruction.

Three of the 113 patients (2.7%) in the FTD-TPI group and 1 of the 57 patients (1.8%) in the placebo group discontinued study treatment due to adverse events. Those adverse events were anal fistula, myocardial ischaemia, small intestinal obstruction, colonic obstruction, disseminated intravascular coagulation, hepatic failure, and renal failure in 1 patient each (0.9%) in the FTD-TPI group, and oedema peripheral, device related infection, and blood creatinine increased in 1 patient each (1.8%) in the placebo group. A causal relationship with study treatment could not be ruled out for myocardial ischaemia, small intestinal obstruction, colonic obstruction, disseminated intravascular coagulation, hepatic failure, or renal failure in 1 patient each in the FTD-TPI group.

4.(iv).(4) Foreign phase I study (TAS102-9801 Study)

Adverse events developed in all patients (100%) in the 50, 60, and 100 mg/m^2/day groups. All the patients experienced adverse events for which a causal relationship with FTD-TPI could not be ruled out. Adverse events observed in ≥40% of patients in any group are listed in the following table.

Adverse events observed in ≥40% of patients in any group

COSTART*	No. of patients (%)					
	50 mg/m^2/day group (n = 6)		60 mg/m^2/day group (n = 6)		100 mg/m^2/day group (n = 2)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	6 (100)	4 (66.7)	6 (100)	6 (100)	2 (100)	2 (100)
General disorders						
Abdominal pain	0	0	4 (66.7)	1 (16.7)	0	0
Asthenia	6 (100)	0	5 (83.3)	0	1 (50.0)	0
Pain	4 (66.7)	0	2 (33.3)	0	0	0
Gastrointestinal disorders						
Anorexia	1 (16.7)	0	2 (33.3)	0	1 (50.0)	0
Diarrhoea	1 (16.7)	0	5 (83.3)	2 (33.3)	0	0
Dyspepsia	0	0	1 (16.7)	0	1 (50.0)	0
Nausea	6 (100)	0	4 (66.7)	0	1 (50.0)	1 (50.0)
Vomiting	2 (33.3)	0	4 (66.7)	1 (16.7)	2 (100)	0
Endocrine disorders						
Adrenal cortex insufficiency	0	0	0	0	1 (50.0)	0
Blood and lymphatic system disorders						
Anaemia	0	0	2 (33.3)	0	1 (50.0)	1 (50.0)
Granulocytopenia	4 (66.7)	4 (66.7)	6 (100)	6 (100)	2 (100)	2 (100)
Metabolism and nutrition disorders						
Oedema	0	0	0	0	1 (50.0)	0
Skin and subcutaneous tissue disorders						
Alopecia	0	0	3 (50.0)	0	1 (50.0)	0
Subcutaneous nodule	0	0	0	0	1 (50.0)	0
Sensory abnormalities						
Taste perversion	5 (83.3)	0	2 (33.3)	0	0	0

* Coding Symbols for a Thesaurus of Adverse Reaction Terms, a terminology of adverse events developed by the US Food and Drug Administration

A serious adverse event developed in 1 of 6 patients (16.7%) in the 60 mg/m^2/day group. The event was intestinal obstruction, and a causal relationship between the event and FTD-TPI was ruled out.

An adverse event that led to treatment discontinuation was granulocytopenia observed in 2 of the 2 patients (100%) in the 100 mg/m^2/day group, for which a causal relationship with FTD-TPI was not ruled out.

4.(iv).(5) Foreign phase I study (Study TAS102-9802)

Adverse events developed in all patients (100%) in the 50, 70, 80, 90, 100, and 110 mg/m^2/day groups. All the patients experienced adverse events for which a causal relationship with FTD-TPI could not be ruled out. Adverse events observed in ≥40% of patients in any group are listed in the following table.

Adverse events observed in ≥40% of patients in any group

COSTART	No. of patients (%)					
	50 mg/m^2/day group (n = 3)		70 mg/m^2/day group (n = 6)		80 mg/m^2/day group (n = 3)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	0	6 (100)	3 (50.0)	3 (100)	0
General disorders						
Abdominal pain	0	0	2 (33.3)	0	2 (66.7)	0
Asthenia	2 (66.7)	0	5 (83.3)	0	3 (100)	0
Pyrexia	2 (66.7)	0	1 (16.7)	0	0	0
Headache	0	0	0	0	0	0
Pain	0	0	1 (16.7)	0	2 (66.7)	0
Gastrointestinal disorders						
Anorexia	1 (33.3)	0	2 (33.3)	0	2 (66.7)	0
Diarrhoea	1 (33.3)	0	0	0	1 (33.3)	0
Nausea	2 (66.7)	0	4 (66.7)	0	2 (66.7)	0
Vomiting	2 (66.7)	0	4 (66.7)	0	0	0
Blood and lymphatic system disorders						
Anaemia	0	0	0	0	0	0
Granulocytopenia	0	0	4 (66.7)	3 (50.0)	0	0
Thrombocytopenia	0	0	0	0	0	0
Metabolism and nutrition disorders						
Oedema peripheral	2 (66.7)	0	1 (16.7)	0	0	0
Nervous system disorders						
Dizziness	0	0	0	0	0	0
Dry mouth	2 (66.7)	0	0	0	0	0
Sensory abnormalities						
Taste perversion	2 (66.7)	0	1 (16.7)	0	1 (33.3)	0

Adverse events observed in ≥40% of patients in any group (continued)

COSTART	No. of patients (%)					
	90 mg/m^2/day group (n = 3)		100 mg/m^2/day group (n = 6)		110 mg/m^2/day group (n = 3)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	3 (100)	6 (100)	6 (100)	3 (100)	3 (100)
General disorders						
Abdominal pain	0	0	2 (33.3)	1 (16.7)	0	0
Asthenia	2 (66.7)	0	4 (66.7)	2 (33.3)	3 (100)	0
Pyrexia	2 (66.7)	1 (33.3)	2 (33.3)	0	2 (66.7)	0
Headache	0	0	1 (16.7)	0	2 (66.7)	0
Pain	0	0	2 (33.3)	2 (33.3)	0	0
Gastrointestinal disorders						
Anorexia	2 (66.7)	0	3 (50.0)	1 (16.7)	2 (66.7)	0
Diarrhoea	2 (66.7)	0	2 (33.3)	0	1 (33.3)	0
Nausea	3 (100)	0	4 (66.7)	0	2 (66.7)	0
Vomiting	0	0	2 (33.3)	0	0	0
Blood and lymphatic system disorders						
Anaemia	3 (100)	1 (33.3)	3 (50.0)	0	2 (66.7)	1 (33.3)
Granulocytopenia	3 (100)	3 (100)	6 (100)	6 (100)	3 (100)	3 (100)
Thrombocytopenia	2 (66.7)	0	0	0	0	0
Metabolism and nutrition disorders						
Oedema peripheral	0	0	0	0	0	0
Nervous system disorders						
Dizziness	0	0	0	0	2 (66.7)	0
Dry mouth	0	0	0	0	0	0
Sensory abnormalities						
Taste perversion	1 (33.3)	0	1 (16.7)	0	1 (33.3)	0

Serious adverse events developed in 1 of 6 patients (16.7%) in the 70 mg/m^2/day group and 3 of 6 patients (50.0%) in the 100 mg/m^2/day group. Of them, the event in the 70 mg/m^2/day group was small intestinal obstruction in 1 patient (16.7%), the events in the 100 mg/m^2/day group were back pain, gait abnormal, nystagmus, and ileus in 1 patient each (16.7%). A causal relationship with FTD-TPI was ruled out for all these adverse events.

Adverse events resulting in discontinuation of FTD-TPI therapy were observed in 1 of the 3 patients (33.3%) in the 90 mg/m^2/day group and 1 of the 6 patients (16.7%) in the 100 mg/m^2/day group. Those were granulocytopenia and leukopenia in 1 patient (33.3%) in the 90 mg/m^2/day group, and granulocytopenia in 1 patient (16.7%) in the 100 mg/m^2/day group, and a causal relationship between these adverse events and FTD-TPI therapy could not be ruled out.

4.(iv).(6) Foreign phase I study (Study TAS102-9803)

Adverse events developed in all patients (100%) in the 100, 110, 120, 130, 140, 150, 160, 170, and 180 mg/m^2/day groups, and those for which a causal relationship with FTD-TPI therapy could not be ruled out were observed in 3 of 3 (100%), 3 of 3 (100%), 8 of 9 (88.9%), 3 of 3 (100%), 3 of 3 (100%), 2 of 3 (66.7%), 5 of 6 (83.3%), 3 of 3 (100%), and 6 of 6 patients (100%) in the respective dose groups. Adverse events observed in ≥40% of patients in any group are listed in the following table.

Adverse events observed in ≥40% of patients in any group

System organ class Preferred term (MedDRA ver.5.0)	No. of patients (%)									
	100 mg/m^2/day group (n = 3)		110 mg/m^2/day group (n = 3)		120 mg/m^2/day group (n = 9)		130 mg/m^2/day group (n = 3)		140 mg/m^2/day group (n = 3)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	2 (66.7)	3 (100)	3 (100)	9 (100)	4 (44.4)	3 (100)	0	3 (100)	3 (100)
Blood and lymphatic system disorders										
Anaemia NOS	0	0	1 (33.3)	0	3 (33.3)	2 (22.2)	0	0	2 (66.7)	1 (33.3)
Neutropenia	0	0	0	0	1 (11.1)	1 (11.1)	0	0	0	0
Gastrointestinal disorders										
Abdominal distension	0	0	0	0	1 (11.1)	0	0	0	1 (33.3)	0
Abdominal pain NOS	0	0	3 (100)	2 (66.7)	2 (22.2)	0	0	0	1 (33.3)	0
Constipation	0	0	3 (100)	0	2 (22.2)	0	0	0	2 (66.7)	0
Diarrhea NOS	1 (33.3)	0	2 (66.7)	0	4 (44.4)	0	0	0	2 (66.7)	0
Queasy	3 (100)	0	3 (100)	0	4 (44.4)	0	1 (33.3)	0	3 (100)	0
Small intestinal obstruction NOS	0	0	2 (66.7)	2 (66.7)	0	0	0	0	0	0
Vomiting NOS	2 (66.7)	0	2 (66.7)	0	1 (11.1)	0	0	0	2 (66.7)	0
General disorders and administration site conditions										
Chest pain	2 (66.7)	0	0	0	0	0	0	0	0	0
Fatigue	2 (66.7)	0	2 (66.7)	1 (33.3)	4 (44.4)	0	2 (66.7)	0	3 (100)	0
Pyrexia	0	0	0	0	2 (22.2)	0	0	0	2 (66.7)	0
Weakness	0	0	1 (33.3)	1 (33.3)	0	0	0	0	2 (66.7)	0
Metabolism and nutrition disorders										
Decreased appetite NOS	0	0	0	0	1 (11.1)	0	2 (66.7)	0	1 (33.3)	0
Dehydration	0	0	0	0	0	0	0	0	2 (66.7)	1 (33.3)
Musculoskeletal and connective tissue disorders										
Back pain	0	0	0	0	0	0	0	0	2 (66.7)	0
Nervous system disorders										
Headache NOS	0	0	0	0	2 (22.2)	0	1 (33.3)	0	2 (66.7)	0
Vascular disorders										
Hot flush NOS	0	0	0	0	0	0	1 (33.3)	0	2 (66.7)	0

NOS, not otherwise specified

Adverse events observed in ≥40% of patients in any group (continued)

System organ class Preferred term (MedDRA ver.5.0)	No. of patients (%)							
	150 mg/m^2/day group (n = 3)		160 mg/m^2/day group (n = 6)		170 mg/m^2/day group (n = 3)		180 mg/m^2/day group (n = 6)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	3 (100)	6 (100)	2 (33.3)	3 (100)	3 (100)	6 (100)	4 (66.7)
Blood and lymphatic system disorders								
Anaemia NOS	0	0	1 (16.7)	1 (16.7)	1 (33.3)	0	1 (16.7)	0
Neutropenia	1 (33.3)	1 (33.3)	1 (16.7)	0	2 (66.7)	2 (66.7)	4 (66.7)	4 (66.7)
Gastrointestinal disorders								
Abdominal distension	2 (66.7)	1 (33.3)	2 (33.3)	0	1 (33.3)	0	1 (16.7)	0
Abdominal pain NOS	0	0	4 (66.7)	0	1 (33.3)	1 (33.3)	2 (33.3)	1 (16.7)
Constipation	2 (66.7)	1 (33.3)	1 (16.7)	0	2 (66.7)	1 (33.3)	1 (16.7)	1 (16.7)
Diarrhoea NOS	1 (33.3)	0	0	0	3 (100)	0	4 (66.7)	0
Queasy	3 (100)	1 (33.3)	4 (66.7)	0	3 (100)	2 (66.7)	6 (100)	0
Small intestinal obstruction NOS	0	0	0	0	1 (33.3)	1 (33.3)	0	0
Vomiting NOS	2 (66.7)	1 (33.3)	0	0	2 (66.7)	0	2 (33.3)	0
General disorders and administration site conditions								
Chest pain	0	0	0	0	1 (33.3)	0	1 (16.7)	0
Fatigue	2 (66.7)	1 (33.3)	2 (33.3)	0	2 (66.7)	0	6 (100)	0
Pyrexia	1 (33.3)	0	3 (50.0)	0	2 (66.7)	0	0	0
Weakness	0	0	0	0	1 (33.3)	0	0	0
Metabolism and nutrition disorders								
Decreased appetite NOS	2 (66.7)	0	0	0	0	0	1 (16.7)	0
Dehydration	0	0	0	0	2 (66.7)	1 (33.3)	0	0
Musculoskeletal and connective tissue disorders								
Back pain	0	0	0	0	1 (33.3)	0	2 (33.3)	1 (16.7)
Nervous system disorders								
Headache NOS	1 (33.3)	0	5 (83.3)	0	1 (33.3)	0	2 (33.3)	0
Vascular disorders								
Hot flush NOS	0	0	1 (16.7)	0	0	0	1 (16.7)	0

NOS, not otherwise specified

Serious adverse events developed in 1 of 3 patients (33.3%) in the 100 mg/m^2/group, 2 of 3 patients (66.7%) in the 110 mg/m^2/group, 1 of 9 patients (11.1%) in the 120 mg/m^2/group, 1 of 3 patients (33.3%) in the 140 mg/m^2/group, 1 of 3 patients (33.3%) in the 150 mg/m^2/day group, 1 of 6 patients (16.7%) in the 160 mg/m^2/day group, and 1 of 3 patients (33.3%) in the 170 mg/m^2/group. Those were deep vein thrombosis in 1 patient (33.3%) in the 100 mg/m^2/day group, small intestinal obstruction in 2 patients (66.7%) in the 110 mg/m^2/day group, cholangitis in 1 patient (11.1%) in the 120 mg/m^2/day group, urinary tract infection in 1 patient (33.3%) in the 140 mg/m^2/day group, vomiting in 1 patient (33.3%) in the 150 mg/m^2/day group, respiratory arrest in 1 patient (16.7%) in the 160 mg/m^2/day group, and small intestinal obstruction in 1 patient (33.3%) in the 170 mg/m^2/day group. A causal relationship with FTD-TPI therapy could not be ruled out for deep vein thrombosis in the patient in the 100 mg/m^2/day group.

Treatment with FTD-TPI was discontinued due to adverse events in 1 of 6 patients (16.7%) in the 160 mg/m^2/day group, 2 of 3 patients (66.7%) in the 170 mg/m^2/day group, and 2 of 6 patients (33.3%) in the 180 mg/m^2/day group. These adverse events were respiratory arrest in 1 patient (16.7%) in the 160

mg/m^2/day group, queasy, vomiting, and small intestinal obstruction in 1 patient each (33.3%) in the 170 mg/m^2/day group, and granulocytopenia, balance disorder, confusion, vision disorder, and paraesthesia in 1 patient each (16.7%) in the 180 mg/m^2/day group. A causal relationship with FTD-TPI therapy could not be ruled out for 1 patient each with queasy and vomiting in the 170 mg/m^2/day group, or for 1 patient each with granulocytopenia, balance disorder, confusion, vision disorder, and paraesthesia in the 180 mg/m^2/day group.

4.(iv).(7) Foreign phase I study (Study TAS102-9804)

Adverse events developed in all patients (100%) in the 50 mg/m^2/day group, in the 60 mg/m^2/day group before study protocol amendment (hereinafter referred to "pre-amendment"), in the 60 mg/m^2/day group after study protocol amendment (hereinafter referred to "post-amendment"), and in the 80 mg/m^2/kg group. All patients in the study experienced adverse events for which a causal relationship with FTD-TPI could not be ruled out. Adverse events observed in ≥40% of patients in any group are listed in the following table.

Adverse events observed in ≥40% of patients in any group

System organ class Preferred term (MedDRA ver.9.0)	No. of patients (%)							
	50mg/m^2/day group (n = 9)		60mg/m^2/day group*1 (n = 5)		60mg/m^2/day group*2 (n = 2)		80mg/m^2/day group (n = 3)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	9 (100)	8 (88.9)	5 (100)	5 (100)	2 (100)	2 (100)	3 (100)	3 (100)
Blood and lymphatic system disorders								
Anaemia	7 (77.8)	1 (11.1)	5 (100)	1 (20.0)	2 (100)	1 (50.0)	3 (100)	0
Neutropenia	8 (88.9)	6 (66.7)	5 (100)	5 (100)	2 (100)	2 (100)	3 (100)	3 (100)
Thrombocytopenia	2 (22.2)	0	3 (60.0)	1 (20.0)	2 (100)	1 (50.0)	1 (33.3)	0
Cardiac disorders								
Tachycardia	0	0	0	0	1 (50.0)	0	0	0
Gastrointestinal disorders								
Constipation	4 (44.4)	1 (11.1)	3 (60.0)	1 (20.0)	0	0	2 (66.7)	1 (33.3)
Diarrhoea	2 (22.2)	0	3 (60.0)	0	2 (100)	0	1 (33.3)	1 (33.3)
Nausea	6 (66.7)	0	4 (80.0)	0	1 (50.0)	0	2 (66.7)	1 (33.3)
Stomatitis	2 (22.2)	0	3 (60.0)	0	0	0	1 (33.3)	0
Vomiting	6 (66.7)	0	4 (80.0)	0	1 (50.0)	0	2 (66.7)	1 (33.3)
General disorders and administration site conditions								
Chest pain	0	0	0	0	1 (50.0)	0	0	0
Chills	0	0	0	0	1 (50.0)	0	0	0
Fatigue	5 (55.6)	2 (22.2)	4 (80.0)	1 (20.0)	1 (50.0)	1 (50.0)	3 (100)	1 (33.3)
Pyrexia	2 (22.2)	0	1 (20.0)	0	1 (50.0)	0	0	0
Infections and infestations								
Urinary tract infection	2 (22.2)	0	1 (20.0)	0	1 (50.0)	0	0	0
metabolism and nutrition disorders								
Hypocalcaemia	0	0	0	0	1 (50.0)	0	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	3 (33.3)	0	2 (40.0)	1 (20.0)	0	0	0	0
Myalgia	4 (44.4)	1 (11.1)	1 (20.0)	0	0	0	3 (100)	0
Nervous system disorders								
Dizziness	1 (11.1)	0	0	0	1 (50.0)	0	1 (33.3)	0
Respiratory, thoracic and mediastinal disorders								
Dyspnoea exertional	0	0	0	0	1 (50.0)	0	0	0
Nasal congestion	1 (11.1)	0	3 (60.0)	0	0	0	0	0
Skin and subcutaneous tissue disorders								
Alopecia	3 (33.3)	0	3 (60.0)	0	1 (50.0)	0	1 (33.3)	0
Vascular disorders								
Hot flush	0	0	0	0	1 (50.0)	0	0	0

*1, pre-amendment; *2, post-amendment

Serious adverse events developed in 1 of 9 patients (11.1%) in the 50 mg/m^2/day group, and 1 of 5 patients (20.0%) in the 60 mg/m^2/day group (pre-amendment), and the events were pulmonary embolism and neck pain, respectively. A causal relationship with FTD-TPI was ruled out for these events.

FTD-TPI therapy was discontinued due to adverse events in 2 of 9 patients (22.2%) in the 50 mg/m^2/day group, and 2 of the 2 patients (100%) in the 60 mg/m^2/day (post-amendment). These adverse events were neutropenia and thrombocytopenia in 1 patient each (11.1%) in the 50 mg/m^2/day group, neutropenia in 2 of 2 patients (100%) and thrombocytopenia in 1 of 2 patients (50%) in the 60 mg/m^2/day (post-amendment). A causal relationship with FTD-TPI could not be ruled out for these events.

4.(iv).(8) Foreign phase I study (Study TAS102-9805)

Adverse events developed in all (100%) patients in the 60, 70, and 80 mg/m^2/day groups, and a causal relationship with FTD-TPI could not be ruled out for all the events. Adverse events observed in ≥40% of patients in any group are listed in the following table.

Adverse events observed in ≥40% of patients in any group

System organ class Preferred term (MedDRA ver.7.1)	No. of patients (%)					
	60 mg/m^2/day group (n = 3)		70 mg/m^2/day group (n = 6)		80 mg/m^2/day group (n = 6)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	3 (100)	6 (100)	6 (100)	6 (100)	6 (100)
Blood and lymphatic system disorders						
Anaemia	2 (66.7)	0	2 (33.3)	0	5 (83.3)	1 (16.7)
Neutropenia	3 (100)	3 (100)	6 (100)	5 (83.3)	5 (83.3)	5 (83.3)
Gastrointestinal disorders						
Abdominal pain	1 (33.3)	0	2 (33.3)	1 (16.7)	4 (66.7)	3 (50.0)
Abdominal pain upper	1 (33.3)	0	2 (33.3)	0	3 (50.0)	1 (16.7)
Diarrhoea	2 (66.7)	0	5 (83.3)	0	5 (83.3)	2 (33.3)
Meteorism	2 (66.7)	0	4 (66.7)	0	3 (50.0)	0
Nausea	2 (66.7)	0	3 (50.0)	1 (16.7)	5 (83.3)	0
Vomiting	1 (33.3)	0	2 (33.3)	1 (16.7)	6 (100)	0
General disorders and administration site conditions						
Asthenia	0	0	0	0	3 (50.0)	0
Fatigue	3 (100)	0	3 (50.0)	1 (16.7)	5 (83.3)	2 (33.3)
Metabolism and nutrition disorders						
Anorexia	1 (33.3)	0	3 (50.0)	0	3 (50.0)	0
Nervous system disorders						
Dizziness	1 (33.3)	0	1 (16.7)	0	3 (50.0)	0
Dysgeusia	2 (66.7)	0	0	0	3 (50.0)	0
Headache	0	0	0	0	3 (50.0)	0
Skin and subcutaneous tissue disorders						
Alopecia	2 (66.7)	0	0	0	0	0

Serious adverse events developed in 1 of 6 patients (16.7%) in the 70 mg/m^2/day group, and 3 of 6 patients (50%) in the 80 mg/m^2/day group. The serious adverse events observed were haematuria and hyperbilirubinaemia in 1 patient each (16.7%) in the 70 mg/m^2/group, and colitis, diarrhoea, duodenal fistula, and metastases to liver in 1 patient each (16.7%) in the 80 mg/m^2/group. A causal relationship with FTD-TPI therapy could not be ruled out for colitis in the patient in the 80 mg/m^2/day group.

FTD-TPI therapy was discontinued in 1 of 3 patients (33.3%) in the 60 mg/m^2/day group, 2 of 6 patients (33.3%) in the 70 mg/m^2/day group, and 2 of 6 patients (33.3%) in the 80 mg/m^2/day group. The adverse events resulting in treatment discontinuation were neutropenia in 1 patient (33.3%) in the 60 mg/m^2/day group, ascites, nausea, and vomiting in 1 patient each (16.7%) in the 70 mg/m^2/day group, and neutropenia and metastases to liver in 1 patient each (16.7%) in the 80 mg/m^2/day group. A causal relationship with FTD-TPI could not be ruled out in neutropenia in 1 patient in the 60 mg/m^2/kg group, nausea and vomiting in 1 patient each in the 70 mg/m^2/day group, or neutropenia in 1 patient in the 80 mg/m^2/group.

4.(iv).(9) Foreign phase II study (Study TAS102-9806)

Adverse events developed in all of the 18 patients (100%) enrolled in the study, and all patients experienced adverse events for which a causal relationship with FTD-TPI could not be ruled out. Adverse events observed in ≥20% of patients in any group are listed in the following table.

Adverse events observed in ≥20% of patients in any group

System organ class Preferred term (MedDRA ver.8.0)	No. of patients (%) 50 mg/m^2/day group (n = 18)	
	All Grades	Grade ≥3
All adverse events	18 (100)	13 (72.2)
Blood and lymphatic system disorders		
Anaemia	11 (61.1)	0
Granulocytopenia	9 (50.0)	6 (33.3)
Leukopenia	8 (44.4)	3 (16.7)
Gastrointestinal disorders		
Constipation	9 (50.0)	0
Diarrhoea	8 (44.4)	0
Dysgeusia	4 (22.2)	0
Dysphagia	4 (22.2)	0
Nausea	16 (88.9)	1 (5.6)
Vomiting	12 (66.7)	0
General disorders and administration site conditions		
Fatigue	16 (88.9)	2 (11.1)
Pyrexia	5 (27.8)	0
Metabolism and nutrition disorders		
Anorexia	10 (55.6)	0
Musculoskeletal and connective tissue disorders		
Back pain	9 (50.0)	1 (5.6)
Musculoskeletal pain	5 (27.8)	1 (5.6)
Nervous system disorders		
Dizziness	6 (33.3)	0
Psychiatric disorders		
Insomnia	8 (44.4)	0
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	7 (38.9)	0
Hiccups	6 (33.3)	0
Skin and subcutaneous tissue disorders		
Alopecia	4 (22.2)	0
Hyperhidrosis	4 (22.2)	0

Serious adverse events developed in 6 of 18 patients (33.3%). Serious adverse events observed in this study were disease progression in 2 patients (11.1%), and melaena, hepatic failure, hypovolaemia, metastases to central nervous system, hepatic encephalopathy, renal failure acute, and pneumonia aspiration in 1 patient each (5.6%), and a causal relationship with FTD-TPI was ruled out for all these adverse events.

Four of the 18 patients (22.2%) discontinued FTD-TPI due to adverse events. Adverse events resulting in discontinuation of FTD-TPI therapy were fatigue in 2 patients (11.1%), metastases to central nervous

system and pneumonia aspiration in 1 patient each (5.6%). A causal relationship with FTD-TPI therapy could not be ruled out for fatigue in 2 patients.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

To be reported in the Review Report (2).

2. PMDA's conclusion on the results of GCP on-site inspection

To be reported in the Review Report (2).

IV. Overall evaluation

Based on the data submitted by the applicant, PMDA has concluded that FTD-TPI is expected to be effective for the treatment of unresectable advanced or recurrent colorectal cancer, and the safety of FTD-TPI is acceptable in view of their observed benefits. FTD-TPI is a combination of FTD, a nucleoside antitumor agent that interferes with DNA function, and TPI, an inhibitor of thymidine phosphorylase that plays a major role in the metabolism of FTD, and is expected to be a clinically significant option for the treatment of unresectable advanced or recurrent colorectal cancer. The efficacy, clinical positioning, indications, dosage and administration, and post-marketing investigations of FTD-TPI will be further discussed at the Expert Discussion.

PMDA considers that FTD-TPI may be approved if it can be concluded that there are no particular problems based on comments from the Expert Discussion.

Review Report (2)

January 14, 2014

I. Product submitted for registration

[Brand name] Lonsurf combination tablets T15 and Lonsurf combination tablets T20
[Non-proprietary name] Trifluridine/tipiracil hydrochloride
[Name of applicant] Taiho Pharmaceutical Co., Ltd.
[Date of application] February 26, 2013

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy and clinical positioning

The Japanese phase II study (TAS102-J003) was conducted to explore the efficacy of the combination product (FTD-TPI) containing trifluridine and tipiracil hydrochloride at molar ratio of 2:1 in patients with unresectable or recurrent colorectal cancer who had a history of 2 or more chemotherapies and who were refractory or intolerant to fluoropyrimidines, irinotecan hydrochloride (CPT-11), and oxaliplatin (L-OHP) (hereinafter referred to as “patients with unresectable or recurrent colorectal cancer who are refractory or intolerant to standard chemotherapy”). Based on the results of the study, PMDA has concluded as follows: Efficacy of FTD-TPI has not been confirmed yet, however, taking account of the findings that FTD-TPI improved overall survival (OS) and indicated an excellent clinical usefulness in the treatment of patients with unresectable or recurrent colorectal cancer who are refractory or intolerant to standard chemotherapy, the efficacy of FTD-TPI is expected for the treatment of such patients.

As a result of its review in "4.(iii).B.(3) Clinical Positioning" in the Review Report (1), PMDA has concluded that FTD-TPI is recommended as a treatment option for patients with unresectable or recurrent colorectal cancer refractory to other antitumor drugs including regorafenib hydrate (regorafenib) and for whom no standard therapies including treatment with anti-EGFR antibodies are available.

At the Expert Discussion, expert advisors supported the above conclusion by PMDA, and expressed the following opinions.

- When the efficacy of a drug is concluded only on the basis of exploratory studies such as the Japanese phase II study of FTD-TPI, the likelihood of being truly effective in this patient population is lower as compared with when the conclusion in terms of efficacy is made on the basis of phase

III studies. It is thus reasonable to make an approval decision after a review of the results of Study TAS102-J003, as well as the results of the global Phase III study (TPU-TAS-102-301), which is currently underway to confirm the superiority of FTD-TPI over placebo in terms of OS in patients with colorectal cancer refractory to standard chemotherapies. However, taking into account that FTD-TPI will be indicated for patients with colorectal cancer refractory to standard therapies, making FTD-TPI available in clinical settings on the basis of the results of Study TAS102-J003 is of a certain significance.

- If no benefits outweighing the risks of FTD-TPI are shown after reviewing the results of Study TPU-TAS-102-301 within a certain period of time post-approval, appropriate measures should be taken including reconsideration of whether or not the marketing approval of FTD-TPI should be maintained.

PMDA considers as follows:
Study TAS102-J003 was conducted in patients with unresectable or recurrent colorectal cancer who are refractory or intolerant to standard chemotherapy. Although no drugs were indicated for this patient population as of February 26, 2013 when the application for FTD-TPI was submitted, regorafenib was approved on March 25, 2013, and patients have had an additional treatment option that was not present at the time of filing of the application for FTD-TPI. Thus, FTD-TPI cannot be recommended over regorafenib until the results of Study TPU-TAS-102-301 are obtained. However, FTD-TPI is a clinically significant treatment option for the patients who are refractory to standard therapies on the basis of the fact that FTD-TPI prolonged OS which indicated an excellent clinical usefulness in Japanese patients, and that there is a certain number of patients who are refractory to treatment with regorafenib.

Based on the comprehensive risk-benefit assessment of FTD-TPI, PMDA has concluded that FTD-TPI may be administered to patients with unresectable or recurrent colorectal cancer refractory to standard therapies provided that the following 4 measures are taken. When the results of ongoing Study TPU-TAS-102-301 become available, the applicant should provide appropriate information on the study promptly and evaluate the study results without delay.

(1) The patient or the family member(s) should be informed clearly of all available options for the treatment of colorectal cancer as well as the fact that no confirmatory studies have been conducted for FTD-TPI, before the consent for treatment with FTD-TPI is obtained.
(2) Eligible patients for the treatment with FTD-TPI should be selected carefully by physicians with adequate knowledge and experience in cancer chemotherapy.
(3) Treatment with FTD-TPI should be limited to patients who are refractory to standard therapies.
(4) Appropriate use of FTD-TPI should be thoroughly ensured through measures including (1) to (3) above after the market launch.

PMDA requested the applicant to take appropriate measures to ensure the requirements above, and the applicant accepted to follow the requirements. The applicant also answered that it will submit a written statement that it will withdraw the marketing authorization for FTD-TPI if the results of ongoing Study

TPU-TAS-102-301 reveal a concern about the lack of beneficial effects of FTD-TPI on overall survival.

PMDA accepted the applicant's explanation.

(2) Safety

As a result of its review in "4.(iii).B.(2) Safety" in the Review Report (1), PMDA has concluded that the patient during FTD-TPI therapy should be observed carefully for bone marrow suppression, infections, gastrointestinal symptoms (diarrhea, nausea, vomiting, decreased appetite), peripheral neuropathy, cardiac disorders, ileus, interstitial lung disease, and hepatic impairment. In view of the above points, PMDA has also concluded that FTD-TPI is tolerable in Japanese patients with colorectal cancer if physicians with sufficient knowledge and experience in cancer chemotherapy monitor their patients carefully for adverse events, manage adverse events if they occur, and perform appropriate measures such as dose reduction, treatment interruption or discontinuation.

At the Expert Discussion, expert advisers supported the conclusion by PMDA.

(3) Indications

As a result of its review in "4.(iii).B.(4) Indications" in the Review Report (1), PMDA has concluded that FTD-TPI should be indicated for patients with unresectable or recurrent colorectal cancer who are refractory to other antitumor drugs including regorafenib, and who are ineligible for any standard therapies including those using anti-EGFR antibodies. PMDA has also concluded that FTD-TPI may be indicated for unresectable advanced or recurrent colorectal cancer with the following precautions in the "Precautions for Indications" section in order to help physicians to appropriately select patients.

Precautions for Indications

- The efficacy and safety of FTD-TPI in first-line or second-line chemotherapy have not been established.
- The efficacy and safety of FTD-TPI in adjuvant chemotherapy have not been established.
- Physicians should be acquainted with the prior treatment history of the patients enrolled in the clinical studies of FTD-TPI via information in the Clinical Studies section in order to fully understand the efficacy and safety of FTD-TPI, and consider carefully for other treatment options before selecting eligible patients for FTD-TPI treatment.

At the Expert Discussion, expert advisers supported the above conclusion by PMDA, and expressed the following opinions.

- Since at present no results of Study TPU-TAS-102-301 have been obtained, clear precautions should be included in the "Indications" section to state that FTD-TPI is indicated for patients with colorectal cancer refractory to standard therapies including those using regorafenib.
- The package insert should include appropriate information stating that Study TAS102-J003 was conducted to explore the efficacy of FTD-TPI, and no results of confirmatory studies have been obtained to date.

PMDA considers as follows:
Since no results of Study TPU-TAS-102-301 have been obtained to date, the "Indications" section should clearly describe that FTD-TPI is indicated only for patients who are ineligible for standard chemotherapies including those using regorafenib, and the "Precautions for Indications" section should include an alert about the fact that no efficacy data have been obtained from confirmatory studies. PMDA considers that the necessity of this alert should be reviewed when the clinical positioning of FTD-TPI has been investigated on the basis of the results of ongoing Study TPU-TAS-102-301 and other relevant data.

PMDA requested the applicant to describe the "Indications" and "Precautions for Indications" sections as follows, and the applicant accepted it.

Indications
Unresectable advanced or recurrent colorectal cancer (only if refractory to standard therapies)

Precautions for Indications
- No results of confirmatory studies of FTD-TPI have been obtained.
- The efficacy and safety of FTD-TPI in first-line or second-line chemotherapy have not been established.
- The efficacy and safety of FTD-TPI in adjuvant chemotherapy have not been established.
- Physicians should be acquainted with the prior treatment history of the patients enrolled in the clinical studies of FTD-TPI via information in the Clinical Studies section in order to fully understand the efficacy and safety of FTD-TPI, and consider carefully for other treatment options before selecting eligible patients for FTD-TPI treatment.

(4) Dosage and administration
As a result of its review in "4.(iii).B.(5) Dosage and administration" in the Review Report (1), PMDA has concluded that the dosage and administration may be specified as proposed by the applicant as follows: “the usual initial adult dose of the combination product of trifluridine and tipiracil tydrochloride (FTD-TPI) is determined based on body surface area (BSA) and shown in the dosing table below, which presents predefined ranges of BSA and the corresponding initial doses (on the basis of trifluridine at approximately 35 mg/m^2/dose). FTD-TPI is orally administered twice daily, after breakfast and after supper in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period. The dose may be reduced according to the patient’s condition.” PMDA has concluded that the "Precautions for Dosage and Administration" section should contain the descriptions proposed by the applicant to provide alerts. PMDA has also concluded that additional precautions should be included in the package insert on the use of FTD-TPI in combination with fluoropyrimidines, fluoropyrimidine therapies including folinate/tegafur/uracil therapy, antifungal drug flucytosine, or antifolate drugs including methotrexate and pemetrexed sodium hydrate (hereinafter referred collectively to as "fluoropyrimidines and other related anti-tumor agents").

*: The table of standard initial doses is not included in this section.

At the Expert Discussion, expert advisers supported the conclusion by PMDA and provided the following opinions.

- Since FTD-TPI, an antimetabolite, shares a similar chemical structure as fluoropyrimidine antitumor drugs, it is preferable that alerts on the use in combination with fluoropyrimidines and other related anti-tumor agents be provided in the Warnings section as with currently available fluoropyrimidine antitumor drugs.

In view of comments from the Expert Discussion, PMDA has concluded that the Dosage and Administration section will be as proposed by the applicant, and that the Warnings section and the Precautions for Dosage and Administration section will contain the descriptions below to provide alerts and information. PMDA has concluded that the Precautions for Dosage and Administration section should alert the fact that C_{max} of trifluridine increases when FTD-TPI is administered in the fasted state [see "4.(i).B.(1) Effects of food"].

Warnings

- Caution should be exercised when FTD-TPI is used in combination with fluoropyrimidines, fluoropyrimidine therapies including folinate/tegafur/uracil therapy, antifungal drug flucytosine, or antifolate drugs including methotrexate and pemetrexed sodium hydrate because serious adverse drug reactions such as bone marrow suppression may develop.

Precautions for Dosage and Administration

- The efficacy and safety of FTD-TPI in combination with other antitumor drugs have not been established.
- FTD-TPI should not be administered to patients in the fasted state because C_{max} of trifluridine is higher in the fasted state than in the postprandial state.
- During treatment with FTD-TPI, the criteria below should be referred to whenever dose reduction or treatment interruption is necessary.
  - FTD-TPI should not be administered to patients who do not meet the criteria for starting treatment at the beginning of each cycle. Treatment with FTD-TPI should be interrupted when adverse events develop and meet the criteria for treatment interruption, and should be restarted after the adverse events have subsided to the levels meeting the criteria for resuming treatment.

	Criteria for starting/resuming treatment	Criteria for treatment interruption
Hemoglobin	≥8.0 g/dL	<7.0 g/dL
Neutrophil count	≥1500/mm^3	<1000/mm^3
Platelet count	≥75,000/mm^3	<50,000/mm^3
Total bilirubin	≤1.5 mg/dL	>2.0 mg/dL
AST, ALT	≤2.5 × ULN (≤5 × ULN for patients with liver metastasis)	>2.5 × ULN (≥5 × ULN for patients with liver metastasis)
Creatinine	≤1.5mg/dL	>1.5mg/dL
Peripheral neuropathy	Grade ≤2	Grade ≥3
Toxicity other than haematotoxicity	Grade ≤1 (excluding alopecia, dysgeusia, pigmentation, and symptoms due to primary disease)	Grade ≥3

(CTCAE v3.0 grading)
AST, aspartate aminotransferase; ALT, alanine aminotransferase
ULN, upper limit of normal

- When adverse events meeting the criteria for dose reduction develop in the previous cycle (including the rest periods), the dose for the next cycle should be reduced by a unit of 10 mg/day. The daily dose should be 30 mg/day at minimum.

	Criteria for dose reduction
Neutrophil count	<500/mm^3
Platelet count	<50,000/mm^3

・ When FTD-TPI is administered at a dose of 50 mg/day, 20 mg should be administered after breakfast and 30 mg after supper.

PMDA requested the applicant to take measures appropriately on the matters described above, and the applicant accepted it.

(5) Risk management plan (draft)

The applicant has planned a use-results survey of FTD-TPI to investigate the safety of FTD-TPI treatment in patients with unresectable advanced or recurrent colorectal cancer in routine clinical use with a target number of patients of 800 and an observation period covering 4 treatment cycles. The priority investigation items in the survey will be bone marrow suppression, infections, and the presence/absence and severity of renal or hepatic impairment at baseline.

As a result of its review in "4.(iii).B.(6) Post-marketing surveillance" in the Review Report (1), PMDA has concluded that a post-marketing surveillance should be conducted to assess the safety of FTD-TPI in routine clinical use in Japan. PMDA has also concluded that the applicant may conduct the use-results survey with the priority investigation items, target number of patients, and observation period as planned. Furthermore, PMDA has concluded that as soon as the results of the global phase III study (TPU-TAS-102-301) become available, efficacy and safety data should be assessed in detail without delay in order to determine whether the use-results survey plan should be modified or not and whether additional pharmacovigilance activities and risk minimization actions are needed or not, and that the results of the survey should be provided to healthcare providers in clinical settings without delay.

At the Expert Discussion, expert advisers supported the conclusion by PMDA.

In view of the above discussions on the proposed risk management plan, PMDA has concluded that it is appropriate, at present, to include the following safety and efficacy specifications, and conduct additional pharmacovigilance activities, investigation/studies on the efficacy, and additional risk minimization actions.

Safety and efficacy specifications in the risk management plan

Safety specifications		
Important identified risks	Important potential risks	Important missing information
・Bone marrow suppression ・Infections	• Ileus • Cardiac disorders • Interstitial lung disease	- Administration to patients with renal impairment - Administration to patients with hepatic impairment
Efficacy specifications		
・Efficacy in routine clinical use		

Outline of additional pharmacovigilance activities, contents of surveillance/studies on efficacy, and additional risk minimization actions

Additional pharmacovigilance activities*	Surveillance/studies on efficacy*	Additional risk minimization actions
・Early post-marketing phase vigilance ・Drug use-results survey [see the table below for the outline]	・Drug use-results survey [see the table below for the outline]	・Providing information through early post-marketing phase vigilance ・Measures to prevent misuse

*: The risk management plan does not include Study TPU-TAS-102-301 because it will be continued as a clinical trial.

Draft outline of drug use-results survey

Purpose	Assessment of safety and other features of FTD-TPI in routine clinical use
Methods	Central registration system
Participants	Patients with unresectable advanced or recurrent colorectal cancer
Observation period	4 cycles
Target number of patients	800 patients
Priority investigation items	Bone marrow suppression, infections, and the presence/absence and severity of renal or hepatic impairment at baseline

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. PMDA has concluded that there should be no major problems with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

A GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1.1). The inspection revealed that investigators in some institutions violated the criteria for contraindication to concomitant medications,

or did not record that informed consent for continuing the study was obtained from participants after providing information that possibly affected their willingness to continue the study. As mentioned above, there were some points to be improved in terms of GCP, but appropriate measures were taken for them. PMDA has concluded that the clinical studies of FTD-TPI were generally conducted according to the GCP, and that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

As a result of its review, PMDA has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following conditions, provided that appropriate cautions will be included in the package insert and information concerning the proper use of the product will be provided appropriately after the market launch, and the product will be used by physicians with sufficient knowledge and experience in cancer chemotherapy in medical institutions fully capable of providing treatment in emergency. The re-examination period for the product is 8 years. Trifluridine, one of the drug substances, and the drug product are classified as powerful drugs. The product is not classified as a biological product or a specified biological product.

[Indication] Unresectable advanced or recurrent colorectal cancer (only if refractory to standard therapies)

[Dosage and Administration]

The usual initial adult dose of the combination product of trifluridine and tipiracil tydrochloride (FTD-TPI) is determined based on body surface area (BSA) and shown in the dosing table below, which presents predefined ranges of BSA and the corresponding initial doses (on the basis of trifluridine at approximately 35 mg/m^2/dose). FTD-TPI is orally administered twice daily, after breakfast and after supper, in 28-day cycles, each consisting of two 5 days on/2 days off treatment sub-cycles, followed by a 14-day rest period.

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

Body surface area (m^2)	Initial dose (as trifluridine)
<1.07	35 mg/dose (70 mg/day)
1.07 - <1.23	40 mg/dose (80 mg/day)
1.23 - <1.38	45 mg/dose (90 mg/day)
1.38 - <1.53	50 mg/dose (100 mg/day)
1.53 - <1.69	55 mg/dose (110 mg/day)
1.69 - <1.84	60 mg/dose (120 mg/day)
1.84 - <1.99	65 mg/dose (130 mg/day)
1.99 - <2.15	70 mg/dose (140 mg/day)
≥2.15	75 mg/dose (150 mg/day)

[Conditions for Approval]

The applicant is required to submit the results of ongoing phase III study that is conducted to confirm the efficacy and safety of the product in patients with unresectable advanced or recurrent colorectal cancer without delay after the completion of the study for review.

[Warnings]

1. Cancer chemotherapy including FTD-TPI should be provided only under supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions fully capable of providing treatment in emergency. Patients or their family members should be thoroughly informed of the efficacy and risk of FTD-TPI, and informed consent should be obtained from them before starting treatment.
2. Caution should be exercised when FTD-TPI is used in combination treatment/therapy with fluoropyrimidines; fluoropyrimidine therapies including folinate/tegafur/uracil therapy; antifungal drug flucytosine; or antifolate drugs including methotrexate and pemetrexed sodium hydrate because serious adverse drug reactions such as bone marrow suppression may develop.

[Contraindications]

1. Patients with a history of serious hypersensitivities to any components of FTD-TPI
2. Pregnant women or women who may be pregnant

[Precautions for Indications]

1. No results of confirmatory studies of FTD-TPI have been obtained.
2. The efficacy and safety of FTD-TPI in first-line or second-line chemotherapy have not been established.
3. The efficacy and safety of FTD-TPI in adjuvant chemotherapy have not been established.
4. Physicians should be acquainted with the prior treatment history of the patients enrolled in the clinical studies of FTD-TPI via information in the Clinical Studies section in order to fully understand the efficacy and safety of FTD-TPI, and consider carefully for other treatment options before selecting eligible patients for FTD-TPI treatment.

[Precautions for Dosage and Administration]

1. The efficacy and safety of FTD-TPI in combination with other antitumor drugs have not been established.
2. FTD-TPI should not be administered to patients in the fasted state because C_{max} of trifluridine is higher in the fasted state than in the postprandial state.
3. During treatment with FTD-TPI, the criteria below should be referred to whenever

dose reduction or treatment interruption is necessary.

・ FTD-TPI should not be administered to patients who do not meet the criteria for starting treatment at the beginning of each cycle. Treatment with FTD-TPI should be interrupted when adverse events develop and meet the criteria for treatment interruption, and should be restarted after the adverse events have subsided to the levels meeting the criteria for resuming treatment.

	Criteria for starting/resuming treatment	Criteria for treatment interruption
Hemoglobin	≥8.0 g/dL	<7.0 g/dL
Neutrophil count	≥1500/mm^3	<1000/mm^3
Platelet count	≥75,000/mm^3	<50,000/mm^3
Total bilirubin	≤1.5 mg/dL	>2.0mg/dL
AST (GOT), ALT (GPT)	≤2.5 × UNL (≤5 × UNL for patients with liver metastasis)	>2.5 × UNL (≥5 × UNL for patients with liver metastasis)
Creatinine	≤1.5mg/dL	>1.5mg/dL
Peripheral neuropathy	Grade ≤2	Grade ≥3
Toxicity other than haematotoxicity	Grade ≤1 (excluding alopecia, dysgeusia, pigmentation, and symptoms due to the tumor)	Grade ≥3

(CTCAE v3.0 grading)

・ When adverse events meeting the criteria for dose reduction develop in the previous cycle (including the rest periods), the dose for the next cycle should be reduced by a unit of 10 mg/day. The daily dose should be 30 mg/day at minimum.

	Criteria for dose reduction
Neutrophil count	<500/mm^3
Platelet count	<50,000/mm^3

4. When FTD-TPI is administered at a dose of 50 mg/day, 20 mg should be administered after breakfast and 30 mg after supper.