Report on the Deliberation Results

December 11, 2020

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

Brand Name	Adlumiz Tablets 50 mg
Non-proprietary Name	Anamorelin Hydrochloride (JAN*)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	November 27, 2018

Results of Deliberation

In its meeting held on December 11, 2020, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is also required to conduct a drug use-results survey involving all patients treated with the product until data from a certain number of patients have been accumulated in the post-marketing setting in order to collect the safety and efficacy data on the product without delay and to take necessary measures to facilitate the proper use of the product.

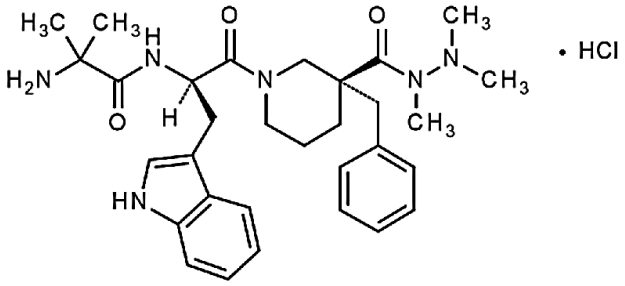
**Japanese Accepted Name (modified INN)*

Review Report

August 20, 2019
Pharmaceuticals and Medical Devices Agency

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

Brand Name Adlumiz Tablets 50 mg
Non-proprietary Name Anamorelin Hydrochloride
Applicant Ono Pharmaceutical Co., Ltd.
Date of Application November 27, 2018
Dosage Form/Strength Tablet: Each film-coated tablet contains 50 mg of anamorelin hydrochloride.
Application Classification Prescription drug, (1) Drug with a new active ingredient
Chemical Structure



Molecular formula: $C_{31}H_{42}N_6O_3 \cdot HCl$
Molecular weight: 583.16
Chemical name:
(3*R*)-3-Benzyl-*N,N',N'*-trimethyl-1-(2-methylalanyl-$_D$-tryptophyl)piperidine-3-carbohydrazide monohydrochloride
Items Warranting Special Mention None
Reviewing Office Office of New Drug I

Results of Review
On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of cancer cachexia, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indication

Cancer cachexia

Dosage and administration

The usual adult dosage is 100 mg of anamorelin hydrochloride administered orally once daily in a fasted state.

Approval conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is also required to conduct a drug use-results survey involving all patients treated with the product until data from a certain number of patients have been accumulated in the post-marketing setting in order to collect the safety and efficacy data on the product without delay and to take necessary measures to facilitate the proper use of the product.

Attachment

Review Report (1)

July 16, 2019

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

Product Submitted for Approval

Brand Name	Adlumiz Tablets 50 mg
Non-proprietary Name	Anamorelin Hydrochloride
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	November 27, 2018
Dosage Form/Strength	Tablet: Each film-coated tablet contains 50 mg of anamorelin hydrochloride.
Proposed Indication	Improvement in body weight loss and anorexia in cancer cachexia
Proposed Dosage and Administration	The usual adult dosage is 100 mg of anamorelin hydrochloride administered orally once daily in a fasted state. Patients should not eat any foods for at least 1 hour after taking Adlumiz.

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List of Abbreviations

See Appendix.

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

Cancer cachexia is a complex metabolic abnormality characterized by persistent loss of body weight (particularly muscle mass) that cannot be fully recovered by conventional nutritional support in patients with cancer and significantly decreases the tolerance to cancer chemotherapies and quality of life (QOL), affecting the prognosis of the patients (*Support care cancer*. 2016;24:3473-80, *BMC Cancer*. 2009;9:255, etc.). In the clinical practice guidelines issued by the European Palliative Care Research Collaborative (EPCRC), cancer cachexia is defined as "a multifactorial syndrome characterized by a persistent loss of skeletal muscle, with or without loss of fat mass that cannot be fully recovered by conventional nutritional support, leading to progressive functional impairment." The clinical significance of therapeutic interventions for cancer cachexia is to improve appetite and prevent the loss of lean body mass (LBM), which mainly consists of skeletal muscle and organ tissues (Clinical practice guidelines on cancer cachexia in advanced cancer patients with a focus on refractory cachexia: European Clinical Guidelines 2011). At present, no drug is approved for the indication of cancer cachexia. Nutrition therapy is provided for patients with cancer cachexia but cannot relieve cancer cachexia that is caused by metabolic abnormalities. Therapeutic agents for cancer cachexia are needed.

Anamorelin hydrochloride (anamorelin) is an agent with a ghrelin-like effect. Ghrelin, a peptide hormone identified as an endogenous agonist for the growth hormone (GH) secretagogue receptor 1a ($GHS\text{-}R_{1a}$), is mainly produced by the stomach and regulates the biological energy metabolism including facilitation of GH secretion, enhancement of appetite, and promotion of fat production (*J Clin Invest.* 2004;114:57-66, *Nat Rev Neurosci.* 2001;2:551-60, etc.). The applicant has developed anamorelin expecting that anamorelin can increase body weight (muscle mass) and improve QOL in patients with cancer.

As of July 2019, anamorelin has not been approved in any countries outside Japan.

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to off-white solid. The general properties of the drug substance, including description, solubility, hygroscopicity, optical rotation, dissociation constant, distribution coefficient, and isomerism have been determined.

The chemical structure of the drug substance has been elucidated by elementary analysis, infrared spectroscopy (IR), nuclear magnetic resonance spectrum (NMR; ^{1}H-NMR and ^{13}C-NMR), mass spectrum (MS), ultraviolet spectrum (UV), single-crystal X-ray crystallography, and powder X-ray diffractometry. The drug substance has 2 chiral centers, and the (R,R)-form is used in the manufacturing process.

2.1.2 Manufacturing process

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

The reaction process step is defined as the critical process step. The [redacted] has been controlled as a critical intermediate.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR and high-performance liquid chromatography [HPLC]), purity (related substances [HPLC], enantiomers [HPLC], residual solvents [gas chromatography (GC)], and [redacted] [GC]), water content, residue on ignition, chloride content, particle size, and assay (HPLC).

2.1.4 Stability of drug substance

The main stability studies performed for the drug substance are shown in Table 1. The photostability testing showed that the drug substance is photolabile.

Table 1. Main stability studies of the drug substance

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term testing	2 batches at pilot scale 1 batch at commercial scale	5 ± 3°C	—	Packed in a low-density polyethylene bag and packed in a low-density polyethylene bag [redacted], and then [redacted] stored in a metal drum.	60 months
Accelerated testing	2 batches at pilot scale 1 batch at commercial scale	25 ± 2°C	60 ± 5%RH		60 months

As shown in the above, a re-test period of [redacted] months has been proposed for the drug substance when packed in a low-density polyethylene bag and packed in a low-density polyethylene bag [redacted], and then [redacted] stored in a metal drum at 5 ± 3°C, protected from light.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a film-coated tablet containing 50 mg of the drug substance. It contains crystalline cellulose, croscarmellose sodium, light anhydrous silicic acid, magnesium stearate, polyvinyl alcohol (partially hydrolyzed), titanium oxide, macrogol 4000, talc, and yellow iron sesquioxide as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through a process consisting of the following steps: [redacted], packaging and labeling, and testing and storage. Process controls and action limits have been specified for the [redacted] process and the [redacted] process.

The [redacted] step is defined as the critical process.

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description (appearance), identification (ultraviolet-visible spectrum [UV/VIS] and HPLC), purity (related substance [HPLC]), uniformity of dosage

units (content uniformity test [HPLC]), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

The main stability studies performed for the drug product are shown in Table 2. The photostability testing showed that the drug product is photostable.

Table 2. Main stability studies for the drug product

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 batches at pilot scale	25 ± 2°C	60 ± 5%RH	PTP packaging	24 months
Accelerated testing	3 batches at pilot scale	40 ± 2°C	75 ± 5%RH		6 months

As shown in the above and in compliance with the ICH Q1E Guidelines, a shelf life of 36 months has been proposed for the drug product when packed in Press Through Package (PTP) (a composite film/aluminum foil of [redacted]) at room temperature. The long-term testing will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

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

In primary pharmacodynamic studies, binding to GHS-R_{1a}, GH secretagogue action, increasing of food consumption, and body weight gain were evaluated. In secondary pharmacodynamic studies, actions to receptors other than GHS-R_{1a}, binding of metabolites (M4 [a monooxidized form of anamorelin] and M6 [an *N*-demethylated form of anamorelin]) to GHS-R_{1a}, and effects on tumor proliferation were evaluated. In safety pharmacology studies, effects on the central nervous system, cardiovascular system, respiratory system, gastrointestinal system, renal system, and urinary system were evaluated. The dose and concentration of anamorelin are expressed as free form (as anamorelin).

3.1 Primary pharmacodynamics

3.1.1 Binding to GHS-R_{1a}

3.1.1.1 *In vitro* binding to human GHS-R_{1a} (CTD 4.2.1.1-1: Study AB78085)

The inhibitory activity of anamorelin against the binding of human ghrelin to human recombinant GHS-R_{1a} was evaluated. Anamorelin competitively inhibited the binding of human ghrelin to GHS-R_{1a}, and the 50% inhibitory concentration (IC_{50}) (mean ± standard error [SE]) was determined to be 7.3 ± 0.6 nmol/L.

3.1.2 GH secretagogue action

3.1.2.1 *In vitro* GH secretagogue action (CTD 4.2.1.1-3: Study E[redacted]QA001)

The primary cells derived from the anterior lobe of the pituitary of rats were spiked with anamorelin 0.01 to 100 nmol/L, and the GH levels in the culture supernatant fluid were determined. Anamorelin increased the GH levels in the culture supernatant fluid in a concentration-dependent manner. The 50% effective concentration (EC_{50} value) [95% CI] of anamorelin was determined to be 0.30 [0.23, 0.40] nmol/L, showing a GH

secretagogue action similar to that for rat ghrelin (EC_{50} value [95% CI] of 1.4 [0.89, 2.1] nmol/L).

3.1.2.2 GH secretagogue action in rats (CTD 4.2.1.1-5: Study E[redacted]QA026)

A single oral dose of anamorelin 3, 10, or 30 mg/kg or a vehicle (water for injection) was administered to rats, and the plasma GH levels for up to 6 hours post-dose were determined. The $AUC_{0\text{-}6h}$ (mean ± standard deviation [SD]) of plasma GH levels for up to 6 hours post-dose was 237.9 ± 44.0, 347.6 ± 97.9, 520.7 ± 99.6, and 768.9 ± 140.8 ng·h/mL in the vehicle control, anamorelin 3, 10, and 30 mg/kg groups, respectively. Anamorelin increased the plasma GH levels in a dose-dependent manner, and the plasma GH levels significantly increased in the anamorelin 10 and 30 mg/kg groups as compared with the vehicle control group.

3.1.3 Effects of anamorelin on food consumption and body weight gain

3.1.3.1 Effects of anamorelin on food consumption and body weight gain in rats (CTD 4.2.1.1-7: Study E[redacted]QA018)

Anamorelin 3, 10, or 30 mg/kg or a vehicle (water for injection) was repeatedly administered orally once daily to rats for 6 days. Changes in food consumption and body weight on Day 7 after the start of administration are shown in Table 3. Anamorelin increased food consumption and body weight in a dose-dependent manner, and food consumption and body weight both significantly increased in all anamorelin groups as compared with the vehicle control group.

Table 3. Cumulative changes in food consumption and changes in body weight on Day 7 after the start of administration of anamorelin in rats

Group	Food consumption			Body weight		
	Day 1 (g/day)	Day 7 (g/day)	Cumulative changes[a)] (g)	Day 1 (g)	Day 7 (g)	Changes[b)] (g)
Vehicle control	26.4 ± 0.6	27.4 ± 1.0	-1.1 ± 3.7	273.5 ± 3.7	318.9 ± 7.0	45.4 ± 4.8
Anamorelin 3mg/kg	26.7 ± 0.6	28.7 ± 0.6	7.1 ± 2.8*	272.5 ± 3.6	326.4 ± 6.0	53.9 ± 3.0*
Anamorelin 10 mg/kg	26.7 ± 0.6	30.0 ± 0.6	17.0 ± 3.4*	275.3 ± 4.5	334.5 ± 4.7	59.2 ± 1.8*
Anamorelin 30 mg/kg	26.6 ± 0.6	32.0 ± 1.0	30.2 ± 1.8*	275.5 ± 4.8	345.2 ± 6.3	69.6 ± 2.1*

n=7, mean ± SE

*: $P<0.05$ (vs. vehicle control, Williams' test)

a) Cumulative changes in food consumption = sum of changes in food consumption on Days 2 to 7
Changes in food consumption on each measurement day = food consumption on each measurement day − food consumption on Day 1

b) Changes in body weight = body weight on Day 7 − body weight on Day 1

3.2 Secondary pharmacodynamics

3.2.1 Evaluation of selectivity (CTD 4.2.1.2-1: Study AB82791)

Effects of anamorelin on a total of 120 entities including receptors, ion channels, and transporters were evaluated. Anamorelin inhibited the ligand binding of rat L-type calcium channel (benzodiazepine binding site and phenylalkylamine binding site) and rat voltage-dependent sodium channel[1)] and the binding of NK_2 receptor antagonist ([^{3}H]-SR48968) to human NK_2 receptors.

The IC_{50} value of anamorelin for the ligand binding of rat L-type calcium channel and rat voltage-dependent sodium channel and the binding of the NK_2 receptor antagonist to human NK_2 receptors were 4.91 to 9.33 µmol/L, 3.57 µmol/L, and 25 nmol/L, respectively, which were 158- to 300-fold, 115-fold, and 0.8-fold higher

[1)] The following ligands were used:
Benzothiazepine binding site of rat L-type calcium channel, [^{3}H]-diltiazem; Phenylalkylamine binding site of rat L-type calcium channel, [^{3}H]-(-)-D-888; and Rat voltage-dependent sodium channel, [^{3}H]-batrachotoxinin

than the C_{max} (629 ng/mL) after administration of anamorelin at a clinically recommended dosage regimen (100 mg, orally administered once daily, in a fasted state) in healthy adults, respectively. The effects of anamorelin on NK_2 receptors were further evaluated with rat deferent ducts which were confirmed to express NK_2 receptors. The investigation showed that the antagonistic effect of anamorelin on NK_2 receptors[2)] was weak with an IC_{50} value of 17.3 μmol/L, which was 556-fold higher than the C_{max} (629 ng/mL) after administration of anamorelin at a clinically recommended dosage regimen (100 mg, orally administered once daily, in a fasted state) in healthy adults.

As shown in the above, the applicant explained that anamorelin is unlikely to affect the ion channels or receptors in clinical practice.

3.2.2 Binding capacity of metabolites to GHS-R_{1a} (CTD 4.2.1.2-2 and 4.2.1.2-3: Studies 1057704 and AB21953 [reference data])

To investigate the effects of M4 (a monooxidized form of anamorelin) and M6 (an *N*-demethylated form of anamorelin) as main metabolites of anamorelin in humans, the inhibitory activity of M4 and M6 on the binding of human ghrelin to human recombinant GHS-R_{1a} was evaluated. Both metabolites competitively inhibited the binding of human ghrelin to human recombinant GHS-R_{1a}, with an inhibition of 29% for M4 at 1 μmol/L and 59% for M6 at 10 nmol/L. In light of the IC_{50} value of 7.3 nmol/L for unchanged anamorelin [see Section 3.1.1.1], the applicant explained that M4 has a lower binding affinity to GHS-R_{1a} than unchanged anamorelin and that M6 has a similar binding affinity to GHS-R_{1a} as unchanged anamorelin.

3.2.3 Effects of anamorelin on tumor proliferation (CTD 4.2.1.2-5: Studies A549-e312, A549-e313, and In Vitro-e50-RJV-01)

Anamorelin has been reported to increase the GH secretion via pituitary GHS-R_{1a} and GH affects tissues including the liver, leading to increases in the concentration of insulin-like growth factor-1 (IGF-1) (*Int J Mol Sci*. 2017;18. PII: E1624. doi: 10.3390/ijms18101624, *Endocr Connect*. 2018;7:R212-22, etc.), and GH and IGF-1 have been reported to affect tumor proliferation (*Endocrinology*. 2008;149:3909-19, *Proc Natl Acad Sci USA*. 2000;97:3455-60, etc.). Therefore, the effects of anamorelin on tumor proliferation were investigated.

Anamorelin 3, 10, or 30 mg/kg or a vehicle (ion-exchanged water) was repeatedly administered orally once daily for 28 days to female nude mice subcutaneously transplanted with human non-small cell lung cancer A549 cells. Percent changes in tumor volume and rates of body weight gain are shown in Table 4. In the comparison with the vehicle control group, body weights significantly increased in the anamorelin 10 and 30 mg/kg groups, and no significant increase in tumor volume was seen in any anamorelin groups.[3)]

[2)] The contraction response of rat deferent duct by [Ala^5,β-Ala^8]-α-Neurokinin (4-10), a ligand, was used as an indicator for evaluation.

[3)] Plasma GH and IGF-1 levels on Day 28 were measured in the anamorelin 30 mg/kg group and the vehicle control group. The $AUC_{0\text{-}60min}$ of plasma GH levels in the anamorelin 30 mg/kg group and the vehicle control group was 29.5 and 9.0 ng·h/mL, respectively. The $AUC_{0\text{-}360min}$ of plasma IGF-1 levels in the anamorelin 30 mg/kg group and the vehicle control group was 3,170 and 2,613 ng·h/mL, respectively.

Table 4. Percent changes in tumor volume and the rates of body weight gain on Day 28 in tumor-bearing mice

Group	Tumor volume			Body weight		
	Day 2 (mm^3)	Day 28 (mm^3)	Percent change in tumor volume[a)] (%)	Day 1 (g)	Day 28 (g)	Rate of body weight gain[b)] (%)
Vehicle control	287.1 ± 17.3	978.2 ± 85.9	247.5 ± 27.9	24.6 ± 0.3	25.7 ± 0.3	4.5 ± 0.7
Anamorelin 3mg/kg	255.8 ± 20.1	1,040.9 ± 128.0	308.4 ± 37.9	24.0 ± 0.5	25.1 ± 0.6	4.7 ± 0.9
Anamorelin 10 mg/kg	243.5 ± 17.7	688.5 ± 94.6	174.7 ± 29.9	23.7 ± 0.5	25.9 ± 0.6	9.2 ± 1.1*
Anamorelin 30 mg/kg	255.6 ± 13.6	1,100.5 ± 146.2	324.0 ± 48.2	24.2 ± 0.4	27.1 ± 0.5	11.7 ± 0.9**
Ghrelin 2 mg/kg	276.7 ± 16.9	938.6 ± 110.3	245.8 ± 41.7	24.0 ± 0.4	26.1 ± 0.5	8.5 ± 1.2

n=15, mean ± SE

*, $P<0.01$; **, $P<0.001$ (vs. the vehicle control group, Kruskal-Wallis test)

a) The percentage of tumor volume on Day 28 relative to that on Day 2

b) The percentage of body weight on Day 28 relative to that on Day 1

3.3 Safety pharmacology

Data from the studies shown in Table 5 were mainly submitted for evaluation of safety pharmacology.

Table 5. Summary of data from safety pharmacology studies

Items	Test system	Endpoints, method, and others	Anamorelin dose	Mode of administration	Findings[a)]	Attached data CTD (Study No.)
Central nervous system	Rats (5 male rats/group)	Modified Irwin method	10, 25, and 50 mg/kg	Single Oral	No effects were observed up to the highest dose of 50 mg/kg.	4.2.1.3-1 (21866)
	Rats (5 male rats/group)	Locomotor activity	10, 25, and 50 mg/kg	Single Oral	No effects were observed up to the highest dose of 50 mg/kg.	4.2.1.3-2 (21990)
	Rats (8 male rats/group)	Body temperature	10, 25, 50, and 100 mg/kg	Single Oral	Decreased body temperature was observed in the anamorelin 100 mg/kg group. The no-observed adverse effect level of anamorelin for body temperature was determined to be 50 mg/kg. The no-observed adverse effect level of anamorelin for the central nervous system in rats was determined to be 50 mg/kg (1.3-fold higher than the safety margin).	4.2.1.3-3 (F[redacted]PD003)
	Dogs (5/sex/group)	Body temperature	0.5, 1, 2, 2.5, 3, 3.5, and 4 mg/kg	Intravenous Continuous	No effects were observed up to the highest dose of 4 mg/kg.	4.2.1.3-4 (05103)
Cardiovascular system	HEK293 cells (5 samples)	hERG current	1, 10, 30, 100, and 300 µmol/L	*In vitro*	Anamorelin at ≥10 µmol/L inhibited the hERG current (IC_{50} value = 34 µmol/L).	4.2.1.3-6 (107404HG)
	Adult cardiac myocytes (3-6 samples)	Voltage-dependent sodium channel current, and L- and T-type calcium channel currents	0.1, 0.3, 1, 10, and 100 µmol/L	*In vitro*	Anamorelin at 100 µmol/L inhibited voltage-dependent sodium channel current and L-type calcium channel current by 15.6% and 11.6%, respectively.	4.2.1.3-9 (HT-[redacted]-01) (Reference data)
	Dogs (4/sex/group)	Blood pressure, heart rate, electrocardiography	1, 5, and 10 mg/kg	Single Oral	Decreased blood pressure was seen in the groups of ≥1 mg/kg, and prolonged PR interval and widened QRS were seen in the groups of ≥5 mg/kg. The no-observed adverse effect level of orally administered anamorelin for the cardiovascular system in dogs was determined to be <1 mg/kg (<0.3-fold higher than the safety margin).	4.2.1.3-8 (N104382)

Items	Test system	Endpoints, method, and others	Anamorelin dose	Mode of administration	Findings[a)]	Attached data CTD (Study No.)
	Dogs (5/sex/group)	Blood pressure, heart rate, electrocardiography	0.5, 1, 2, 2.5, 3, 3.5, and 4 mg/kg	Intravenous Continuous	Decreased blood pressure and prolonged PR interval were seen in the groups of ≥0.5 mg/kg, widened QRS was seen in the groups of ≥2 mg/kg, and increased heart rate was seen in the groups of ≥3 mg/kg. The no-observed adverse effect level of intravenously administered anamorelin for the cardiovascular system in dogs was determined to be <0.5 mg/kg (<0.6-fold higher than the safety margin).	4.2.1.3-4 (05103)
Respiratory system	Dogs (4/sex/group)	WBP (respiratory rate, tidal volume, minute ventilation)	1, 5, and 10 mg/kg	Single Oral	No effects were observed up to the highest dose of 10 mg/kg. The no-observed adverse effect level of anamorelin for the respiratory system in dogs was determined to be 10 mg/kg (2.9-fold higher than the safety margin).	4.2.1.3-8 (N104382)
Gastrointestinal system	Rats (5 male rats/group)	Transit rate of activated charcoal powder in the small intestine (gastrointestinal motility)	10, 25, and 50 mg/kg	Single Oral	Decreased transit rate of activated charcoal powder (decreased gastrointestinal motility) in the small intestine was seen in the 50 mg/kg group. The no-observed adverse effect level of anamorelin for the gastrointestinal system in rats was determined to be 25 mg/kg (0.6-fold higher than the safety margin).	4.2.1.3-12 (21824)
Renal/urinary system	Rats (5 male rats/group)	Urine output, urine characteristics (e.g., specific gravity and pH), creatinine, NAG, urinary electrolytes (Na^+, Ca^{2+}, K^+, Cl^-, IP)	10, 25, and 50 mg/kg	Single Oral	No effects were observed up to the highest dose of 50 mg/kg. The no-observed adverse effect level of anamorelin for the renal/urinary system in rats was determined to be 50 mg/kg (1.3-fold higher than the safety margin).	4.2.1.3-13 (22444)

a) The safety margin was calculated as a C_{max} (629 ng/mL) after administration of anamorelin at a clinically recommended dosage regimen (100 mg, orally administered once daily, in a fasted state) in healthy adults.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effects

The applicant's explanation about the pharmacological effects of anamorelin:

Anamorelin is a GHS-R_{1a} agonist, and GHS-R_{1a} has been reported to be involved via its stimulation of GH release in the pituitary gland and increased appetite in the hypothalamus (*J Clin Invest.* 2002;109:1429-36). Preclinical studies demonstrated that anamorelin increases the GH secretion from the pituitary gland, which is mediated by the activation of GHS-R_{1a}, resulting in increases in food consumption and body weight. In nude mice subcutaneously transplanted with human non-small cell lung cancer A549 cells, anamorelin significantly increased body weight as compared with the vehicle control [See Section 3.2.3], indicating that anamorelin is effective even in patients presenting with pathological conditions of cancer cachexia.

M4 and M6, main metabolites of anamorelin, were demonstrated to bind to GHS-R_{1a}. The binding affinity of M4 to GHS-R_{1a} was lower than that of unchanged anamorelin, whereas the binding affinity of M6 seemed comparable to that of unchanged anamorelin [see Section 3.2.2]. In foreign clinical studies conducted in healthy adults (Studies HT-ANAM-112 and HT-ANAM-114), the ratio of plasma exposure ($AUC_{0-\infty}$) of M4 and M6 after a single oral dose of anamorelin 100 mg to that of unchanged anamorelin was <10%, suggesting that M4

and M6 are very unlikely to influence the effects of anamorelin during its clinical use.

PMDA asked the applicant to explain the possibility that the type of cancer may influence the effects of anamorelin on increases in food consumption or body weight gain.

The applicant's explanation:
Cancer cachexia is considered to be caused by inflammatory reactions induced by abnormal production of cytokines in cancer cells or host immune tissues (*Nat Rev Clin Oncol.* 2013;10:90-9). In foreign phase II studies conducted in patients with various types of cancer (Studies RC-1291-203 and RC-1291-205), no remarkable effects of the type of cancer on the efficacy of anamorelin were observed. These findings suggest that the type of cancer is unlikely to influence the therapeutic effects of anamorelin.

On the basis of the submitted data from the primary pharmacodynamic studies and the discussions made by the applicant, PMDA considers that anamorelin has an agonist effect on GHS-R_{1a} and is expected to increase food consumption and body weight via the activation of GHS-R_{1a} in patients with cancer cachexia. The applicant's discussion can be understood to a certain extent that the therapeutic effects of anamorelin are unlikely to vary among types of cancer.

3.R.2 Effects of anamorelin on tumor proliferation

The applicant's explanation about the effects of anamorelin on tumor proliferation:
Anamorelin showed no effects on tumor proliferation in nude mice subcutaneously transplanted with human non-small cell lung cancer A549 cells [see Section 3.2.3]. In *in vitro* studies, A549 cells and SK-MES-1 cells expressing GH receptors and IGF-1 receptors were spiked with GH (final concentrations, 1-1,000 ng/mL) and IGF-1 (final concentrations, 130-1,000 ng/mL) in the presence of human serum, and GH and IGF-1 up to 1,000 ng/mL showed no effects on tumor proliferation. In all Japanese clinical studies of anamorelin, the maximum serum GH and IGF-1 levels after administration of anamorelin as a single dose or repeated doses once daily was determined to be 164 ng/mL and 683 ng/mL, respectively, suggesting that GH or IGF-1 at the levels increased by administration of anamorelin has no effects on proliferation of tumor cells *in vivo* in humans. Accordingly, anamorelin is considered to be unlikely to influence tumor proliferation during clinical use even in patients with cancer other than non-small cell lung cancer. No tumor proliferation was seen with treatment with anamorelin in Japanese or foreign clinical studies [see Section 7.R.2.3.4].

PMDA considers that although no significant problems have been identified at present, information on the effects of anamorelin on tumor proliferation should be continuously collected via post-marketing surveillance.

3.R.3 Safety pharmacology

The applicant's explanation about findings available from safety pharmacology studies:
As a result of evaluating the effects of anamorelin on the central nervous system, body temperature decreased in rats. Intracerebroventricular administration of ghrelin to rats reduced energy consumption and led to a decrease in body temperature (*Endocrinology*. 2002;143:155-62), and intracerebroventricular or

intraperitoneal administration of ghrelin to mice reduced energy consumption via the activation of GHS-R_{1a} in the hypothalamus (*Gastroenterology*. 2001;120:337-45). These findings suggest an agonistic effect of anamorelin on GHS-R_{1a} in the hypothalamus. Although the safety margin for a decrease in body temperature was 1.3-fold higher, no decrease in body temperature was observed after continuous intravenous administration of anamorelin in dogs (safety margin, 5.4- to 5.6-fold), and no effects on body temperature were observed in clinical studies, suggesting that anamorelin is unlikely to affect body temperature during its clinical use.

As cardiovascular findings, decreased blood pressure, increased heart rate, and prolonged PR interval and widened QRS were observed in dogs. With regard to decreased blood pressure, anamorelin has an agonistic effect on GHS-R_{1a}, and ghrelin has been reported to decrease blood pressure through vasodilation and suppression of the sympathetic nervous system (*Curr Hypertens Rep.* 2016;18:15). Therefore, decreased blood pressure is considered to represent changes due to the agonistic effect of anamorelin on GHS-R_{1a}. Increased heart rate is considered to represent a reflex response to the decrease in blood pressure. The safety margin for decreased blood pressure and heart rate was <1-fold and 4.4-fold higher, respectively, and the possibility cannot be ruled out that decreases in blood pressure may occur during clinical use or anamorelin. However, the decrease in blood pressure observed in dogs was mild in severity with a decrease of 15% to 20% compared with pre-dose blood pressure levels, and no significant decrease in blood pressure was reported also in clinical studies. Therefore, it is considered that anamorelin is unlikely to cause clinically significant decreased blood pressure during its clinical use when blood pressure is monitored on a regular basis.

The prolongation of PR intervals and widened QRS are attributable to the inhibitory effects of anamorelin on voltage-dependent sodium channel current. The safety margin for prolongation of PR intervals and widened QRS was <1-fold higher, and the possibility cannot be ruled out that these findings may occur during the clinical use of anamorelin. Therefore, precautions should be provided that electrocardiography should be performed regularly during the clinical use of anamorelin and that appropriate measures, including treatment interruption and treatment discontinuation, should be taken if PR interval prolonged or QRS widened.

Decreased gastrointestinal function in the small intestine was observed in rats. The finding is considered to be caused by the inhibitory effects of anamorelin on the L-type calcium channel current. The safety margin for the gastrointestinal system was <1-fold higher, and the possibility cannot be ruled out that gastrointestinal function may decrease during the clinical use of anamorelin. However, no findings suggestive of decreases in gastrointestinal function, such as decreased defecation, were observed even at the highest dose of 45 mg/kg and 5 mg/kg, respectively, in the 26-week repeated oral dosing toxicity studies in rats and dogs. Also in clinical studies, no increase in the incidence of constipation was seen in the anamorelin groups as compared with the placebo group. At present, decreased gastrointestinal function is unlikely to become clinically significant during the clinical use of anamorelin.

PMDA accepted the applicant's explanation.

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

Pharmacokinetics after administration of unlabeled anamorelin, ^{3}H-anamorelin, and ^{14}C-anamorelin in rats and dogs was investigated. The liquid chromatography-tandem mass spectrometry (LC/MS/MS) was used to measure anamorelin concentrations in plasma with a lower limit of quantification of 1 ng/mL. The liquid scintillation counter method and the high-performance liquid chromatography equipped with a radioactivity detector (Radio-HPLC) were used to measure the radioactivity for ^{3}H-anamorelin and ^{14}C-anamorelin.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1 and 4.2.2.2-2: Studies 22438 and 22861)

Pharmacokinetic parameters after administration of a single oral or intravenous dose of anamorelin to male and female rats are shown in Table 6. No major differences in the pharmacokinetics of anamorelin were observed between male and female rats.

Table 6. Plasma pharmacokinetic parameters after single administration of anamorelin in rats

Sex	Administration route	Anamorelin dose (mg/kg)	C_{max}[a)] (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	Extent of bioavailability[b)] (%)
Male	Oral	50	759 ± 512	0.5	3,660	2.2	50
	Intravenous	0.6	—	—	87.3	1.4	—
Female	Oral	50	1,021 ± 614	0.5	3,782	1.7	56
	Intravenous	0.6	—	—	81.7	1.3	—

Mean at each time point in 3 animals; —, not calculated.
a) Mean ± SD
b) ($AUC_{0-\infty}$ after oral administration/oral dose) / ($AUC_{0-\infty}$ after intravenous administration/intravenous dose) × 100

Pharmacokinetic parameters after administration of a single oral or intravenous dose of anamorelin to male and female dogs are shown in Table 7, and the exposure after oral dosing increased more than dose-proportionally. No major differences in the pharmacokinetics of anamorelin were observed between male and female dogs.

Table 7. Plasma pharmacokinetic parameters after single administration of anamorelin in dogs

Sex	Administration route	Anamorelin dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	Extent of bioavailability[a)] (%)
Male	Oral	0.1	4.1 ± 2.6	0.4 ± 0.3	7.6[b)]	0.7[b)]	11.4 ± 7.6
		0.5	62.2 ± 16.0	0.5 ± 0.2	72.5 ± 29.6	1.4 ± 0.2	36.5 ± 9.1
		1	153 ± 120	0.4 ± 0.1	149 ± 78.2	1.3 ± 0.3	36.4 ± 11.7
		5	1,764 ± 1,122	0.5 ± 0.4	2,292 ± 1,365	1.8 ± 0.2	110.7 ± 48.5
	Intravenous	0.25	—	—	97.5 ± 31.0	1.6 ± 0.2	—
Female	Oral	0.1	5.7 ± 3.4	0.4 ± 0.1	6.4 ± 4.1[c)]	0.6 ± 0.4[c)]	14.4 ± 7.1
		0.5	99.3 ± 55.3	0.6 ± 0.3	100 ± 49.7	1.2 ± 0.1	45.6 ± 12.1
		1	202 ± 44.9	0.4 ± 0.1	168 ± 75.8	1.3 ± 0.1	39.0 ± 8.2
		5	1,965 ± 1,006	0.4 ± 0.1	1,968 ± 718	1.5 ± 0.1	93.8 ± 13.8
	Intravenous	0.25	—	—	105 ± 31.6	1.4 ± 0.1	—

n = 4; Mean ± SD; —, not calculated
a) ($AUC_{0-\infty}$ after oral administration/oral dose) / ($AUC_{0-\infty}$ after intravenous administration/intravenous dose) × 100
AUC at the last observation was used for calculation in animals without $t_{1/2}$.
b) n = 1
c) n = 3

4.1.2 Repeated-dose studies

4.1.2.1 Repeated-dose study in rats (CTD 4.2.3.2-2: Study 22727)

Toxicokinetics after 4-week repeated oral administration of anamorelin to male and female rats was investigated in a toxicity study. Plasma pharmacokinetic parameters after 4-week repeated administration of anamorelin to male and female rats are shown in Table 8, and the exposure increased more than dose-

proportionally. Despite wide variability, no major differences in the pharmacokinetics of anamorelin were observed between male and female rats. The C_{max} and $AUC_{0\text{-}8h}$ on Day 1 were comparable to those on Day 28.

Table 8. Plasma pharmacokinetic parameters after 4-week repeated oral administration of anamorelin in rats

	Anamorelin dose (mg/kg/day)	Time point	C_{max}[a)] (ng/mL)	t_{max} (h)	$AUC_{0\text{-}8h}$ (ng·h/mL)
Male	15	Day 1	31.8 ± 16.6	4.0	155
		Day 28	208 ± 162	2.0	592
	30	Day 1	534 ± 159	2.0	1,233
		Day 28	954 ± 374	1.0	2,527
	60	Day 1	914 ± 485	2.0	3,437
		Day 28	969 ± 226	2.0	3,774
Female	15	Day 1	132 ± 78	2.0	318
		Day 28	315 ± 65	1.0	938
	30	Day 1	576 ± 151	2.0	1,524
		Day 28	438 ± 177	2.0	1,624
	60	Day 1	1,070 ± 225	2.0	4,318
		Day 28	769, 1,720[b)]	2.0	4,787

Mean at each time point in 3 animals
a) Mean ± SD
b) Values in 2 animals

4.1.2.2 Repeated-dose study in dogs (CTD 4.2.3.2-7: Study 22728)

Toxicokinetics after 4-week repeated oral administration of anamorelin to male and female dogs was investigated in a toxicity study. Plasma pharmacokinetic parameters after 4-week repeated oral administration of anamorelin to male and female dogs are shown in Table 9, and the exposure increased more than dose-proportionally. No major differences in the pharmacokinetics of anamorelin were observed between male and female dogs. The C_{max} and AUC on Day 1 were comparable to those on Day 28 ($AUC_{0\text{-}\infty}$ on Day 1 and $AUC_{0\text{-}24h}$ on Day 28).

Table 9. Plasma pharmacokinetic parameters after 4-week repeated oral administration of anamorelin in dogs

	Anamorelin dose (mg/kg/day)	Time point	C_{max} (ng/mL)	t_{max} (h)	AUC[a)] (ng·h/mL)	$t_{1/2}$ (h)
Male	1	Day 1	162 ± 25.1	1.2 ± 0.9	258[b)]	1.62[b)]
		Day 28	207 ± 45.7	1.0 ± 0.0	326 ± 54.4	1.68 ± 0.72
	3	Day 1	654 ± 336	0.4 ± 0.1	963 ± 426	1.37 ± 0.14
		Day 28	727 ± 363	0.8 ± 0.3	1,109 ± 522	1.45 ± 0.18
	5	Day 1	2,298 ± 1,115	0.4 ± 0.1	3,711 ± 1,899	1.66 ± 0.24
		Day 28	1,753 ± 662	0.6 ± 0.3	3,460 ± 2,266	1.69 ± 0.35
Female	1	Day 1	163 ± 69.4	0.6 ± 0.3	239 ± 112	1.49 ± 0.26
		Day 28	279 ± 171	0.4 ± 0.1	369 ± 129	1.49 ± 0.97
	3	Day 1	842 ± 169	0.6 ± 0.3	1,140 ± 298	1.41 ± 0.30
		Day 28	949 ± 388	0.4 ± 0.1	1,125 ± 402	1.44 ± 0.37
	5	Day 1	1,762 ± 1,101	0.4 ± 0.1	2,328 ± 980	1.44 ± 0.14
		Day 28	1,866 ± 972	0.8 ± 0.3	3,048 ± 1,452	1.46 ± 0.07

n = 4, Mean ± SD
a) $AUC_{0\text{-}\infty}$ for Day 1 and $AUC_{0\text{-}24h}$ for Day 28
b) n = 2

4.2 Distribution

4.2.1 Tissue distribution in rats (CTD 4.2.2.3-1: Study PK[redacted]-043)

Male albino rats were administered a single oral dose of ^{14}C-anamorelin 30 mg/kg to evaluate the radioactivity concentrations in tissues up to 120 hours post-dose.[4)] The radioactivity concentrations reached the maximum by 4 hours post-dose in most tissues, and the radioactivity concentration was highest in the small intestine,

[4)] Radioactivity concentrations were evaluated in the plasma, blood, brain, eyeball, thyroid gland, thymus, heart, lung, liver, kidney, spleen, adipose tissue, muscle, bone marrow, skin, testis, seminal vesicle, stomach, small intestine, and large intestine.

followed by large intestine, liver, stomach, and kidney, which was 89.3-, 52.9-, 22.2-, 7.8-, and 6.8-fold higher than that in plasma, respectively. The radioactivity concentration in the brain at 48 hours post-dose was 1.6-fold higher than that in the plasma. The half-life of radioactivity in the brain, heart, thymus, and seminal vesicle was longer than that in the plasma ($t_{1/2}$ in the brain, heart, thymus, and seminal vesicle, 284.3-655.7 h; $t_{1/2}$ in the plasma, 132.9 h). The applicant considered that anamorelin is unlikely to accumulate in the body during repeated oral administration in light of the following findings: (a) that the $t_{1/2}$ in the plasma after single oral administration of anamorelin to albino rats ranged 1.7 to 2.2 h [see Section 4.1.1], suggesting the $t_{1/2}$ of radioactivity reflects that of its metabolites; (b) that the pharmacokinetics (C_{max} and AUC) of anamorelin after repeated oral administration of anamorelin in rats and dogs was comparable between Days 1 and 28 [see Section 4.1.2]; and (c) in a human mass balance study, all radioactivity was recovered after single oral administration of ^{14}C-anamorelin [see Section 6.2.3].

Male pigmented rats were administered a single oral dose of ^{14}C-anamorelin 30 mg/kg to evaluate the radioactivity concentrations, and no major differences in the radioactivity concentrations were observed as compared to those in albino rats.[5)] The $t_{1/2}$ of radioactivity in eyeballs (424.7 hours in pigmented rats and 226.4 hours in albino rats [calculated with the tissue radioactivity in 2 or 3 animals at each point]) was comparable to the $t_{1/2}$ of radioactivity in plasma (354.9 hours in pigmented rats and 132.9 hours in albino rats [calculated with the tissue radioactivity in 2 or 3 animals at each point]). As shown in these findings, the applicant considered that anamorelin or its metabolites did not accumulate in eyeballs and explained that anamorelin and its metabolites are unlikely to accumulate in melanin-containing tissues.

4.2.2 Protein binding (CTD 4.2.2.3-2 and 5.3.2.1-1: Studies 22835 and VREJV5901PB)

The protein binding of ^{3}H-anamorelin (0.1-1.0 μmol/L) was evaluated with rat and canine plasma, and the mean protein binding was 92.0% to 93.2% in rat plasma and 95.7% to 97.4% in canine plasma, showing no concentration dependency.

4.2.3 Distribution in blood cells (CTD 4.2.2.3-1 and 4.2.2.3-3: Studies PK[redacted]-043 and 23002)

Male rats were administered a single oral dose of ^{14}C-anamorelin 30 mg/kg, and the ratio of radioactivity in blood to that in plasma at 4 hours post-dose was 0.867. Male dogs were administered a single oral dose of ^{3}H-anamorelin 1 mg/kg, and the ratio of radioactivity in blood to that in plasma at 4 hours post-dose was 0.7. The applicant explained that anamorelin in blood is distributed mainly in the plasma fraction.

4.2.4 Placental transfer and fetal transfer

The possibility of placental or fetal transfer of anamorelin has not been studied. In light of the molecular weight of anamorelin (546.70), its high lipid solubility[6)], and the fact that anamorelin is a weak base,[7)] the applicant considered that anamorelin may cross the placenta and be transferred to fetuses.

[5)] Radioactivity concentrations in the plasma, blood, eyeball, and skin were evaluated.
[6)] The 1-octanol-water partition coefficient of anamorelin was 2.98.
[7)] The dissociation constant (pKa) of anamorelin was 7.74 to 7.84.

4.3 Metabolism

4.3.1 Evaluation of *in vitro* metabolites (CTD 4.2.2.4-1 and 4.2.2.4-2: Studies 22588 and BD000039)

Metabolites of anamorelin were evaluated with rat and canine liver microsomes. M4 (a monooxidized form of anamorelin) and M6 (an *N*-demethylated form of anamorelin) were detected as the main metabolites in both animal species. The major metabolites in rat and canine liver microsomes were the same as those in human liver microsomes [see Section 6.1.1.2].

4.3.2 Percentage of unchanged anamorelin and metabolites in the plasma, urine, and feces (CTD 4.2.2.4-3 and 4.2.2.3-3: Studies 23001 and 23002)

Male rats were administered a single oral dose of ^{3}H-anamorelin 15 mg/kg to evaluate the percentage of unchanged anamorelin, and metabolites[8)] in the plasma, urine, and feces. The percentage of unchanged anamorelin to the total plasma radioactivity was 73.1% at 2 hours post-dose and 34.7% at 6 hours post-dose. The percentage of anamorelin metabolites to the total plasma radioactivity was 26.8% at 2 hours post-dose and 65.3% at 6 hours post-dose. A total of 1.0% and 102.0% of dosed radioactivity was recovered in urine and feces, respectively, up to 24 hours post-dose. Unchanged anamorelin (65.0% of the total radioactivity in urine) and metabolites were detected in urine, and unchanged anamorelin (85.4% of the total radioactivity in feces) was mainly observed in feces.

Male dogs were administered a single oral dose of ^{3}H-anamorelin 1 mg/kg to evaluate the percentage of unchanged anamorelin and metabolites[8)] in plasma, urine, and feces. The percentage of unchanged anamorelin to the total radioactivity in plasma was 87.0% at 0.5 hours post-dose and 42.7% at 4 hours post-dose. The percentage of the metabolite which was the most commonly observed in the plasma to the total radioactivity in plasma was 3.4% at 0.5 hours post-dose and 32.9% at 4 hours post-dose. A total of 10.3% and 70.9% of dosed radioactivity was recovered in urine and feces, respectively, up to 48 hours post-dose. Unchanged anamorelin (7.24% of the total radioactivity in urine) and metabolites were detected in urine, and unchanged anamorelin (26.2% of the total radioactivity in feces) and metabolites were observed in feces.

4.4 Excretion

4.4.1 Excretion in urine, feces, and expired air in rats (CTD 4.2.2.4-3: Study 23001)

Male rats were administered a single oral dose of ^{3}H-anamorelin 15 mg/kg, and the excretion rate of radioactivity in urine and feces up to 168 hours post-dose and in expired air up to 48 hours post-dose was 1.5%, 106.1%, and 0.03%, respectively. Male rats were administered a single intravenous dose of ^{3}H-anamorelin 1.5 mg/kg, and the excretion rate of radioactivity in urine and feces up to 168 hours post-dose and in expired air up to 48 hours post-dose was 8.9%, 84.2%, and 0.04%, respectively. The applicant explained that, in rats, unchanged anamorelin and metabolites are excreted mainly in feces, some in urine, and only a little in expired air.

[8)] No metabolites were identified.

4.4.2 Excretion in urine and feces in dogs (CTD 4.2.2.3-3: Study 23002)

Male dogs were administered a single oral dose of ^{3}H-anamorelin 1 mg/kg to evaluate the excretion in urine and feces in dogs, and the excretion rate of radioactivity in urine and feces up to 168 hours post-dose was 11.0% and 74.7%, respectively. After a single intravenous dose of ^{3}H-anamorelin 0.25 mg/kg to dogs, the excretion rate of radioactivity in urine and feces up to 168 hours post-dose was 15.7% and 75.2%, respectively. The applicant explained that, in dogs, unchanged anamorelin and metabolites are excreted mainly in feces and some in urine.

4.4.3 Excretion in milk

The possibility of excretion of anamorelin in milk has not been studied. In light of the high lipid solubility[6)] and the fact that anamorelin is a weak base,[7)] the applicant considered that anamorelin may be transferred to milk.

4.R Outline of the review conducted by PMDA

4.R.1 Pharmacokinetics of orally administered anamorelin

PMDA asked the applicant to explain the possible accumulation of anamorelin after repeated doses because the exposure of anamorelin tended to increase more than dose-proportionally in the single and repeated oral dose studies in dogs (4.2.2.2-2 and 4.2.3.2-7) and a repeated oral dose study in rats (4.2.3.2-2).

The applicant's explanation:

In the single and repeated oral dose studies in dogs, no differences in the half-life of anamorelin were observed among the doses. In the repeated oral dose study in rats, the half-life of anamorelin was not calculated, but an analysis of changes in plasma anamorelin concentrations demonstrated a tendency in which anamorelin was eliminated with a similar slope. Although no saturation seemed to occur in the process of elimination from the circulating blood, the first-pass effect might have been saturated. In rats and dogs, the C_{max} and AUC on Days 1 and 28 ($AUC_{0\text{-}8h}$ in rats; and $AUC_{0\text{-}\infty}$ on Day 1 and $AUC_{0\text{-}24h}$ on Day 28 in dogs) were comparable [see Section 5.2], and anamorelin showed no tendency toward accumulating after its repeated doses.

PMDA accepted the applicant's explanation.

5. Toxicity and Outline of the Review Conducted by PMDA

The following toxicity studies of anamorelin were conducted: single-dose toxicity, repeated-dose toxicity, genotoxicity, reproductive and developmental toxicity, and local tolerance studies. In the *in vivo* studies, the vehicle used was distilled water for oral administration and physiological saline solution for intravenous administration, unless otherwise specified.

5.1 Single-dose toxicity

Single oral and intravenous dose studies were conducted in mice and rats (Table 10). The approximate lethal dose of anamorelin after oral administration was determined to be 400 mg/kg and 200 mg/kg in mice and rats, respectively.

Table 10. Single-dose toxicity studies

Test system	Administration route	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached data CTD
Male and female mice (ICR)	Oral	400 and 600	Death or moribund sacrifice: 600 (5 of 5 males and 5 of 5 females) and 400 (2 of 5 males and 2 of 5 females); decreased locomotor activity; staggering gait; collapse; and labored respiration. 400: Decreased locomotor activity; and abnormal respiratory sound.	400	4.2.3.1-1
Male and female rats (SD)	Oral	100 and 200	100: Labored respiration (females); and body weight decreased (females).	200[a)]	4.2.3.1-3
Female mice (ICR)	Intravenous	2, 10, 15, and 20	Deaths: 20 (2 of 2 females) ≥2: Black discoloration of the tail. 15: Decreased locomotor activity; and staggering gait.	20	Reference data 4.2.3.1-2
Male and female rats (SD)	Intravenous	10	Deaths: 10 (1 of 5 male); staggering gait; decreased locomotor activity; and labored respiration. 10: Staggering gait; decreased locomotor activity; labored respiration; and body weight decreased.	10	Reference data 4.2.3.1-4

a) In the dose-finding study, 1 of 2 females in the 200 mg/kg group died.

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies in rats and dogs (4, 13, and 26 weeks) were conducted (Table 11). Major toxicity findings included high body weight and high food consumption, inflammatory changes in the upper respiratory tract and abnormal respiration attributable to the contact to the irritating anamorelin solution, and effects on the liver such as high blood aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. In the 26-week oral dose toxicity study in rats and the 26-week oral dose toxicity study in dogs, the exposure (AUC and C_{max}) at the no-observed adverse effect level (30 mg/kg/day in rats and 5 mg/kg/day in dogs) was 0.9- to 1.3-fold higher and 0.7- to 1.5-fold higher, respectively, in rats and 1.6- to 1.8-fold higher and 2.8- to 3.0-fold higher, respectively, in dogs, than the $AUC_{0\text{-}24h}$ (1,880 ng·h/mL) and C_{max} (629 ng/mL) after administration of anamorelin at a clinically recommended dosing regimen (100 mg, orally administered once daily, in a fasted state) in healthy adults.

Table 11. Repeated-dose toxicity studies

Test system	Administra-tion route	Duration	Dose (mg/kg/day)	Main findings	No-observed adverse effect level (mg/kg/day)	Attached data CTD
Male and female rats (SD)	Oral	4 weeks (once daily)	0[a)], 15, 30, and 60[b)]	Death and moribund sacrifice[c)] 60 (2 of 10 males and 1 of 10 female); abnormal respiration[d)] (e.g., wheezing, gasping respiration, and irregular respiration); decreased locomotor activity; hunched posture; body weight decreased; rhinitis[e)]; nasopharyngitis[e)]; pharyngeal transitional epithelial metaplasia[e)]; bronchiolar epithelial necrosis[e)]; alveolar edema[e)]; intra-alveolar pulmonary hemorrhage[e)]; and necrosis of tissues below the tracheal epithelial mucosa[e)]. ≥15: High body weight and high body weight gain; high food consumption; rhinitis[d)]; nasopharyngitis[d)]; and pharyngeal transitional epithelial metaplasia[d)]. ≥30: Abnormal respiration[d)] (e.g., wheezing, gasping respiration, and irregular respiration) (male); and salivation[f)] (female). 60: Abnormal respiration[d)] (e.g., wheezing, gasping respiration, and irregular respiration) (female);	<15	4.2.3.2-2

Test system	Administration route	Duration	Dose (mg/kg/day)	Main findings	No-observed adverse effect level (mg/kg/day)	Attached data CTD
				salivation[f] (male); decreased locomotor activity (male); tracheitis[d]; and infiltration of inflammatory cells into the lamina propria of the tracheal mucosa[d] (male).		
Male and female rats (SD)	Oral	13 weeks (once daily) with a 6-week rest	0, 15, 30, and 45	Death[g]: 45 (1 of 25 male and 2 of 25 females), 30 (1 of 25 male and 1 of 25 female), and 15 (2 of 25 females). ≥15: High body weight and high body weight gain; and high food consumption (males). ≥30: High food consumption (females). 45: Abnormal respiration[d] (rales, respiration with murmur, and dyspnoea). Reversible	30	4.2.3.2-3
Male and female rats (SD)	Oral	26 weeks (once daily)	0, 15, 30, and 45	≥15: High body weight and high body weight gain; and high food consumption. 45: Abnormal respiration[d] (respiration with murmur and dyspnoea); and high blood AST, ALT, and SDH.	30	4.2.3.2-4
Male and female dogs (Beagles)	Oral	4 weeks (once daily)	0[a], 1, 3, and 5[b]	≥1: High body weight gain (males). ≥3: High body weight gain (females). 5: High body weight (females); high blood ALT (females); inflammation around the hepatic portal vein; increased pigmentation (females); and aggregation of inflammatory cells with pigmentation (females).	3	4.2.3.2-7
Male and female dogs (Beagles)	Oral	13 weeks (once daily) with a 6-week rest	0, 1, 3, and 5	Sacrificed moribund[h]: 3 (1 of 7 male). ≥1: High body weight and high body weight gain; and high food consumption (males). Reversible	5	4.2.3.2-8
Male and female dogs (Beagles)	Oral	26 weeks (once daily)	0, 1, 3, and 5	Sacrificed moribund[i]: 3 (1 of 4 female); generalized infection of *Demodex folliculorum*; and severe lymphocyte depletion of the thymus (suggestive of congenital or acquired immunodeficiency). ≥1: High body weight and high body weight gain (males); and high food consumption (females). ≥3: High body weight and high body weight gain (females); and high food consumption (males).	5	4.2.3.2-9

a) Water for injection
b) Anamorelin free base was spiked with 1 mol/L of hydrochloric acid and was diluted into the water for injection adjusted to pH 4.5 with 1 mol/L of sodium hydroxide solution.
c) In the male that died, the tissues were autolyzed markedly, and a relationship with anamorelin could not be assessed.
d) It was considered to represent changes induced by the stimulation of the upper respiratory tract and trachea by anamorelin.
e) It was considered that inflammation of the upper respiratory tract caused abnormal respiration, resulting in worsening of state. Administration error of the drug into the trachea was considered to be responsible for the worsening of state.
f) It was considered to represent changes induced by the irritation or bitter taste of the administration solution.
g) Autopsy or histopathological examinations suggested changes due to administration error or accidental death.
h) It was considered to represent accidental vaginal prolapse and unrelated to the administration of anamorelin.
i) Since no similar changes were observed at higher doses, it was considered to be unrelated to the administration of anamorelin.

5.3 Genotoxicity

Bacterial reverse mutation tests and a chromosomal aberration assay with mammalian cultured cells were conducted as *in vitro* studies, and as a micronucleus test in rodents with murine bone marrow was conducted as an *in vivo* study (Table 12). The reverse mutation tests and the *in vivo* micronucleus test in rodents with murine bone marrow yielded negative results, whereas the chromosomal aberration assay revealed the induction of numerical aberrations. The applicant concluded that anamorelin in a clinical use induces no chromosomal aberration *in vivo* because of the following: (a) that the murine micronucleus test with the

maximum tolerated dose yielded negative results; and (b) that the concentration of unchanged anamorelin (20 μg/mL) observed in the chromosomal aberration assay that showed no numerical aberrations was approximately 32-fold higher than the C_{max} (629 ng/mL) after administration of anamorelin at a clinically recommended dosage regimen (100 mg, orally administered once daily, in a fasted state) in healthy adults.

Table 12. Genotoxicity studies

Study type		Test system	Metabolic activation (treatment)	Concentration (μg/plate or mL) Dose (mg/kg/day)	Results	Attached data CTD
In vitro	Bacterial reverse mutation test (Ames)	*Salmonella typhimurium*: TA98, TA100, TA1535, and TA1537 *Escherichia coli*: WP2uvrA	S9-/+	0, 31, 63, 125, 250, 500, and 1000	Negative	4.2.3.3.1-1
	Chromosomal aberration assay with mammalian cultured cells	Chinese hamster ovary cells	S9- (22 hours)	0, 10, 20, 40, 75, and 100	Positive (numerical aberrations) (≥40)	4.2.3.3.1-2
			S9-/+ (6 hours)	0, 39, 75[b)], 78, 100[b)], 150[b)], and 156	Negative	
In vivo	Micronucleus test in rodents	Bone marrow from male mice (ICR)		0, 50, 100, and 200[a)] (oral, once daily, for 2 days)	Negative	4.2.3.3.2-1

a) Anamorelin free base was spiked with 1 mol/L of hydrochloric acid and was diluted into distilled water adjusted to pH 5 with 1 mol/L of sodium hydroxide solution.
b) Performed for S9+ alone.

5.4 Carcinogenicity

The applicant explained that no carcinogenicity study was conducted in accordance with the Revision of Guidelines for Carcinogenicity Studies of Drugs (Notification No. 1127001, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare, dated November 27, 2008).

5.5 Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation in rats and studies for effects on embryo-fetal development in rats and rabbits were conducted (Table 13). The study of fertility and early embryonic development to implantation demonstrated no effects of anamorelin on the fertility and reproductive potential, and the studies for effects on embryo-fetal development showed no effects of anamorelin on the fetuses.

The applicant explained that no study was conducted for pre- and postnatal development, including maternal function because anamorelin should be used in patients with cachexia associated with radically unresectable, radical irradiation-unfeasible advanced cancer.

Table 13. Reproductive and developmental toxicity studies

Study type	Test system	Administration route	Treatment duration	Dose (mg/kg/day)	Main findings	No-observed adverse effect level (mg/kg/day)	Attached data CTD
Fertility and early embryonic development to implantation	Male and female rats (SD)	Oral	Male: from 2 weeks before mating to the previous day of autopsy, 56 days in total (once daily) Female: from 2 weeks before mating to Gestation Day 7 (once daily)	0[a], 15, 30, and 60	Death: 60 (1 of 22 male[b]), 30 (1 of 22 male[c]), and 15 (1 of 22 male[c]). ≥15: High body weight and high body weight gain; and high food consumption.	Parental animals (general toxicity): 60 Parental animals (fertility, reproductive potential, early embryonic development): 60	4.2.3.5.1-1
Effects on embryo-fetal development	Female rats (SD)	Oral	Gestation Days 6-17 (once daily)	0[a], 15, 30, and 80	Dams: ≥15: High body weight and high body weight gain; and high food consumption. 80: Respiration with murmur; and labored respiration. Fetuses: No abnormalities.	Parental animals (general toxicity): 30 Embryo-fetal development: 80	4.2.3.5.2-2
	Female rabbits (NZW)	Oral	Gestation Days 7-20 (once daily)	0[a], 10, 30, and 75/50[d]	Dams: Death: 75 (4 of 20 animals); decreased locomotor activity; tachypnea; irregular respiration; tremor; and ataxia. ≥10: High body weight gain and high food consumption. 75/50: Decreased locomotor activity; ataxia; tremor; and tachypnea. Fetuses: No abnormalities.	Parental animals (general toxicity): 30 Embryo-fetal development: 75/50	4.2.3.5.2-4

a) Water for injection
b) The autopsy showed fading discoloration of the lungs and pleural effusion, which were considered to be related to a drug administration error.
c) No abnormalities were observed in the general condition or autopsy, and no changes in general conditions related to administration of anamorelin at a higher dose, 60 mg/kg, were seen. Based on these findings, the death was considered unrelated to anamorelin.
d) In the anamorelin 75 mg/kg group, 4 of 20 animals died on their Gestation Days 9 to 14, and the dose of anamorelin after Gestation Days 13 to 16 was reduced to 50 mg/kg.

5.6 Local tolerance

A primary skin irritation assay in rabbits and an opacity and transport study with bovine corneas were conducted (Table 14). The opacity and transport study with bovine corneas showed a moderate irritant.

Table 14. Local tolerance studies

Test system	Application site	Study method	Main findings	Attached data CTD
Male rabbits (NZW)	Skin (untreated site or abrasion site)	A single application of anamorelin 500 mg (anamorelin moistened with deionized water to form paste was applied, was covered with a gauze patch, and was removed 24 hours later)	No irritant effect	4.2.3.6-1
Isolated bovine corneas	*In vitro*	Corneal opacity and penetration of fluorescein sodium were determined after dropping 20% anamorelin solution.	Irritant effect (moderate)	4.2.3.6-2

5.R Outline of the review conducted by PMDA

5.R.1 Effects of anamorelin on the liver

The 26-week repeated-dose toxicity study in rats showed effects of anamorelin on the liver including high blood AST and ALT levels, but no histopathological changes were found in the livers. The 4-week repeated-dose toxicity study in dogs showed high ALT levels, and the observed histopathological changes included inflammation around the hepatic portal vein, increases in pigmentation in the Kupffer cells and hepatocytes, and aggregation of inflammatory cells with pigmentation.

In light of the fact that effects of anamorelin on the liver were observed in non-clinical repeated-dose toxicity studies, PMDA reviewed the effects of anamorelin on the hepatic function in humans in a clinical section [see Section 7.R.2.3.3].

5.R.2 Photosafety of anamorelin

The applicant's explanation:

Anamorelin showed a maximum absorption at 291 nm, and the molar absorptivity was 4,958 L/mol·cm. The applicant did not conduct a photosafety study of anamorelin because no concerns for the photosafety were identified in the preceding foreign clinical studies of anamorelin. Although no protective measures for the skin or other relative tissues were taken in the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), the Japanese phase III study (ONO-7643-05), or the foreign phase III studies (Studies HT-ANAM-301 and HT-ANAM-302), treatment with anamorelin did not cause photosensitivity allergic reaction, photosensitivity reaction, photoelectric conjunctivitis, photodermatosis, retinal phototoxicity, or photophobia in any of the studies.

PMDA confirmed that no adverse events related to the photosafety occurred in Japanese or foreign clinical studies. PMDA considers that the photosafety of anamorelin is unlikely to be of clinical significance.

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

6.1 Biopharmaceutic studies and associated analytical methods

The formulations shown in Table 15 were used in the Japanese clinical studies which were submitted for this application for approval. A dissolution study was conducted for the changes in formulations, and the formulation used in the Japanese phase III study was confirmed to be biologically comparable to that used in the Japanese phase II study. According to the applicant's explanation, a dissolution study demonstrated the

comparability between the formulations used in the Japanese phase I studies and those used in the Japanese phase II and III studies.

Table 15. Formulations used in Japanese clinical studies

Clinical study	Formulation
Single-dose, phase I study (ONO-7643-01)	**Formulation A:** **Capsules (a capsule containing 5 mg of anamorelin)**
Single-dose, phase I study (ONO-7643-01) **Multiple-dose phase I study (ONO-7643-02)**	**Formulation B:** **Film-coated tablets (a tablet containing 25 mg of anamorelin)**
Phase II study (ONO-7643-03)	**Formulation C:** **Film-coated tablets (a tablet containing 50 mg of anamorelin)**
Phase II study (ONO-7643-04) **Phase III study (ONO-7643-05)**	**Formulation D (proposed for marketing):** **Film-coated tablets (a tablet containing 50 mg of anamorelin)**

Plasma concentrations of unchanged anamorelin and metabolites, plasma concentrations of unbound unchanged anamorelin, and urinary concentrations of unchanged anamorelin were determined with validated LC/MS/MS. The lower limit of quantification for plasma concentrations of unchanged anamorelin was 0.0800 to 25.0 ng/mL. The lower limit of quantification for plasma concentrations of M4 and M6 was 0.500 ng/mL. The lower limit of quantification for plasma concentrations of unbound unchanged anamorelin was 1.00 ng/mL. The lower limit of quantification for urinary concentrations of unchanged anamorelin was 0.080 to 30.00 ng/mL.

6.1.1 Studies using human biomaterials

6.1.1.1 Plasma protein binding (CTD 4.2.2.3-2 and 5.3.2.1-1: Studies 22835 and VREJV5901PB)

Human plasma was spiked with ^{3}H-anamorelin (0.1-1.0 μmol/mL), and the mean plasma protein binding was determined to be 97.3% to 98.3%, showing no concentration-dependency. Human plasma was spiked with ^{14}C-anamorelin (100-375 ng/mL), and the plasma protein binding was determined to be 94.2% to 95.4%. The binding of ^{14}C-anamorelin (200 and 375 ng/mL) to human serum albumin and human α1-acid glycoprotein was determined to be 36.4% to 37.3% and 97.0% to 97.2%, respectively, suggesting that anamorelin binds mainly to α1-acid glycoprotein in human plasma.

6.1.1.2 Evaluation of metabolites *in vitro* (CTD 4.2.2.4-1 and 4.2.2.4-2: Studies 22588 and BD000039)

Metabolites of anamorelin were investigated with human liver microsomes. M4 (a monooxidized form of anamorelin) and M6 (an *N*-demethylated form of anamorelin) were detected as main metabolites. The main metabolites in human liver microsomes are the same as those in rats and dogs, and no metabolites specific to humans were identified [see Section 4.3.1].

6.1.1.3 Evaluation of CYP isoforms involved in the metabolism of anamorelin (CTD 4.2.2.4-2 and 5.3.2.2-2: Studies BD000039 and 196103)

Human cytochrome P450 (CYP) isoforms expressing system (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) was spiked with anamorelin (1-100 μmol/L). The metabolite of anamorelin (M4) was formed from CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and the metabolite of anamorelin (M6) was formed from CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

Human liver microsomes were spiked with anamorelin (1-10 μmol/L) and agents inhibiting individual CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4)[9]. Ketoconazole, an agent of CYP3A4 inhibitor, reduced the elimination rate for M4 and M6 to 6.8% and 10.3% to 26.7% of that for control, respectively.

As a result of the above evaluation, the applicant considered CYP3A4 as the CYP isoform mainly involved in the metabolism of anamorelin.

6.1.1.4 Inhibitory effects of anamorelin on human hepatic drug-metabolizing enzymes (CTD 5.3.2.2-1, 5.3.2.2-2, and 5.3.2.2-3: Studies 22377, 196103, and 787917)

Human liver microsomes were used to evaluate the inhibitory effects of anamorelin (0.1-100 μmol/L) on CYP isoforms[10] (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4).

Anamorelin inhibited CYP3A4, and the IC_{50} value for metabolism of midazolam, a typical substrate of CYP3A4, was determined to be 11.34 μmol/L.

Anamorelin also inhibited CYP2C8, and the inhibition rate for metabolism of paclitaxel, a typical substrate of CYP2C8, was determined to be 8.8% to 26% at anamorelin 0.1 to 10 μmol/L, 39% at 30 μmol/L, and 36% at 100 μmol/L. In light of the fact that the maximum plasma concentration of anamorelin was 2.29 μmol/L at steady state after administration of anamorelin at a clinically recommended dosage regimen (100 mg, orally administered once daily, in a fasted state) in Japanese patients with cancer cachexia [see Section 6.2.4], the applicant explained that anamorelin is unlikely to inhibit CYP2C8 and to affect the pharmacokinetics of concomitant medications.

6.1.1.5 Induction effects of anamorelin on human hepatic drug-metabolizing enzymes (CTD 5.3.2.2-4 and 5.3.2.2-5: Studies Y[redacted]AG013 and 196632)

Human frozen hepatocytes were incubated with anamorelin (0.2-20 μmol/L) to evaluate the changes in levels of expression of messenger ribonucleic acid (mRNA) of CYP2B6 and CYP3A4. Anamorelin did not induce CYP2B6 mRNA, whereas CYP3A4 mRNA expression increased in a concentration-dependent manner with the maximum fold induction (a fold induction of anamorelin 20 μmol/L) of 5.40-fold. Human frozen hepatocytes were used to evaluate the induction effects of anamorelin (0.2-20 μmol/L) on CYP1A2, CYP2B6, and CYP3A4, and the enzyme activity increased <2-fold for all of these CYP isoforms over the tested range of anamorelin concentrations. The applicant explained that the induction effect of anamorelin on CYP3A4 is unlikely to affect the pharmacokinetics of concomitant drugs because the plasma anamorelin concentrations on Day 7 did not decrease as compared with that on Day 1 in the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05) [see Sections 6.2.5 and 6.2.6] and because data from a

[9] The following agents were used:
CYP1A2, furafylline; CYP2A6, 8-mercaptopurine; CYP2B6, thiotepa; CYP2C8, quercetin; CYP2C9, sulfaphenazole; CYP2C19, ticlopidine; CYP2D6, quinidine; CYP2E1, diethyldithiocarbamate; and CYP3A4, ketoconazole.

[10] The following agents were used as substrates:
CYP1A2, ethoxyresorufin; CYP2A6, coumarin; CYP2B6, bupropion; CYP2C8, paclitaxel: CYP2C9, tolbutamide; CYP2C19, S-mephenytoin; CYP2D6, bufuralol; CYP2E1, chlorzoxazone; and CYP3A4, midazolam, testosterone, and nifedipine.

pharmacokinetic study on the possible interaction with midazolam, a substrate of CYP3A4, suggest that anamorelin is unlikely to have clinically significant effects on the pharmacokinetics of midazolam [see Section 6.2.7].

6.1.1.6 Investigation of transport mediated by transporters (CTD 5.3.2.3-1: Study HT-ANAM-PK/TK-24)

Madin-Darby canine kidney II (MDCKII) cells expressing P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) were used to evaluate the transport of P-gp or BCRP by anamorelin 1 to 100 µmol/L. Anamorelin was found to be a substrate of P-gp and was considered unlikely to be a substrate of BCRP.

Chinese hamster ovary (CHO) cells expressing OATP1B1, OATP1B3, or OCT1 were used to the transport of OATP1B1, OATP1B3, or OCT1 by anamorelin 1 and 10 µmol/L. Anamorelin was found to be a substrate of OATP1B3 and was considered unlikely to be a substrate of OATP1B1 or OCT1. At present, the applicant considered that no precautionary statements are required in the package insert for an interaction between anamorelin and drugs inhibiting OATP1B3 because the incidence of adverse events did not increase with the concomitant use of anamorelin and drugs inhibiting OATP1B3 in Japanese and foreign clinical studies.[11)]

6.1.1.7 Investigation of inhibitory effects of anamorelin on transporters (5.3.2.3-1 and 5.3.2.3-2: Studies HT-ANAM-PK/TK-24 and Y[redacted]AG005)

Concerning of inhibitory effects of anamorelin on P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, and MRP2, cells expressing these transporters or membrane vesicles were used to evaluate the effects of anamorelin on the transport of reference materials[12)]. Anamorelin inhibited P-gp, BCRP, BSEP, OATP1B3, OAT1, OCT1, OCT2, MATE1, and MATE2-K, and the IC_{50} value was >120.0 µmol/L, 218.1 µmol/L, 210.5 µmol/L, 24.0 µmol/L, 171.6 µmol/L, 26.7 µmol/L, 33.0 µmol/L, 7.7 µmol/L, and 209.9 µmol/L, respectively. In light of the fact that the maximum plasma concentration of anamorelin was 2.29 µmol/L at steady state after administration of anamorelin at a clinically recommended dosage regimen (100 mg, orally administered once daily, in a fasted state) in Japanese patients with cancer cachexia, the applicant evaluated the possibility that the inhibitory effects of anamorelin on MATE1 affect the pharmacokinetics of concomitant drugs. In Japanese and foreign clinical studies[13)], no adverse events occurred that were considered to be related to an interaction between anamorelin and drugs as substrates of MATE1. As shown in these findings, the applicant considered that no precautionary statements are required in the package insert at present for the interaction mediated by the inhibitory effects of anamorelin on MATE1.

[11)] The Japanese phase II study (ONO-7643-04), the Japanese phase III study (ONO-7643-05), and the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302).

[12)] The following reference materials were used:
P-gp, ^{3}H-digoxin; BCRP, ^{3}H-estrone-3-sulfate; BSEP, ^{3}H-taurocholate; OATP1B1, ^{3}H-estrone-3-sulfate; OATP1B3, Fluo-3; OAT1, ^{3}H-*p*-aminohippuric acid; OAT3, ^{3}H-estrone-3-sulfate; OCT1, ^{14}C-metformin; OCT2, ^{14}C-metformin; MATE1, ^{14}C-metformin; MATE2-K, ^{14}C-metformin; and MRP2, ^{3}H-estradiol-17-β-D-glucuronide-sulfate.

[13)] The Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), the Japanese phase III study (ONO-7643-05), and the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302)

6.2 Clinical pharmacology

6.2.1 Japanese phase I single-dose study (CTD 5.3.3.1-6: Study ONO-7643-01 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind study was conducted at a study site in Japan to evaluate the pharmacokinetics and safety of a single oral dose of anamorelin in Japanese healthy men (target sample size of 48 subjects; 8 subjects in each step [2 subjects in the placebo group and 6 subjects in the anamorelin group]; a total of 6 steps).

A single oral dose of placebo or anamorelin 10, 25, 50, 75, 100, or 125 mg was to be administered in a fasted state.

All of the 48 subjects treated (12 in the placebo group and 36 in the anamorelin groups) were included in the safety analysis set, and 36 subjects in the anamorelin groups were included in the pharmacokinetics analysis set.

Concerning pharmacokinetics, the plasma pharmacokinetic parameters of unchanged anamorelin are shown in Table 16. The C_{max} and $AUC_{0-\infty}$ increased more than dose-proportionally for the doses tested (10-125 mg). Anamorelin did not accumulate after multiple doses at 50 to 150 mg once daily [see Section 6.2.2].

The cumulative urinary excretion rate of unchanged anamorelin up to 48 hours after a single oral dose of anamorelin 10 mg was 0.7% of the administered dose.

Table 16. Pharmacokinetic parameters of unchanged anamorelin in plasma after a single oral dose of anamorelin in a fasted state in Japanese healthy adults

Anamorelin dose	N	C_{max} (ng/mL)	t_{max} [a)] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
10 mg	6	12 ± 6	0.9 (0.5, 3.0)	49 ± 18	6.6 ± 2.9
25 mg	6	59 ± 24	1.6 (0.3, 3.0)	179 ± 78	8.8 ± 2.0
50 mg	6	176 ± 63	1.8 (0.5, 2.5)	639 ± 263	9.2 ± 1.0
75 mg	6	519 ± 177	1.3 (0.5, 1.5)	1,380 ± 410	8.7 ± 0.8
100 mg	6	707 ± 307	0.8 (0.5, 2.0)	1,970 ± 890	8.8 ± 0.9
125 mg	6	1,230 ± 590	0.5 (0.3, 0.8)	2,900 ± 1,200	8.2 ± 0.7

Mean ± SD
a) Median (minimum, maximum)

After administration of study drug in a fasted state, adverse events were reported in 8.3% (1 of 12) of subjects in the placebo group (urine ketone body present and white blood cells urine positive [1 subject each] [the subject had more than 1 event]), 33.3% (2 of 6) of subjects in the anamorelin 25 mg group (dizziness postural, feeling abnormal, and blood creatine phosphokinase increased [1 subject each] [1 subject had more than 1 event]), 0% (0 of 6) of subjects in the anamorelin 75 mg group, 16.7% (1 of 6) of subjects in the anamorelin 100 mg group (feeling hot), and 50.0% (3 of 6) of subjects in the anamorelin 125 mg group (feeling hot, thirst, nasal congestion, and nasopharyngitis [1 subject each] [1 subject had more than 1 event]). Dizziness postural and feeling abnormal in the anamorelin 25 mg group, feeling hot in the anamorelin 100 mg group, and feeling hot and thirst in the anamorelin 125 mg group were assessed as adverse events for which causal relationship with anamorelin could not be ruled out (hereafter referred to as "adverse drug reactions"). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.2 Japanese phase I single-dose and multiple-dose study (CTD 5.3.3.1-7: Study ONO-7643-02 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind (Parts A and C) and open-label (Part B) study was conducted at a study site in Japan to evaluate the pharmacokinetics and safety of a single or multiple oral doses of anamorelin in Japanese healthy men (target sample size of 48 subjects [Part A, 2 subjects in the placebo group and 6 subjects in the anamorelin group; Part B, 8 subjects in the anamorelin group; and Part C, 2 subjects in the placebo group and 6 subjects in the anamorelin group in each step, a total of 4 steps]).

Part A: Single oral dosing

A single oral dose of placebo or anamorelin 150 mg was to be administered in a fasted state.

All of the 8 subjects treated (2 subjects in the placebo group and 6 subjects in the anamorelin 150 mg group) were included in the safety analysis set, and 6 subjects in the anamorelin 150 mg group were included in the pharmacokinetics analysis set.

The plasma pharmacokinetic parameters of unchanged anamorelin are shown in Table 17.

Table 17. Plasma pharmacokinetic parameters of unchanged anamorelin after a single oral dose of anamorelin in a fasted state in Japanese healthy adults

Anamorelin dose	N	C_{max} (ng/mL)	t_{max} [a)] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
150 mg	**6**	**1,060 ± 350**	**0.5 (0.5, 2.5)**	**3,290 ± 1,010**	**7.9 ± 1.1**

Mean ± SD
a) Median (minimum, maximum).

Adverse events were reported in 0% (0 of 2) of subjects in the placebo group and 33.3% (2 of 6) of subjects in the anamorelin 150 mg group (hyperhidrosis [2 subjects]). Hyperhidrosis reported in 33.3% (2 of 6) of subjects in the anamorelin 150 mg group was assessed as an adverse drug reaction. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

Part B: Food effects

Part B consisted of Periods I to III with a 1-day rest period between the Periods.

A single dose of anamorelin 50 mg was to be administered in a fasted state[14)] (Period I), 1 hour before a meal (Period II), and 2 hours after a meal (Period III).

All of the 8 subjects treated were included in the safety analysis set. Among the 8 subjects, 7 were included in the pharmacokinetics analysis set, excluding 1 subject who discontinued the study with a withdrawal of consent after the completion of Period II.

The plasma pharmacokinetic parameters of unchanged anamorelin are shown in Table 18.

[14)] The study drug was to be administered at 9:00 a.m., and the subjects fasted from 11:00 p.m. on the day before the administration of the study drug until 4 hours after the administration.

Table 18. Plasma pharmacokinetic parameters of unchanged anamorelin after a single oral dose of anamorelin in a fasted state, 1 hour before a meal, or 2 hours after a meal in Japanese healthy adults

Anamorelin dose	Regimen (Timing of administration of anamorelin)	N	C_{max} (ng/mL)	t_{max} a) (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
50 mg	Fasted state (Period I)	7	211 ± 96	1.0 (0.5, 2.0)	648 ± 254	8.2 ± 1.1
	1 hour before a meal (Period II)	7	225 ± 90	1.5 (0.5, 1.5)	521 ± 217	9.5 ± 1.0
	2 hours after a meal (Period III)	7	73 ± 49	1.0 (0.8, 3.0)	316 ± 112	10 ± 1

Mean ± SD
a) Median (minimum, maximum).

The geometric mean [95% CI] of the ratio of C_{max} and $AUC_{0-\infty}$ for administration 1 hour before a meal (Period II) to those for administration in a fasted state (Period I) (1 hour before a meal/fasting) was 1.09 [0.85, 1.40] and 0.80 [0.66, 0.96], respectively, showing no food effects. The geometric mean [95% CI] of C_{max} and $AUC_{0-\infty}$ for administration 2 hours after a meal (Period III) to those for administration in a fasted state (Period I) (2 hours after a meal/fasting) was 0.31 [0.20, 0.49] and 0.49 [0.44, 0.55], respectively, showing that administration of anamorelin 2 hours after a meal affected the plasma exposure of anamorelin. Since data from a foreign phase I study (RC-1291-108) investigating the interaction between anamorelin and pantoprazole demonstrated that an increase in gastric pH had no effects on the absorption of anamorelin, the exposure of anamorelin was considered to decrease by interaction with dietary components. In subsequent clinical studies, anamorelin was administered orally in a fasted state, and subjects were instructed not to eat for 1 hour after the administration of anamorelin based on the above findings.

Adverse events were reported in 25.0% (2 of 8) of subjects (feeling hot and hyperhidrosis [2 subjects each] [the subjects had more than 1 event]) for administration in a fasted state (Period I), 25.0% (2 of 8) of subjects (feeling hot and feeling abnormal [1 subject each]) for administration 1 hour before meal (Period II), and 14.3% (1 of 7) of subjects (blood uric acid increased) for administration 2 hours after meal (Period III). Feeling hot in 25.0% (2 of 8) of subjects and hyperhidrosis in 25.0% (2 of 8) of subjects for administration in a fasted state (Period I), and feeling hot in 12.5% (1 of 8) of subjects for administration 1 hour before a meal (Period II) were considered as adverse drug reactions. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

Part C: Multiple oral dosing

Placebo or anamorelin 50, 100, 125, or 150 mg was to be repeatedly administered once daily in a fasted state for 7 days.

All of the 32 subjects treated (8 subjects in the placebo group and 24 subjects in the anamorelin group) were included in the safety analysis set, and 24 subjects in the anamorelin group were included in the pharmacokinetics analysis set.

The plasma pharmacokinetic parameters of unchanged anamorelin are shown in Table 19. The C_{max} and AUC_{0-}

$_{24h}$ increased more than dose-proportionally for the doses tested (50-150 mg). The C_{max} and AUC_{0-24h} of unchanged anamorelin were comparable between Days 1 and 7 in the anamorelin 100 mg group, in which anamorelin was administered in healthy adults with the same dosage regimen as that of clinically recommended (100 mg, orally administered, once daily, in a fasted state), showing no accumulation after multiple dosing.

Table 19. Plasma pharmacokinetic parameters of unchanged anamorelin after multiple oral doses of anamorelin in a fasted state in Japanese healthy adults

Anamorelin dose	N	Time points	C_{max} (ng/mL)	t_{max} [a)] (h)	AUC_{0-24h} (ng·h/mL)	$t_{1/2}$ (h)
50 mg	6	Day 1	224 ± 69	1.8 (0.5, 3.0)	574 ± 87	5.8 ± 0.7
		Day 7	158 ± 53	2.0 (0.5, 4.0)	574 ± 132	9.4 ± 0.7
100 mg	6	Day 1	605 ± 276	0.9 (0.5, 1.5)	1,670 ± 570	5.6 ± 0.7
		Day 7	629 ± 203	0.9 (0.5, 1.5)	1,880 ± 430	9.4 ± 0.6
125 mg	6	Day 1	905 ± 515	0.5 (0.5, 0.8)	2,230 ± 970	5.5 ± 0.6
		Day 7	835 ± 362	0.8 (0.5, 1.0)	2,320 ± 780	9.2 ± 0.4
150 mg	6	Day 1	696 ± 255	0.8 (0.5, 2.0)	2,340 ± 630	5.8 ± 0.3
		Day 7	891 ± 216	0.9 (0.8, 4.0)	2,940 ± 1,170	9.6 ± 1.8

Mean ± SD
a) Median (minimum, maximum)

Adverse events were reported in 25.0% (2 of 8) of subjects in the placebo group, 16.7% (1 of 6) of subjects in the anamorelin 50 mg group, 16.7% (1 of 6) of subjects in the anamorelin 100 mg group, 16.7% (1 of 6) of subjects in the anamorelin 125 mg group, and 83.3% (5 of 6) of subjects in the anamorelin 150 mg group. The following adverse events occurred in ≥2 subjects in any group: ALT increased (0% [0 of 8] of subjects in the placebo group, 0% [0 of 6] of subjects in the anamorelin 50 mg group, 16.7% [1 of 6] of subjects in the anamorelin 100 mg group, 0% [0 of 6] of subjects in the anamorelin 125 mg group, and 50.0% [3 of 6] of subjects in the anamorelin 150 mg group); and blood triglycerides increased (0% [0 of 8] of subjects in the placebo group, 0% [0 of 6] of subjects in the anamorelin 50 mg group, 0% [0 of 6] of subjects in the anamorelin 100 mg group, 16.7% [1 of 6] of subjects in the anamorelin 125 mg group, and 33.3% [2 of 6] of subjects in the anamorelin 150 mg group). Adverse drug reactions were reported in 0% (0 of 8) of subjects in the placebo group, 0% (0 of 6) of subjects in the anamorelin 50 mg group, 16.7% (1 of 6) of subjects in the anamorelin 100 mg group, 0% (0 of 6) of subjects in the anamorelin 125 mg group, and 66.7% (4 of 6) of subjects in the anamorelin 150 mg group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.3 Foreign phase I study (mass balance study) (CTD 5.3.3.1-3: Study RC-1291-103 [[redacted] 20[redacted]] [reference data])

An open-label study was conducted at a study site outside Japan to evaluate the mass balance after a single oral dose of ^{14}C-anamorelin in non-Japanese healthy men (target sample size of 8 subjects).

A single oral dose of ^{14}C-anamorelin 25 mg (solution) was to be administered in a fasted state.

All 8 subjects enrolled in the study were included in the pharmacokinetics and safety analysis sets.

The pharmacokinetic parameters of unchanged anamorelin are shown in Table 20. The ratio of unchanged anamorelin, metabolites M4, and M6 to the total plasma radioactivity was determined to be approximately 88%

to 90%, approximately 7.5% to 9.5%, and approximately 2.5%, respectively, and unchanged anamorelin was mainly detected in plasma.

Table 20. Pharmacokinetic parameters of unchanged anamorelin in plasma after single oral dose of ^{14}C-anamorelin in a fasted state in non-Japanese healthy adults

Anamorelin dose	N	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng·h/mL)	$t_{1/2}$ (h)
25 mg	**8**	**27.0 ± 16.7**	**1.6 ± 0.9**	**125 ± 40**	**13.4 ± 6.1**

Mean ± SD

The urinary and fecal excretion rate of ^{14}C-anamorelin up to 192 hours post-dose was 7% to 8% and 92% to 93% of the administered radioactivity, respectively. In urine, M12 (a metabolite derived from M4, 6%-7% of the administered radioactivity) was mainly detected in urine, and unchanged anamorelin was marginally detected (<1% of the administered radioactivity). In feces, unchanged anamorelin (87%-89% of the administered radioactivity) was mainly detected, and metabolites including M6 (<2.5% of the administered radioactivity) and M4 (<1.5% of administered radioactivity) were detected.

Adverse events were reported in 75.0% (6 of 8) of subjects, and adverse events reported in ≥2 subjects were dysgeusia (3 subjects), constipation and hunger (2 subjects each). Dysgeusia in 37.5% (3 of 8) of subjects, constipation in 25.0% (2 of 8) of subjects, and headache in 12.5% (1 of 8) of subjects were assessed as adverse drug reactions. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.4 Japanese phase II study (CTD 5.3.5.1-1: Study ONO-7643-03 [March 2011 to September 2012])

Plasma concentrations of anamorelin and unbound anamorelin were evaluated after multiple oral doses of anamorelin in Japanese patients with non-small cell lung cancer and cachexia (target sample size of 162 subjects, 54 subjects in each group).

Placebo or anamorelin 50 or 100 mg was to be administered orally once daily in a fasted state for 12 weeks [see Section 7.1 for the outlines of the study and results of efficacy and safety].

Plasma concentrations of unchanged anamorelin and unbound anamorelin are shown in Table 21. Although changes in plasma anamorelin concentrations substantially varied among individuals, the plasma anamorelin concentrations in the study population did not markedly differ from those in healthy adults who received multiple doses of anamorelin 100 mg orally once daily in a fasted state.

Table 21. Plasma concentrations of unchanged anamorelin and unbound unchanged anamorelin after multiple oral doses of anamorelin in a fasted state in Japanese patients with non-small cell lung cancer and cachexia (ng/mL)

	Week	Starting date	Week 4 or 8 of treatment[a)]		
		1 hour post-dose	Before dosing	1-2 hours post-dose	4-6 hours post-dose
Anamorelin 50 mg	Number of subjects	65	55	54	54
	Plasma concentrations of unchanged anamorelin	543 ± 683	11 ± 11	405 ± 443	146 ± 125
	Plasma concentrations of unbound unchanged anamorelin	49 ± 52	—	32 ± 29	15 ± 15
Anamorelin 100 mg	Number of subjects	55	47	47	47
	Plasma concentrations of unchanged anamorelin	1,430 ± 1,370	29 ± 28	1,250 ± 1,090	452 ± 474
	Plasma concentrations of unbound unchanged anamorelin	128 ± 118	—	107 ± 87	40 ± 36

Mean ± SD

a) Blood samples were to be collected before dosing, 1 to 2 hours post-dose, and 4 to 6 hours post-dose on a day in Week 4 or 8 of treatment. Plasma concentrations of unbound unchanged anamorelin were not determined before dosing in Week 4 or 8 of treatment.

6.2.5 Japanese phase II study (CTD 5.3.5.1-2: Study ONO-7643-04 [May 2014 to October 2015])

Plasma concentrations of anamorelin and unbound anamorelin were evaluated after multiple oral doses of anamorelin in Japanese patients with non-small cell lung cancer and cachexia (target sample size of 170 subjects, 85 subjects in each group).

Placebo or anamorelin 100 mg was to be administered orally once daily in a fasted state for 12 weeks [see Section 7.2 for the outlines of the study and results of efficacy and safety].

Plasma concentrations of unchanged anamorelin and unbound anamorelin are shown in Table 22. Although changes in plasma anamorelin concentrations substantially varied among individuals, the plasma anamorelin concentrations in the study population did not markedly differ from those in healthy adults who received multiple doses of anamorelin 100 mg orally once daily in a fasted state.

Table 22. Plasma concentrations of unchanged anamorelin and unbound unchanged anamorelin after multiple oral doses of anamorelin in a fasted state in Japanese patients with non-small cell lung cancer and cachexia (ng/mL)

	Week	Starting date	Week 1, 3, or 6 of treatment[a)]		
		1 hour post-dose	Before dosing	1 hour post-dose	4-6 hours post-dose
Anamorelin 100 mg	Number of subjects	83	76	76	76
	Plasma concentrations of unchanged anamorelin	1,130 ± 990	26 ± 25	1,120 ± 922	385 ± 324
	Plasma concentrations of unbound unchanged anamorelin	83 ± 85	—	78 ± 78	27 ± 22

Mean ± SD

a) Blood samples were to be collected before dosing, 1 hour post-dose, and 4 to 6 hours post-dose on a day in Week 1, 3 or 6 of treatment. Plasma concentrations of unbound unchanged anamorelin were not determined before dosing in Week 1, 3, or 6 of treatment.

6.2.6 Japanese phase III study (CTD 5.3.5.2-1: Study ONO-7643-05 [February 2017 to April 2018])

Plasma concentrations of anamorelin and unbound anamorelin were evaluated after multiple oral doses of anamorelin in Japanese cachexic patients with colorectal cancer, gastric cancer, or pancreatic cancer (target sample size of 50 subjects).

Anamorelin 100 mg was to be administered orally once daily in a fasted state for 12 weeks [see Section 7.3 for the outlines of the study and results of efficacy and safety].

Plasma concentrations of unchanged anamorelin and unbound anamorelin are shown in Table 23. Although changes in plasma anamorelin concentrations substantially varied among individuals, the plasma anamorelin concentrations in the study population did not markedly differ from those in healthy adults who received multiple doses of anamorelin 100 mg orally once daily in a fasted state.

Table 23. Plasma concentrations of unchanged anamorelin and unbound unchanged anamorelin after multiple oral doses of anamorelin in a fasted state in Japanese cachexic patients with colorectal cancer, gastric cancer, or pancreatic cancer (ng/mL)

	Week	Starting date	Week 1, 3, or 6 of treatment[a)]		
		1 hour post-dose	Before dosing	1 hour post-dose	4-6 hours post-dose
Anamorelin 100 mg	Number of subjects	49	44	44	43
	Plasma concentrations of unchanged anamorelin	761 ± 703	21 ± 18	711 ± 559	287 ± 248
	Plasma concentrations of unbound unchanged anamorelin	50 ± 43	—	49 ± 37	18 ± 14

Mean ± SD

a) Blood samples were to be collected before dosing, 1 hour post-dose, and 4 to 6 hours post-dose on a day in Week 1, 3 or 6 of treatment. Plasma concentrations of unbound unchanged anamorelin were not determined before dosing in Week 1, 3, or 6 of treatment

6.2.7 Foreign phase I study (a study for drug interaction with a CYP3A4 substrate) (CTD 5.3.3.4-1: Study RC-1291-104 [[redacted] to [redacted]] [reference data])

A placebo-controlled, randomized, double-blind study was conducted at a study site outside Japan to evaluate the effects of anamorelin on the pharmacokinetics of midazolam (a CYP3A4 substrate) in non-Japanese healthy adults (target sample size of 10 subjects: 2 subjects in the placebo group and 8 subjects in the anamorelin 75 mg group).

Placebo or anamorelin 75 mg was to be repeatedly administered orally once daily in a fasted state for 6 days, and midazolam (solution)[15)] was to be orally administered at 6 mg 2 days before the start of administration of anamorelin and at 3 mg on Day 6 of administration of anamorelin.

All of the 9 subjects randomized[16)] (1 subject in the placebo group and 8 subjects in the anamorelin 75 mg group) received the study drug, and 8 subjects in the anamorelin group were included in the pharmacokinetics analysis set.

Table 24 shows the geometric mean ratio (combined use/monotherapy) of the C_{max} and $AUC_{0-\infty}$ of midazolam corrected with the midazolam dose in the combined use of anamorelin and midazolam (Day 6 of the administration of anamorelin) to those in midazolam monotherapy (without anamorelin) (2 days before the administration of anamorelin). The dose-corrected C_{max} and $AUC_{0-\infty}$ of midazolam after its administration in combination with anamorelin increased by 18% and decreased by 5.4%, respectively, as compared to those after midazolam monotherapy. The applicant concluded that anamorelin has no clinically significant effects on the pharmacokinetics of midazolam because the intra-individual changes in C_{max} and $AUC_{0-\infty}$ of midazolam after its administration have been reported to be 20.5% and 16.2%, respectively (*Pharmacology*. 2018;101:170-5).

15) The oral formulation of midazolam has not been approved in Japan. On the basis of the plasma pharmacokinetic parameters of midazolam after a single oral dose of midazolam solution 2 or 6 mg in non-Japanese healthy subjects (*J Clin Pharmacol*. 2003;43:1091-100, *Clin Pharmacol Ther*. 1999;66:461-71), the applicant explained that the parameters would be linear after oral administration of midazolam at 2 to 6 mg.

16) A total of 10 subjects were included, but a subject was excluded because of infection with influenza.

Table 24. Effects of anamorelin on the plasma pharmacokinetic parameters of midazolam

Concomitant drug (oral administration)	Number of subjects	Geometric mean ratio [90% CI] of pharmacokinetic parameters of midazolam (in combination with anamorelin/without anamorelin)	
		C_{max}/Dose	$AUC_{0-\infty}$/Dose
Midazolam[a)]	8	1.18 [0.90, 1.54]	0.946 [0.78, 1.14]

a) 6 mg when administered without anamorelin, and 3 mg when administered with anamorelin.

6.2.8 Foreign phase I study (a drug interaction study with CYP3A4 inhibitor) (CTD 5.3.3.4-2: Study RC-1291-105 [20 to 20] [reference data])

A randomized, open-label, cross-over study was conducted at a study site outside Japan to evaluate the effects of ketoconazole (a CYP3A4 inhibitor) on the pharmacokinetics of anamorelin in non-Japanese healthy men (target sample size of 12 subjects: 2 subjects in each group).

In Period A, a single oral dose of anamorelin 25 mg was to be administered in a fasted state. In Period C, a single oral dose of anamorelin 25 mg was to be administered in a fasted state, and ketoconazole 200 mg was to be administered every 12 hours, 3 doses in total. The treatment periods were separated with 5 to 10 days of rest period.

Of 13 subjects enrolled in this study, 12 subjects were included in the pharmacokinetics analysis set, excluding 1 subject who discontinued the study because of noncompliance with the study protocol after the completion of the first treatment period.

The pharmacokinetic parameters of unchanged anamorelin without ketoconazole (Period A) and with ketoconazole (Period C) are shown in Table 25. The C_{max} and $AUC_{0-\infty}$ of anamorelin in combination with ketoconazole increased to 31.2-fold and 3.22-fold of those without ketoconazole, respectively. In light of the findings, the applicant concluded that interaction with ketoconazole exists.

Table 25. Plasma pharmacokinetic parameters of unchanged anamorelin with or without ketoconazole

Anamorelin dose	Concomitant drug	N	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
25 mg	Without ketoconazole	12	118 ± 114	1.53 ± 0.704	261 ± 127	7.25 ± 1.92
	With ketoconazole	12	368 ± 120	0.638 ± 0.221	840 ± 193	8.59 ± 1.66

Mean ± SD

6.2.9 Foreign phase I study (a drug interaction study with CYP3A4 inducer and CYP2D6 inhibitor) (CTD 5.3.3.4-5: Study HT-ANAM-114 [20 to 20] [reference data])

An open-label study was conducted at a study site outside Japan to evaluate the effects of rifampicin (CYP3A4 inducer) and paroxetine (CYP2D6 inhibitor) on the pharmacokinetics of anamorelin in non-Japanese healthy adults (target sample size of 32 subjects; 16 subjects in each part).

In Part 1, anamorelin 100 mg was to be orally administered once daily on Days 1 and 18 or once daily on Days 8 and 18, and rifampicin 600 mg was to be administered orally once daily from Days 11 through 18. In Part 2, anamorelin 100 mg was to be administered orally once daily on Days 1 and 13, and paroxetine 20 mg was to be administered orally once daily from Days 4 through 14.

All of the 32 subjects enrolled in the study were included in the pharmacokinetics analysis set.

The pharmacokinetic parameters of unchanged anamorelin with or without rifampicin are shown in Table 26. The C_{max} and $AUC_{0-\infty}$ of unchanged anamorelin in combination with rifampicin decreased to 0.43-fold and 0.32-fold of those without rifampicin, respectively. In light of the findings, the applicant concluded that rifampicin (CYP3A4 inducer) affected the pharmacokinetics of anamorelin.

Table 27 shows the geometric mean ratio (combined use/monotherapy) of C_{max} and $AUC_{0-\infty}$ anamorelin administered with paroxetine to those without paroxetine. Although the 90% confidence interval for the ratio of the geometric mean of C_{max} and $AUC_{0-\infty}$ of anamorelin administered in combination with paroxetine fell out of the range of 0.8 to 1.25, the intra-individual changes in C_{max} and $AUC_{0-\infty}$ of anamorelin after oral dosing was 19.0% to 33.6% and 19.7% to 29.9%, respectively. As shown in the above, the applicant concluded that paroxetine has no clinically significant effects on the pharmacokinetics of anamorelin.

Table 26. Plasma pharmacokinetic parameters of unchanged anamorelin with or without rifampicin

Anamorelin dose	Concomitant drug (Timing of administration of anamorelin)	N	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
100 mg	Without rifampicin	16	1,005.9 ± 340.2	1.0 ± 0.7	2,390.7 ± 1,019.2	6.8 ± 3.1
	With rifampicin	16	454.3 ± 209.3	0.9 ± 0.5	779.0 ± 454.6	3.6 ± 1.2

Mean ± SD

Table 27. Effects of paroxetine on the plasma pharmacokinetic parameters of anamorelin

Concomitant drug (Oral administration)	Number of subjects	Geometric mean ratio [90% CI] of the pharmacokinetic parameters of anamorelin (in combination with paroxetine/without paroxetine)	
		C_{max}	$AUC_{0-\infty}$
Paroxetine 20 mg	16[a)]	1.29 [1.14, 1.45]	0.87 [0.77, 0.99]

a) 15 subjects received anamorelin in combination with paroxetine.

6.2.10 Foreign phase I study (a thorough QT/QTc study) (5.3.4.1-1: Study HT-ANAM-113 [20 to 20] [reference data])

A placebo and active-controlled, randomized, double-blind, 4-group, 4-period, crossover study was conducted at a study site outside Japan to evaluate the effects of a single oral dose of anamorelin on QT/QTc intervals in non-Japanese healthy adults aged 18 to 45 years (target sample size of 60 subjects).

A single oral dose of placebo, anamorelin 100 or 300 mg[17)], or moxifloxacin 400 mg as a positive control was to be administered in a fasted state with a rest period of 5 to 7 days.

All of the 60 subjects receiving the study drug[18)] were included in the safety analysis set, and 56 of the 60 subjects were included in the pharmacokinetics analysis set.

Adverse events were reported in 10.3% (6 of 58) of subjects in the placebo group, 22.2% (12 of 54) of subjects in the anamorelin 100 mg group, 46.4% (26 of 56) of subjects in the anamorelin 300 mg group, and 12.3% (7

[17)] Initially, at the start of the study, the maximum dose of anamorelin was specified to be 400 mg. However, QRS widened was reported in 1 subject receiving anamorelin 400 mg in Period I. Because of a safety concern, the administration of anamorelin 400 mg was discontinued after the completion of Period I. Considering the safety of subjects, the study was resumed with a maximum anamorelin dose of 300 mg. For the plasma pharmacokinetic parameters of unchanged anamorelin in subjects receiving anamorelin 400 mg, C_{max} was 2,934.1 [2,409.1, 3,573.6] ng/mL, and $AUC_{0\text{-}last}$ was 3,421.85 [3,041.16, 3,850.19] ng· h/mL (the geometric mean [95% CI] in 7 subjects).

[18)] Excluding the first cohort.

of 57) of subjects in the moxifloxacin group. Adverse drug reactions were reported in 3.4% (2 of 58) of subjects in the placebo group, 20.4% (11 of 54) of subjects in the anamorelin 100 mg group, 46.4% (26 of 56) of subjects in the anamorelin 300 mg group, and 10.5% (6 of 57) of subjects in the moxifloxacin group. Adverse events and adverse drug reactions reported in ≥3 subjects in any group are shown in Tables 28 and 29, respectively. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

Table 28. Adverse events reported in ≥3 subjects in any group

	Placebo (n = 58)	Anamorelin 100 mg (n = 54)	Anamorelin 300 mg (n = 56)	Moxifloxacin (n = 57)
Overall	**10.3 (6)**	**22.2 (12)**	**46.4 (26)**	**12.3 (7)**
Feeling hot	**1.7 (1)**	**13.0 (7)**	**23.2 (13)**	**0 (0)**
Dizziness	**0 (0)**	**0 (0)**	**19.6 (11)**	**3.5 (2)**
Hyperhidrosis	**0 (0)**	**7.4 (4)**	**12.5 (7)**	**0 (0)**
Diarrhoea	**0 (0)**	**1.9 (1)**	**10.7 (6)**	**0 (0)**
Asthenia	**0 (0)**	**3.7 (2)**	**5.4 (3)**	**0 (0)**

MedDRA/J ver.15.0
Incidence, % (number of subjects with adverse events)

Table 29. Adverse drug reactions reported in ≥3 subjects in any group

	Placebo (n = 58)	Anamorelin 100 mg (n = 54)	Anamorelin 300 mg (n = 56)	Moxifloxacin (n = 57)
Overall	**3.4 (2)**	**20.4 (11)**	**46.4 (26)**	**10.5 (6)**
Feeling hot	**0 (0)**	**13.0 (7)**	**23.2 (13)**	**0 (0)**
Dizziness	**0 (0)**	**0 (0)**	**19.6 (11)**	**3.5 (2)**
Hyperhidrosis	**0 (0)**	**7.4 (4)**	**12.5 (7)**	**0 (0)**
Diarrhoea	**0 (0)**	**1.9 (1)**	**10.7 (6)**	**0 (0)**
Asthenia	**0 (0)**	**3.7 (2)**	**5.4 (3)**	**0 (0)**

MedDRA/J ver.15.0
Incidence, % (number of subjects with adverse drug reactions)

The maximum difference (the upper limit of one-sided 95% CI) in placebo-adjusted change from baseline in QTcF (ΔΔQTcF) was 6.16 (7.73) ms in the anamorelin 100 mg group and 7.38 (10.31) ms in the anamorelin 300 mg group. For the moxifloxacin group, the lower limit of 90% confidence interval for ΔΔQTcF was >5 ms at all prespecified 4 time points (1, 2, 3, and 4 hours postdose), indicating analytical sensitivity.

As a result of evaluating plasma pharmacokinetic parameters of unchanged anamorelin, the geometric mean [95% CI] of C_{max} and $AUC_{0\text{-last}}$ was 680.9 [607.1, 763.6] ng/mL and 641.59 [575.43, 715.35] ng·h/mL, respectively, in the anamorelin 100 mg group and 2,295.4 [2,103.4, 2,504.9] ng/mL and 2,620.56 [2,389.44, 2,874.05] ng·h/mL, respectively, in the anamorelin 300 mg group.

The effects of anamorelin on cardiac functions are discussed in a clinical section [see Section 7.R.2.3.1].

6.R Outline of the review conducted by PMDA

6.R.1 Accumulation of anamorelin after multiple doses

In the Japanese phase I studies (Studies ONO-7643-01 and ONO-7643-02) in which a single oral dose of anamorelin was administered in Japanese healthy adults, the exposure of anamorelin (C_{max} and AUC) increased more than dose-proportionally. The applicant provided the following explanation about the possible accumulation of anamorelin after multiple doses.

After a single oral dose of anamorelin 10 to 150 mg and multiple oral doses of anamorelin 50 to 150 mg in

Japanese healthy adults, the C_{max} and AUC of anamorelin ($AUC_{0-\infty}$ for single dose and AUC_{0-24h} for multiple doses) increased more than dose-proportionally. Meanwhile, there were no differences in $t_{1/2}$ of anamorelin after single dose and multiple doses. Therefore, more than dose-proportional increases in the C_{max} and AUC may be attributable to the dose-dependent increase in bioavailability, rather than the saturation in the elimination process from the circulating blood. The transporters for excretion or the first-pass effect might have been saturated in the absorption process, but the C_{max} and AUC_{0-24h} of unchanged anamorelin after multiple oral doses of anamorelin 100 mg once daily were similar between Days 1 and 7, indicating no accumulation of anamorelin after its multiple administration [see Section 6.2.2].

PMDA accepted the applicant's explanation.

6.R.2 Drug interactions mediated by CYP3A4

The applicant's explanation about drug interactions mediated by CYP3A4:

The *in vitro* studies using human liver microsomes showed that anamorelin is metabolized mainly by CYP3A4 [see Section 6.1.1.3]. In the foreign phase I study (RC-1291-105), the C_{max} and $AUC_{0-\infty}$ of anamorelin after administration of anamorelin 25 mg in combination with ketoconazole was 3.12-fold and 3.22-fold higher than those after administration of anamorelin without ketoconazole [see Section 6.2.8]. As shown in these findings, the combined use with potent CYP3A4 inhibitors should be contraindicated.

The combined use of anamorelin with moderately potent CYP3A4 inhibitors was evaluated. The incidences of adverse events and adverse drug reactions after multiple oral doses of anamorelin 100 mg once daily for 12 weeks with or without moderately potent CYP3A4 inhibitors were compared in the Japanese phase II study (ONO-7643-04), the Japanese phase III study (ONO-7643-05), and the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302). The incidence of adverse events was 78.1% (503 of 644 subjects; 19.6% for Grade 3, 3.6% for Grade 4, and 13.5% for Grade 5) in subjects receiving anamorelin without the CYP3A4 inhibitor and 95.5% (63 of 66 subjects; 28.8% for Grade 3, 9.1% for Grade 4, and 16.7% for Grade 5) in subjects receiving anamorelin in combination with the CYP3A4 inhibitor. The incidence of adverse drug reactions was 18.5% (119 of 644 subjects; 2.5% for Grade 3, 0.2% for Grade 4, and 0.2% for Grade 5) in subjects receiving anamorelin without the CYP3A4 inhibitor and 30.3% (20 of 66 subjects; 3.0% for Grade 3, 1.5% for Grade 4, and 0% for Grade 5) in subjects receiving anamorelin in combination with the CYP3A4 inhibitor. An adverse drug reaction occurring with an incidence of ≥5 percentage points higher in the subjects receiving anamorelin in combination with the CYP3A4 inhibitor than in subjects receiving anamorelin without the CYP3A4 inhibitor was nausea Grade 2 (0.2% in subjects receiving anamorelin without the CYP3A4 inhibitor and 6.1% in patients receiving anamorelin with the CYP3A4 inhibitor) but none were serious. These findings suggest that precautions should be included in the package insert for the concomitant use of anamorelin and moderately potent CYP3A4 inhibitors.

The interaction between anamorelin and CYP3A4 inducers was evaluated. The C_{max} and $AUC_{0-\infty}$ of unchanged anamorelin after administration of anamorelin in combination with rifampicin decreased to 0.43-fold and 0.32-fold, respectively, of those without rifampicin [see Section 6.2.9]. These findings suggest that precautions

should be included in the package insert for the concomitant use of anamorelin and CYP3A4 inducers (e.g., rifampicin, carbamazepine, and phenytoin).

PMDA understands that the concomitant use of anamorelin and potent CYP3A4 inhibitors should be contraindicated. PMDA also understands that precautions should be provided for the concomitant use of anamorelin and moderately potent CYP3A4 inhibitors or CYP3A4 inducers. However, because of the limited number of cases investigated in the clinical studies at present, PMDA considers that information should be continuously collected via post-marketing surveillance.

6.R.3 Drug interaction mediated by P-gp

The applicant's explanation about the effects of P-gp inhibitors on the pharmacokinetics of anamorelin:
In light of the fact that anamorelin is a substrate of P-gp [see Section 6.1.1.6], the incidence of adverse events and adverse drug reactions after multiple oral doses of anamorelin 100 mg once daily with or without P-gp inhibitors were compared in the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), the Japanese phase III study (ONO-7643-05), and the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302). The incidence of adverse events was 79.6% (622 of 781 subjects; 20.0% for Grade 3, 5.0% for Grade 4, and 13.7% for Grade 5) in subjects receiving anamorelin without a P-gp inhibitor and 91.1% (51 of 56 subjects; 35.7% for Grade 3, 5.4% for Grade 4, and 10.7% for Grade 5) in subjects receiving anamorelin with a P-gp inhibitor. The incidence of adverse drug reactions was 21.1% (165 of 781 subjects; 3.3% for Grade 3, 0.3% for Grade 4, and 0.1% for Grade 5) in subjects receiving anamorelin without a P-gp inhibitor and 30.4% (17 of 56 subjects; 3.6% for Grade 3 and 0% for Grades 4 and 5) in subjects receiving anamorelin with a P-gp inhibitor. An adverse drug reaction occurring with an incidence of ≥5 percentage points higher in the subjects receiving anamorelin with a P-gp inhibitor than in subjects receiving anamorelin without a P-gp inhibitor was nausea Grade 2 (0.3% in subjects receiving anamorelin without a P-gp inhibitor and 5.4% in subjects receiving anamorelin with a P-gp inhibitor) but was not serious.

P-gp is known to be expressed in the blood-brain barrier. The incidence of adverse events considered to be related to the central nervous system in the Japanese and foreign clinical studies was 14.3% (112 of 781 subjects; 0.9% for Grade 3, 0.3% for Grade 4, and 0.3% for Grade 5) in subjects receiving anamorelin without a P-gp inhibitor and 23.2% (13 of 56 subjects; 3.6% for Grade 3 and 0% for Grades 4 and 5) in subjects receiving anamorelin with a P-gp inhibitor. The incidence of adverse drug reactions considered to be related to the central nervous system was 1.7% (13 of 781 subjects; 0.1% for Grade 3 and 0% for Grades 4 and 5) in subjects receiving anamorelin without a P-gp inhibitor and 3.6% (2 of 56 subjects; 0 % for Grades 3, 4, and 5) in subjects receiving anamorelin with a P-gp inhibitor. There were no differences in the incidence of adverse events between the administration of anamorelin with or without P-gp inhibitors.

The above results indicates that there is no need to include precautions for a possible drug interaction between anamorelin and P-gp inhibitors in the package insert for anamorelin.

PMDA's view:

PMDA understands the applicant's claim that there is no need to include precautions for a possible drug interaction between anamorelin and P-gp inhibitors in the package insert for anamorelin at present. However, because of the limited number of cases investigated in the clinical studies, PMDA considers that information should be continuously collected via post-marketing surveillance.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from 3 Japanese clinical studies shown in Table 30.

Table 30. Outline of main clinical studies for efficacy and safety

Phase	Study No.	Population	Study design	Treatment duration	Groups (number of subjects)	Primary endpoint for efficacy[a)]
II	ONO-7643-03	Patients with non-small cell lung cancer and cachexia	Double-blind, parallel-group study	12 weeks	Placebo group: 58 Anamorelin 50 mg group: 65 Anamorelin 100 mg group: 55	• Mean change from baseline in LBM to Week 12 • Mean change from baseline in non-dominant handgrip strength to Week 12
II	ONO-7643-04	Patients with non-small cell lung cancer and cachexia	Double-blind, parallel-group study	12 weeks	Placebo group: 90 Anamorelin 100 mg group: 83	• Mean change from baseline in LBM to Week 12
III	ONO-7643-05	Cachexic patients with colorectal cancer, gastric cancer, or pancreatic cancer	Open-label, uncontrolled study	12 weeks	Anamorelin 100 mg: 49	• Percentage of subjects who maintained or gained LBM

a) Dual energy X-ray absorptiometry (DEXA) was used to determine LBM that was used as the primary endpoint in Japanese clinical studies.

7.1 Japanese phase II study (CTD 5.3.5.1-1: Study ONO-7643-03 [March 2011 to September 2012])

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 32 study sites in Japan to evaluate the efficacy and safety of anamorelin in patients with non-small cell lung cancer and cachexia aged ≥20 years (Tables 31 and 32) (target sample size of 162 subjects, 54 subjects in each group). Prohibited treatment and concomitant therapies are shown in Table 33.

Table 31. Main inclusion criteria

- **Patients with (cytologically or histologically documented) diagnosis of non-small cell lung cancer, inoperable Stage III or IV, according to the tumor, node, metastasis classification of the International Union Against Cancer (UICC-TNM) version 7, or relapsed non-small cell lung cancer indicated for chemotherapy**
- **Patients with involuntary body weight loss of ≥5% over the preceding 6 months**
- **Patients meeting at least 3 of the following 5 criteria during the observation period:**
  - **Anorexia[a)]**
  - **Fatigue or malaise[a)]**
  - **General muscle weakness[a)]**
  - **Arm muscle circumference (cm) of <10th percentile**
  - **Any one or more of (a) C-reactive protein (CRP) >5.0 mg/L; (b) hemoglobin (Hb) <12 g/dL; and (c) albumin <3.2 g/dL**
- **Patients with the Eastern Cooperative Oncology Group (ECOG) Performance Status of 1 or 2**
- **Patients with an estimated life expectancy of ≥4 months**

a) Assessed as Grade ≥1 according to the Japanese version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, translated by the Japan Clinical Oncology Group (JOCG).

Table 32. Main exclusion criteria

- **Patients with recurrent cancer following radiation monotherapy**
- **Patients with diseases that cause difficulty with or affect oral intake, digestion, and absorption (e.g., chronic nausea or vomiting, esophageal obstruction, hypercalcaemia, patients undergoing parenteral nutrition management, and organic gastrointestinal disorders associated with radiotherapy)**
- **Patients with ascites, pleural effusion, or pericardial effusion requiring drainage or thoracentesis or treatment with diuretics**
- **Patients with total bilirubin of ≥3.0 mg/dL or AST or ALT of ≥2.5 times the upper limit of the local laboratory range (or ≥100 IU/L)**
- **Patients with serum creatinine of ≥2.0 mg/dL**

Table 33. Prohibited treatment and concomitant therapies

- **Radiotherapy during a period from Day -28 to the completion of the study treatment (except palliative radiotherapy for bone metastasis or radiotherapy for brain metastases)**
- **Systemic corticosteroids with prednisolone equivalent of >5 mg/day (except prophylaxis of nausea/vomiting and hypersensitivity associated with antineoplastic treatments, prophylaxis of hypersensitivity associated with contrast medium, and prophylaxis of cerebral edema associated with radiotherapy)**
- **Growth hormone preparations during a period from Day -28 to the completion of the study treatment**
- **Medroxyprogesterone acetate and megestrol acetate during a period from Day -28 to the completion of the study treatment**
- **Chinese herbal medicines for anorexia during a period from Day -7 to the completion of the study treatment**
- **Antiarrhythmic drugs**
- **Antitumor anthracyclines**
- **CYP3A4 inhibitors during a period from Day -7 to the completion of the study treatment**
- **CYP3A4 inducers during a period from Day -28 to the completion of the study treatment**
- **Grapefruit (including grapefruit-containing products) during a period from Day -7 to the completion of the study treatment.**
- **St. John's wort (including St. John's wort-containing products) during a period from Day -28 to the completion of the study treatment**
- **Other investigational treatments during a period from Day -28 to the completion of the study treatment**

This study consisted of a 15-day observation period, a 12-week treatment period, and a 28-day follow-up period after the completion of the study treatment, and the safety of the study drug was assessed for the treatment and follow-up periods.

Placebo or anamorelin 50 or 100 mg was to be orally administered once daily in a fasted state before breakfast for 12 weeks. Subjects were instructed not to eat for 1 hour after the administration of the study drug.

Among 180 subjects randomized (60 subjects in the placebo group, 65 subjects in the anamorelin 50 mg group, and 55 subjects in the anamorelin 100 mg group), all of the 178 subjects receiving the study drug (58 subjects in the placebo group, 65 subjects in the anamorelin 50 mg group, and 55 subjects in the anamorelin 100 mg group) were included in the safety analysis set, and 115 subjects meeting both criteria for the treatment period and the adherence rate specified in the study protocol (42 subjects in the placebo group, 42 subjects in the anamorelin 50 mg group, and 31 subjects in the anamorelin 100 mg group) were included in the per protocol set (PPS), which was specified as the primary efficacy analysis set. The study drug was prematurely discontinued in 74 subjects (20 subjects in the placebo group, 29 subjects in the anamorelin 50 mg group, and 25 subjects in the anamorelin 100 mg group) due to "consent withdrawal" in 17 subjects (3 subjects in the placebo group, 8 subjects in the anamorelin 50 mg group, and 6 subjects in the anamorelin 100 mg group), "adverse events" in 33 subjects (6 subjects in the placebo group, 14 subjects in the anamorelin 50 mg group, and 13 subjects in the anamorelin 100 mg group), "worsening of the primary disease and the investigator's decision that study treatment is difficult to continue" in 4 subjects (2 subjects in the placebo group, 1 subject in the anamorelin 50 mg group, and 1 subject in the anamorelin 100 mg group), and "the investigator's decision that study treatment is difficult to continue" in 20 subjects (9 subjects in the placebo group, 6 subjects in the anamorelin 50 mg group, and 5 subjects in the anamorelin 100 mg group).

Data on the primary efficacy endpoints "mean change from baseline in LBM to Week 12" and "mean change

from baseline in handgrip strength of non-dominant hand to Week 12" are shown in Table 34. No statistically significant differences in these endpoints were demonstrated for the comparison between any of the anamorelin groups and the placebo group. Although the superiority of anamorelin to placebo was not seen in the anamorelin groups, the "mean change from baseline in LBM to Week 12" in the anamorelin groups tended to be higher than that in the placebo group.

Table 34. Results for primary endpoints (PPS)

	Placebo (n = 42)	Anamorelin 50 mg (n = 42)	Anamorelin 100 mg (n = 31)
LBM			
LBM at baseline (kg) (Mean ± SD)	38.77 ± 6.68	37.39 ± 5.58	38.60 ± 6.99[b)]
Mean change from baseline to Week 12 (kg) (Least square mean ± SE)	0.55 ± 0.29	0.85 ± 0.26	1.15 ± 0.31[b)]
Difference from placebo[a)] (kg) [95% CI]	—	0.30 [-0.26, 0.87]	0.60 [0.00, 1.21]
P value[c)]	—	0.2903	0.0516
Handgrip strength of non-dominant hand			
Handgrip strength at baseline (kg) (Mean ± SD)	24.18 ± 9.56	24.57 ± 7.68	23.30 ± 9.59
Mean change from baseline to Week 12 (kg) (Least square mean ± SE)	0.45 ± 0.62	0.02 ± 0.55	1.07 ± 0.67
Difference from placebo[a)] (kg) [95% CI]	—	-0.43 [-1.67, 0.81]	0.62 [-0.71, 1.95]
P value[c)]	—	0.4952	0.3597

a) An analysis of covariance with treatment, time point (week), and degree of body weight loss (≥5% and ≤15% vs. >15%) as factors and their baseline values as covariates, assuming an unstructured covariance structure between time points.
b) Data from 30 subjects, excluding 1 subject without values at baseline and after administration of the study drug.
c) Two-sided significance level of 5%.

Although patients receiving the study drug for ≥6 weeks were included in the efficacy analysis set as one of its conditions, lack of efficacy may be explained by the number of subjects who prematurely discontinued or withdrawn from the study was higher than initially expected. In addition, since many factors including inflammation and general status affect the assessment of handgrip strength (*BMC Geriatr.* 2013;13:7), it seems difficult to improve the handgrip strength with the intervention of anamorelin alone. Therefore, in the next Japanese phase II study (ONO-7643-04), it has been decided to include subjects who prematurely discontinued in the efficacy analysis set, and the mean change in LBM was specified as the sole primary endpoint so that the efficacy could be evaluated based on the pathological conditions of patients with cancer cachexia.

Adverse events were reported in 100% (58 of 58) of subjects in the placebo group, 93.8% (61 of 65) of subjects in the anamorelin 50 mg group, and 96.4% (53 of 55) of subjects in the anamorelin 100 mg group. Adverse drug reactions were reported in 20.7% (12 of 58) of subjects in the placebo group, 38.5% (25 of 65) of subjects in the anamorelin 50 mg group, and 52.7% (29 of 55) of subjects in the anamorelin 100 mg group. Adverse events and adverse drug reactions reported by ≥5% of subjects in any group are shown in Tables 35 and 36, respectively.

Table 35. Adverse events reported in ≥5% of subjects in any group

	Placebo (n = 58)	Anamorelin 50 mg (n = 65)	Anamorelin 100 mg (n = 55)		Placebo (n = 58)	Anamorelin 50 mg (n = 65)	Anamorelin 100 mg (n = 55)
All adverse events	100 (58)	93.8 (61)	96.4 (53)	Oedema peripheral	3.4 (2)	4.6 (3)	7.3 (4)
Nausea	17.2 (10)	13.8 (9)	30.9 (17)	Dysgeusia	1.7 (1)	4.6 (3)	7.3 (4)
White blood cell count decreased	31.0 (18)	30.8 (20)	25.5 (14)	Blood calcium increased	1.7 (1)	3.1 (2)	7.3 (4)
Neutrophil count decreased	25.9 (15)	29.2 (19)	23.6 (13)	Delirium	1.7 (1)	3.1 (2)	7.3 (4)
Haemoglobin decreased	25.9 (15)	21.5 (14)	20.0 (11)	Anaemia	8.6 (5)	1.5 (1)	7.3 (4)
Glycosylated haemoglobin increased	0 (0)	6.2 (4)	20.0 (11)	Blood sodium decreased	8.6 (5)	12.3 (8)	5.5 (3)
CRP increased	32.8 (19)	24.6 (16)	18.2 (10)	Stomatitis	12.1 (7)	7.7 (5)	5.5 (3)
Lymphocyte count decreased	27.6 (16)	16.9 (11)	18.2 (10)	Hyperglycaemia	5.2 (3)	6.2 (4)	5.5 (3)
γ-GTP increased	12.1 (7)	9.2 (6)	18.2 (10)	Blood chloride decreased	1.7 (1)	4.6 (3)	5.5 (3)
Blood glucose increased	1.7 (1)	4.6 (3)	18.2 (10)	Diabetes mellitus	0 (0)	3.1 (2)	5.5 (3)
Malignant neoplasm progression	20.7 (12)	16.9 (11)	16.4 (9)	Palpitations	0 (0)	3.1 (2)	5.5 (3)
Decreased appetite	12.1 (7)	15.4 (10)	16.4 (9)	Blood potassium increased	12.1 (7)	1.5 (1)	5.5 (3)
Constipation	10.3 (6)	18.5 (12)	14.5 (8)	Cheilitis	3.4 (2)	1.5 (1)	5.5 (3)
Blood alkaline phosphatase increased	12.1 (7)	4.6 (3)	12.7 (7)	Hyperkalaemia	3.4 (2)	1.5 (1)	5.5 (3)
Blood lactate dehydrogenase increased	10.3 (6)	4.6 (3)	12.7 (7)	Abdominal pain upper	0 (0)	0 (0)	5.5 (3)
Rash	13.8 (8)	3.1 (2)	12.7 (7)	Pneumonia	12.1 (7)	10.8 (7)	3.6 (2)
Vomiting	17.2 (10)	21.5 (14)	10.9 (6)	Platelet count decreased	15.5 (9)	7.7 (5)	3.6 (2)
White blood cell count increased	20.7 (12)	16.9 (11)	10.9 (6)	Alopecia	5.2 (3)	6.2 (4)	3.6 (2)
AST increased	15.5 (9)	12.3 (8)	10.9 (6)	Blood creatinine increased	15.5 (9)	4.6 (3)	3.6 (2)
ALT increased	10.3 (6)	12.3 (8)	10.9 (6)	Protein total decreased	6.9 (4)	3.1 (2)	3.6 (2)
Diarrhoea	12.1 (7)	9.2 (6)	10.9 (6)	Epistaxis	5.2 (3)	3.1 (2)	3.6 (2)
Insomnia	8.6 (5)	4.6 (3)	10.9 (6)	Blood urea increased	19.0 (11)	9.2 (6)	1.8 (1)
Red blood cell count decreased	15.5 (9)	12.3 (8)	9.1 (5)	Pneumonia aspiration	5.2 (3)	6.2 (4)	1.8 (1)
Blood albumin decreased	15.5 (9)	10.8 (7)	9.1 (5)	Blood urine present	10.3 (6)	4.6 (3)	1.8 (1)
Haematocrit decreased	13.8 (8)	9.2 (6)	9.1 (5)	Blood triglycerides increased	5.2 (3)	4.6 (3)	1.8 (1)
Malaise	6.9 (4)	7.7 (5)	9.1 (5)	Pleural effusion	8.6 (5)	3.1 (2)	1.8 (1)
Cancer pain	1.7 (1)	7.7 (5)	9.1 (5)	Febrile neutropenia	5.2 (3)	3.1 (2)	1.8 (1)
Nasopharyngitis	1.7 (1)	4.6 (3)	9.1 (5)	Contusion	5.2 (3)	1.5 (1)	1.8 (1)
Glucose urine present	3.4 (2)	1.5 (1)	9.1 (5)	Blood calcium decreased	5.2 (3)	1.5 (1)	1.8 (1)
Neutrophil count increased	6.9 (4)	7.7 (5)	7.3 (4)	Blood creatine phosphokinase increased	8.6 (5)	0 (0)	1.8 (1)
Tumour associated fever	1.7 (1)	7.7 (5)	7.3 (4)	Decubitus ulcer	5.2 (3)	0 (0)	1.8 (1)
Pyrexia	13.8 (8)	6.2 (4)	7.3 (4)	Dehydration	5.2 (3)	4.6 (3)	0 (0)
Dyspnoea	0 (0)	6.2 (4)	7.3 (4)	Hypoglycaemia	5.2 (3)	0 (0)	0 (0)

MedDRA/J ver.15.1
Incidence, % (number of subjects)

Table 36. Adverse drug reactions reported in ≥5% of subjects in any group

	Placebo (n = 58)	Anamorelin 50 mg (n = 65)	Anamorelin 100 mg (n = 55)
All adverse drug reactions	20.7 (12)	38.5 (25)	52.7 (29)
Glycosylated haemoglobin increased	0 (0)	3.1 (2)	16.4 (9)
Blood glucose increased	0 (0)	0 (0)	12.7 (7)
γ-GTP increased	0 (0)	3.1 (2)	9.1 (5)
Glucose urine present	0 (0)	1.5 (1)	7.3 (4)
Hyperglycaemia	0 (0)	3.1 (2)	5.5 (3)
Malaise	1.7 (1)	0 (0)	5.5 (3)

MedDRA/J ver.15.1
Incidence, % (number of subjects)

Deaths were reported in 20.7% (12 of 58) of subjects in the placebo group, 12.3% (8 of 65) of subjects in the anamorelin 50 mg group, and 10.9% (6 of 55) of subjects in the anamorelin 100 mg group (Table 37).

Table 37. Causes of death

Group	Events
Placebo	Malignant neoplasm progression[a)] (9 subjects); pneumonia aspiration, gastrointestinal haemorrhage, and cerebral infarction (1 subject each).
Anamorelin 50 mg	Malignant neoplasm progression (3 subjects); lung disorder[a)], hypoxia, respiratory failure, oesophageal haemorrhage, and pulmonary alveolar haemorrhage (1 subject each).
Anamorelin 100 mg	Malignant neoplasm progression (5 subjects); and interstitial pneumonia (1 subject).

MedDRA/J ver15.1
a) An adverse event for which a causal relationship with the study drug was not ruled out (a causal relationship with the study drug was not ruled out in 1 of 9 subjects with malignant neoplasm progression in the placebo group.)

Serious adverse events were reported in 50.0% (29 of 58) of subjects in the placebo group, 40.0% (26 of 65) of subjects in the anamorelin 50 mg group, and 30.9% (17 of 55) of subjects in the anamorelin 100 mg group. Serious adverse events reported in ≥5% of subjects in any group were malignant neoplasm progression (19.0% [11 of 58] of subjects in the placebo group, 12.3% [8 of 65] of subjects in the anamorelin 50 mg group, and 16.4% [9 of 55] of subjects in the anamorelin 100 mg group) and pneumonia (5.2% [3 of 58] of subjects in the placebo group, 6.2% [4 of 65] of subjects in the anamorelin 50 mg group, and 3.6% [2 of 55] of subjects in the anamorelin 100 mg group). The following serious adverse drug reactions were reported in 6.9% (4 of 58) of subjects in the placebo group (malignant neoplasm progression; decreased appetite and nausea; hyperkalaemia and hyponatraemia; and pneumonitis in 1 subject each), 4.6% (3 of 65) of subjects in the anamorelin 50 mg group (lung disorder; pneumonia and dehydration; and hyperglycaemia in 1 subject each), and 0% (0 of 55) of subjects in the anamorelin 100 mg group. Among these serious adverse drug reactions, the outcome was reported as “death” for malignant neoplasm progression in the placebo group and lung disorder in the anamorelin 50 mg group; “lost to follow-up” for pneumonitis in the placebo group and pneumonia in the anamorelin 50 mg group; “recovering” for hyponatraemia in the placebo group; and “recovered” for hyperkalaemia, and decreased appetite and nausea in the placebo group, and dehydration and hyperglycaemia in the anamorelin 50 mg group.

Adverse events leading to treatment discontinuation were reported in 10.3% (6 of 58) of subjects in the placebo group, 21.5% (14 of 65) of subjects in the anamorelin 50 mg group, and 23.6% (13 of 55) of subjects in the anamorelin 100 mg group. Adverse events leading to treatment discontinuation reported in ≥5% of subjects in any group were malignant neoplasm progression (1.7% [1 of 58] of subjects in the placebo group, 6.2% [4 of 65] of subjects in the anamorelin 50 mg group, and 10.9% [6 of 55] of subjects in the anamorelin 100 mg group). Adverse drug reactions leading to treatment discontinuation were reported in 3.4% (2 of 58) of subjects

in the placebo group (hyperkalaemia, hyponatraemia, and electrocardiogram T wave abnormal; and pneumonitis [1 subject each]), 6.2% (4 of 65) of subjects in the anamorelin 50 mg group (diarrhoea; asthenia and feeling hot; pneumonia and dehydration; and lung disorder [1 subject each]), and 9.1% (5 of 55) of subjects in the anamorelin 100 mg group (AST increased, ALT increased, γ-GTP increased, blood lactate dehydrogenase increased, blood cholesterol increased, and blood alkaline phosphatase increased; hyperglycaemia; tachycardia; malaise; and type 2 diabetes mellitus, hyperglycaemia, glycosylated haemoglobin increased, and glucose urine present [1 subject each]). Among these adverse drug reactions leading to treatment discontinuation, the outcome was reported as "recovering" for hyponatraemia in the placebo group, and hyperglycaemia and glycosylated haemoglobin increased in the anamorelin 100 mg group; "lost to follow-up" for electrocardiogram T wave abnormal and pneumonitis in the placebo group, pneumonia and lung disorder in the anamorelin 50 mg group, and malaise in the anamorelin 100 mg group; and "recovered" for the remaining adverse drug reactions leading to treatment discontinuation.

7.2 Japanese phase II study (CTD 5.3.5.1-2: Study ONO-7643-04 [May 2014 to October 2015])

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 43 study sites in Japan to evaluate the efficacy and safety of anamorelin in patients with non-small cell lung cancer and cachexia aged ≥20 years (Tables 38 and 39) (target sample size of 170 subjects, 85 subjects in each group). Prohibited treatment and concomitant therapies are shown in Table 40.

Table 38. Main inclusion criteria

- **Patients with histologically or cytologically documented diagnosis of non-small cell lung cancer, Stage III indicated for chemoradiotherapy or radical irradiation-unfeasible Stage III or IV, according to the UICC-TNM version 7, or postoperative relapse of non-small cell lung cancer**
  - **Patients with or without previous treatment for non-small cell lung cancer**
  - **Patients who have received epidermal growth factor receptors (EGFR) tyrosine kinase inhibitors for ≥28 days continuously at the time of informed consent**
- **Patients with involuntary body weight loss of ≥5% over the preceding 6 months (Patient's body weight in the observation period is ≥5% less than the maximum weight measured at the medical institution over the preceding 6 months [180 days])**
- **Patients meeting at least 3 (including anorexia) of the following 5 criteria during the observation period:**
  - **Anorexia[a)]**
  - **Fatigue or malaise[a)]**
  - **General muscle weakness[a)]**
  - **Arm muscle circumference (cm) of <10th percentile**
  - **Any one or more of (a) CRP >5.0 mg/L; (b) Hb <12 g/dL; and (c) albumin <3.2 g/dL**
- **Patients with the ECOG Performance Status of 1 or 2**
- **Patients evaluable for the Response Evaluation Criteria in Solid Tumors (RECIST) with or without measurable lesions**
- **Patients with an estimated life expectancy of ≥4 months**

a) Assessed as Grade ≥1 according to the Japanese version of the NCI CTCAE version 4.0, translated by the JOCG.

Table 39. Main exclusion criteria

- **Patients with diseases that cause difficulty with or affect oral intake, digestion, and absorption of foods and oral medications (e.g., chronic nausea or vomiting, esophageal obstruction, hypercalcemia, management with parenteral nutrition, and organic gastrointestinal disorders associated with radiotherapy)**
- **Patients with ascites, pleural effusion, or pericardial effusion requiring drainage or thoracentesis or treatment with diuretics**
- **Patients with heart rate of ≥120 beats/min at rest**
- **Patients with a systolic blood pressure of >180 mmHg and diastolic blood pressure of >100 mmHg at rest**
- **Patients with any of the following criteria for cardiac function:**
  - **Patients with concurrent angina pectoris or myocardial infarction or prior treatment of angina pectoris or myocardial infarction**
  - **Patients with second- or third-degree atrioventricular block**
  - **Patients with sinus bradycardia with a heart rate of <40 beats/min, sinoatrial block, or sick sinus syndrome**
  - **Patients with complete left bundle branch block, complete right bundle branch block with severe axis deviation, or severe ventricular extrasystoles (multifocal, short run , or R on T phenomenon)**
  - **Patients with congestive cardiac failure or decreased cardiac function**
  - **Patients with a QRS width of ≥110 ms**
- **Patients with inadequately controlled diabetes mellitus.**
- **Patients with total bilirubin of ≥3.0 mg/dL or AST or ALT of ≥2.5 times the upper limit of the local laboratory range (or ≥100 IU/L).**
- **Patients with serum creatinine of ≥2.0 mg/dL.**

Table 40. Prohibited treatment and concomitant therapies

- **Radiotherapy during a period from Day -28 to the completion of the study treatment (except palliative radiotherapy for bone metastases or radiotherapy for brain metastases)**
- **Systemic corticosteroids with prednisolone equivalent of >5 mg/day (except prophylaxis of nausea/vomiting and hypersensitivity associated with antineoplastic treatments, prophylaxis of hypersensitivity associated with contrast medium, and prophylaxis of cerebral edema associated with radiotherapy)·**
- **Growth hormone preparations during a period from Day -28 to the completion of the study treatment**
- **Medroxyprogesterone acetate and megestrol acetate during a period from Day -28 to the completion of the study treatment**
- **Chinese herbal medicines for anorexia during a period from Day -7 to the completion of the study treatment**
- **Antiarrhythmic drugs**
- **Antitumor anthracyclines**
- **CYP3A4 inhibitors during a period from Day -7 to the completion of the study treatment**
- **CYP3A4 inducers during a period from Day -28 to the completion of the study treatment**
- **Grapefruit (including grapefruit-containing products) during a period from Day -7 to the completion of the study treatment**
- **St. John's wort (including St. John's wort-containing products) during a period from Day -28 to the completion of the study treatment**
- **Other investigational treatments during a period from Day -28 to the completion of the study treatment**

This study consisted of a 15-day observation period, a 12-week treatment period, and a 28-day follow-up period after the completion of the study treatment, and the safety of the study drug was assessed for the treatment and follow-up periods.

Placebo or anamorelin 100 mg was to be orally administered once daily in a fasted state before breakfast for 12 weeks. Subjects were instructed not to eat for 1 hour after the administration of the study drug.

Among 174 subjects randomized (90 subjects in the placebo group and 84 subjects in the anamorelin 100 mg group), one subject received no study drug (in the anamorelin 100 mg), and the remaining 173 subjects (90 subjects in the placebo group and 83 subjects in the anamorelin 100 mg group) were included in the safety analysis set. Of the 173 subjects, excluding an ineligible subject (in the anamorelin 100 mg), 172 subjects (90 subjects in the placebo group and 82 subjects in the anamorelin 100 mg group) were included in the full analysis set (FAS), which was specified as the primary efficacy analysis set.

The study drug was prematurely discontinued in 55 subjects (27 subjects in the placebo group and 28 subjects in the anamorelin 100 mg group) due to "adverse events" in 7 subjects (2 subjects in the placebo group and 5 subjects in the anamorelin 100 mg group), "worsening of cancer cachexia" in 6 subjects (5 subjects in the

placebo group and 1 subject in the anamorelin 100 mg group), and "others[19]" in 42 subjects (20 subjects in the placebo group and 22 subjects in the anamorelin 100 mg group).

Data on the primary efficacy endpoint "mean change from baseline in LBM to Week 12" are shown in Table 41, and a statistically significant differences were demonstrated for the comparison between the anamorelin 100 mg group and the placebo group (P<0.0001, an analysis of covariance, a two-sided significance level of 5%).

Table 41. Mean change from baseline in LBM to Week 12 (FAS)

	Placebo (n = 90)	Anamorelin 100 mg (n = 82)
LBM at baseline (kg) (Mean ± SD)	37.06 ± 6.34	38.77 ± 7.04
Mean change from baseline to Week 12 (kg) (Least square mean ± SE)	-0.17 ± 0.17[c]	1.38 ± 0.18[d]
Difference from placebo[a] (kg) [95% CI]	—	1.56[d] [1.11, 2.00]
P value[b]	—	<0.0001

a) An analysis of covariance with treatment, time point (week), and degree of body weight loss (≥5% and ≤10% vs. >10%) as factors and their baseline values as covariates
b) Two-sided significance level of 5%
c) Data from 83 subjects, excluding 7 subjects without values at baseline and after administration of the study drug
d) Data from 73 subjects, excluding 9 subjects without values at baseline and after administration of the study drug

Adverse events were reported in 81.1% (73 of 90) of subjects in the placebo group and 89.2% (74 of 83) of subjects in the anamorelin 100 mg group. Adverse drug reactions were reported in 22.2% (20 of 90) of subjects in the placebo group and 41.0% (34 of 83) of subjects in the anamorelin 100 mg group. Adverse events reported by ≥5% of subjects in either group are shown in Table 42. Adverse drug reactions reported by ≥5% of subjects in any group included rash (1.1% [1 of 90] of subjects in the placebo group and 6.0%[5 of 83] of subjects in the anamorelin 100 mg group), atrioventricular block first degree (0% [0 of 90] of subjects in the placebo group and 6.0% [5 of 83] of subjects in the anamorelin 100 mg group), and nausea (5.6% [5 of 90] of subjects in the placebo group and 1.2% [1 of 83] of subjects in the anamorelin 100 mg group).

Table 42. Adverse events reported in 5% of subjects in either group

	Placebo (n = 90)	Anamorelin 100 mg (n = 83)		Placebo (n = 90)	Anamorelin 100 mg (n = 83)
All adverse events	81.1 (73)	89.2 (74)	White blood cell count decreased	6.7 (6)	6.0 (5)
Diarrhoea	10.0 (9)	14.5 (12)	Malaise	2.2 (2)	6.0 (5)
Oedema peripheral	0 (0)	12.0 (10)	Decreased appetite	2.2 (2)	6.0 (5)
Nausea	10.0 (9)	9.6 (8)	Neuropathy peripheral	2.2 (2)	6.0 (5)
Anaemia	4.4 (4)	9.6 (8)	γ-GTP increased	1.1 (1)	6.0 (5)
Rash	3.3 (3)	9.6 (8)	Delirium	0 (0)	6.0 (5)
Epistaxis	2.2 (2)	9.6 (8)	Stomatitis	5.6 (5)	4.8 (4)
Neutrophil count decreased	8.9 (8)	7.2 (6)	Vomiting	10.0 (9)	3.6 (3)
Constipation	5.6 (5)	7.2 (6)	Alopecia	7.8 (7)	1.2 (1)
Insomnia	4.4 (4)	7.2 (6)	Atrioventricular block first degree	0 (0)	6.0 (5)

MedDRA/J ver.16.0
Incidence, % (number of subjects)

Deaths were reported in 12.2% (11 of 90) of subjects due to natural course of cancer in all cases in the placebo

[19] Other reasons included "decisions by the investigator or the sub-investigator that the study treatment should not be continued" in 27 subjects, "request from the subjects to discontinue the participation in the study" in 13 subjects, and "violation of the exclusion criteria" in 2 subjects.

group, and 7.2% (6 of 83) of subjects in the anamorelin 100 mg group due to natural course of cancer in 5 subjects and lung infection in 1 subject. Of these events, lung infection in 1 subject was considered as an adverse event leading to death, but its causal relationship to anamorelin was denied.

Serious adverse events were reported in 8.9% (8 of 90) of subjects in the placebo group (febrile neutropenia, abdominal pain, enterocolitis, cholecystitis, hypoglycaemia, decreased appetite, metastases to meninges, pneumonitis, and palmar-plantar erythrodysaesthesia syndrome [1 subject each] [1 subject had more than 1 event]) and 19.3% (16 of 83) of subjects in the anamorelin 100 mg group (lung infection [2 subjects]; anaemia, pericarditis, diarrhoea, diverticulum intestinal haemorrhagic, duodenal ulcer haemorrhage, nausea, campylobacter gastroenteritis, infection, pneumonia, thoracic vertebral fracture, neutrophil count decreased, dehydration, colon cancer, cancer pain, loss of consciousness, prostatitis, and cataract operation [1 subject each] [some subjects had more than one event]). Serious adverse drug reactions were loss of consciousness and prostatitis in the anamorelin 100 mg group, and the outcome was reported as "recovered" for both cases.

Adverse events leading to treatment discontinuation were reported in 2.2% (2 of 90) of subjects in the placebo group (bundle branch block right and metastases to meninges [1 subject each]) and 3.6% (3 of 83) of subjects in the anamorelin 100 mg group (lung infection, loss of consciousness, and pleural effusion [1 subject each]). Adverse drug reactions leading to treatment discontinuation were loss of consciousness and pleural effusion in the anamorelin 100 mg group, and the outcome was reported as "recovered" for loss of consciousness and "not recovered" for pleural effusion.

7.3 Japanese phase III study (CTD 5.3.5.2-1: Study ONO-7643-05 [February 2017 to April 2018])

A multicenter, open-label, uncontrolled study was conducted at 19 study sites in Japan to evaluate the efficacy and safety of anamorelin in cachexic patients with colorectal cancer, gastric cancer, or pancreatic cancer aged ≥20 years (Tables 43 and 44) (target sample size of 50 subjects). Prohibited treatment and concomitant therapies are shown in Table 45.

Table 43. Main inclusion criteria

- **Patients with histologically or cytologically documented colorectal cancer, gastric cancer, or pancreatic cancer**
- **Patients with radically unresectable, radical irradiation-unfeasible advanced cancer, or postoperative relapsed cancer, with or without previous treatment**
- **Patients with involuntary body weight loss of ≥5% over the preceding 6 months**
- **Patients meeting at least 3 (including anorexia) of the following 5 criteria during the observation period:**
  - **Anorexia[a)]**
  - **Fatigue or malaise[a)]**
  - **General muscle weakness[a)]**
  - **Arm muscle circumference (cm) of <10th percentile.**
  - **Any one or more of (a) CRP >0.5 mg/L; (b) Hb <12 g/dL; and (c) albumin <3.2 g/dL**
- **Patients with the ECOG Performance Status of 0, 1, or 2 (Patients with pancreatic cancer and the ECOG Performance Status of 0 or 1)**
- **Patients with an estimated life expectancy of ≥4 months**

a) Assessed as Grade ≥1 according to the Japanese version of the NCI CTCAE version 4.0, translated by the JOCG.

Table 44. Main exclusion criteria

- **Patients with simultaneous multiple primary cancer: Patients with completely resected basal cell carcinoma, Stage I squamous cell carcinoma of the skin, carcinoma in situ, intramucosal carcinoma, superficial bladder cancer, or other cancer without recurrence for ≥5 years**
- **Patients with diseases that cause difficulty with or affect oral intake, digestion, and absorption of foods and oral medications (e.g., chronic nausea or vomiting, esophageal obstruction, hypercalcemia, management with parenteral nutrition, and organic gastrointestinal disorders associated with radiotherapy)**
- **Patients with a history of surgery that had apparently affected body weight loss in the previous 6 months in the opinion of the investigator or sub-investigator or patients with a planned surgery during the treatment period**
- **Patients with a body mass index (BMI) of >30 kg/m2**
- **Patients with ascites extending from the pelvic cavity to the upper abdomen, documented by computed tomography (CT)**
- **Patients with ascites, pleural effusion, or pericardial effusion requiring drainage or thoracentesis or edema requiring treatment with diuretics**
- **Patients who meet any of the following cardiac function criteria for:**
  - **Patients with complicated angina pectoris or myocardial infarction or prior treatment of angina pectoris or myocardial infarction**
  - **Patients with second- or third-degree atrioventricular block**
  - **Patients with sinus bradycardia with a heart rate of <40 beats/min, sinoatrial block, or sick sinus syndrome**
  - **Patients with complete left bundle branch block, complete right bundle branch block with severe axis deviation, or severe ventricular extrasystole (multifocal, short run, or R on T phenomenon)**
  - **Patients with congestive cardiac failure or decreased cardiac function**
  - **Patients with a QRS width of ≥110 ms**
- **Patients with inadequately controlled hypothyroidism or hyperthyroidism**
- **Patients on oxygen therapy**
- **Patients with diseases (e.g., uncontrolled infections) with an increase in CRP levels**
- **Patients with evident bleeding with a decrease in Hb levels**
- **Patients with symptomatic brain metastases**
- **Patients with inadequately controlled diabetes mellitus**
- **Patients with total bilirubin of 1.5 times the upper limit of the local laboratory range or AST or ALT of ≥3.0 times (5.0 times for patients with liver metastases) the upper limit of the local laboratory range**
- **Patients with serum creatinine of ≥2.0 mg/dL**

Table 45. Prohibited treatment and concomitant therapies

- **Radiotherapy during a period from Day -28 to the completion of the study treatment (except palliative radiotherapy for bone metastasis or radiotherapy for brain metastases)**
- **Systemic corticosteroids with prednisolone equivalent of >5 mg/day (except prophylaxis of nausea/vomiting and hypersensitivity associated with antineoplastic treatments, prophylaxis of hypersensitivity associated with contrast medium, and prophylaxis of cerebral edema associated with radiotherapy)·**
- **Growth hormone preparations during a period from Day -28 to the completion of the study treatment**
- **Medroxyprogesterone acetate and megestrol acetate during a period from Day -28 to the completion of the study treatment**
- **Chinese herbal medicines for anorexia during a period from Day -7 to the completion of the study treatment**
- **Antiarrhythmic drugs**
- **Antitumor anthracyclines**
- **CYP3A4 inhibitors during a period from Day -7 to the completion of the study treatment**
- **CYP3A4 inducers during a period from Day -28 to the completion of the study treatment**
- **Grapefruit (including grapefruit-containing products) during a period from Day -7 to the completion of the study treatment**
- **St. John's wort (including St. John's wort-containing products) during a period from Day -28 to the completion of the study treatment**
- **Other investigational treatments during a period from Day -28 to the completion of the study treatment**

This study consisted of a 15-day observation period, a 12-week treatment period, and a 28-day follow-up period after the completion of the study treatment, and the safety of the study drug was assessed for the treatment and follow-up periods.

Anamorelin 100 mg was to be orally administered once daily in a fasted state before breakfast for 12 weeks. Subjects were instructed not to eat for 1 hour after the administration of the study drug.

Of the 50 subjects enrolled in this study, 49 subjects received anamorelin, excluding 1 subject who requested to discontinue the participation in the study. The 49 subjects were included in the FAS and the safety analysis set, and FAS was specified as the primary efficacy analysis set.

The study drug was discontinued in 19 subjects. The reasons for discontinuation were "request from the subject

to discontinue the participation in the study" in 6 subjects, "otherwise, decision of the investigator or sub-investigator that the study treatment should not be continued" in 6 subjects, "decision of the investigator or sub-investigator that continuation of the study treatment was difficult due to adverse event(s), regardless of the causal relationship with the study drug, or because the subject met the treatment discontinuation criterion (6) on cardiac functions during the study treatment" in 3 subjects, and "others[20)]" in 4 subjects.

The percentage of subjects who maintained or gained LBM[21)], the primary efficacy endpoint, is shown in Table 46. The lower limit of the 95% confidence interval exceeded the prespecified threshold for efficacy (30.7%[22)]).

Table 46. Percentage of subjects who maintained or gained LBM (FAS)

	Anamorelin 100 mg (n = 49)
Percentage of subjects in % (number of subjects) [95% CI][a)]	**63.3 (31) [48.3, 76.6]**

a) CI using the Clopper-Pearson exact method

Adverse events were reported in 79.6% (39 of 49) of subjects, and adverse drug reactions were reported in 42.9% (21 of 49) of subjects. The adverse events reported by ≥5% of subjects and the incidences were as follows: malaise (10.2%, 5 of 49 subjects); diarrhoea (10.2%, 5 of 49 subjects); alopecia (10.2%, 5 of 49 subjects); γ-GTP increased (8.2%, 4 of 49 subjects); nasopharyngitis (8.2%, 4 of 49 subjects); hypertension (8.2%, 4 of 49 subjects); nausea (8.2%, 4 of 49 subjects); oedema peripheral (8.2%, 4 of 49 subjects); electrocardiogram QRS complex prolonged (6.1%, 3 of 49 subjects); hyperglycaemia (6.1%, 3 of 49 subjects); stomatitis (6.1%, 3 of 49 subjects); upper respiratory tract infection (6.1%, 3 of 49 subjects); and neuropathy peripheral (6.1%, 3 of 49 subjects). Adverse drug reactions reported by ≥5% of subjects were γ-GTP increased (8.2%, 4 of 49 subjects), hyperglycaemia (6.1%, 3 of 49 subjects), and electrocardiogram QRS complex prolonged (6.1%, 3 of 49 subjects).

Deaths occurred in 6 subjects (due to natural course of cancer in all cases), and none of the adverse events caused deaths.

Serious adverse events were reported in 5 subjects (oesophageal varices haemorrhage, drug hypersensitivity, lung infection, diabetes mellitus, and type 2 diabetes mellitus [1 subject each]). Of these events, serious adverse drug reactions were diabetes mellitus and type 2 diabetes mellitus, and the outcome was reported as "recovered" for both cases.

Adverse events led to treatment discontinuation in 5 subjects (malaise; supraventricular extrasystoles; malaise and asthenia; electrocardiogram QRS complex prolonged; and type 2 diabetes mellitus [1 subject each]). The

[20)] Others were "violation of exclusion criteria," "Grade ≥3 and poorly controlled ascites," "development of a disease that causes difficulty with or affect oral intake, digestion, and absorption of foods or medications," and "worsening of the primary disease" in 1 subject each.
[21)] Subjects whose changes from baseline in LBM had never reached <0.
[22)] The threshold was defined based on data from the placebo groups in 5 studies: the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), the foreign phase II studies (RC-1291-203 and RC-1291-205), the foreign phase III study (HT-ANAM-301), and the foreign phase III study (HT-ANAM-302).
* In the foreign clinical studies, except for the foreign phase II studies (RC-1291-203 and RC-1291-205), anamorelin 100 mg was orally administered once daily in a fasted state before breakfast for 12 weeks to patients with non-small cell lung cancer and cachexia. In the foreign phase II studies (RC-1291-203 and RC-1291-205), anamorelin 100 mg was orally administered once daily in a fasted state before breakfast for 12 weeks to patients with various types of cancer.

outcome was reported as “not recovered” for malaise in 1 subject and as “recovered” for the remaining cases.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy and clinical significance of anamorelin

(a) Development of anamorelin in the US and Europe

The applicant’s explanation about the data from clinical studies and development status of anamorelin in the US and Europe:

In the US and Europe, 2 foreign phase III studies (HT-ANAM-301[23] and HT-ANAM-302[24]) were conducted, and co-primary endpoints were specified for these studies. Since the therapeutic intervention to cancer cachexia is intended to prevent the decrease in LBM consisting of skeletal muscles and organ tissues, “LBM” was specified as one of the co-primary endpoint. “Handgrip strength” was specified as the other co-primary endpoint to directly assess the contribution of increased LBM in improvement of motor function. In both of the 2 foreign phase III studies (HT-ANAM-301 and HT-ANAM-302), significant differences in the primary endpoint “mean change from baseline in LBM to Week 12” were observed between the anamorelin 100 mg group and the placebo group, but no significant differences in the other endpoint “mean change from baseline in handgrip strength to Week 12” were observed between the anamorelin 100 mg group and the placebo group.

Helsinn, the licensor of anamorelin, [redacted]. The Committee for Medicinal Products for Human Use (CHMP) of the European Monetary Agreement (EMA) requested Helsinn to provide a justification for submitting data from the clinical study where the primary endpoint was not achieved as the pivotal data. In response to that, Helsinn claimed the clinical significance of anamorelin, but a negative opinion was issued, and anamorelin has not been approved by the EMA. After consultation with the Food and Drug Agency (FDA) and the EMA, Helsinn is conducting 2 new foreign phase III studies (ANAM-17-20 and ANAM-17-21)[25] with co-primary endpoints of “body weight gain” and “improvement in appetite” to obtain approval for anamorelin in the US and Europe.

In the 2 foreign phase III studies (HT-ANAM-301, and HT-ANAM-302) conducted in the US and Europe, as [redacted], the efficacy of anamorelin 100 mg was not demonstrated for the primary endpoint of “handgrip strength” as compared with placebo. However, anamorelin 100 mg increased LBM

[23] Placebo or anamorelin 100 mg was orally administered once daily for 12 weeks to evaluate the efficacy and safety of anamorelin in patients with non-small cell lung cancer and cachexia. As for the 2 primary endpoints, significant differences were observed in the primary endpoint “mean change from baseline in LBM to Week 12” (-0.47 kg in the placebo group and 0.99 kg in the anamorelin 100 mg group [$P < 0.001$]), whereas no significant differences were observed in the other primary endpoint “mean change from baseline in handgrip strength to Week 12” (-1.58 kg in the placebo group and -1.10 kg in the anamorelin 100 mg group [$P = 0.148$]).

[24] Placebo or anamorelin 100 mg was orally administered once daily for 12 weeks to evaluate the efficacy and safety of anamorelin in patients with non-small cell lung cancer and cachexia. As for the 2 primary endpoints, significant differences were observed in the primary endpoint “mean change from baseline in LBM to Week 12” (-0.98 kg in the placebo group and 0.65 kg in the anamorelin 100 mg group [$P < 0.001$]), whereas no significant differences were observed for the other endpoint “mean change from baseline in handgrip strength to Week 12” (-0.95 kg in the placebo group and -1.49 kg in the anamorelin 100 mg group [$P = 0.648$]).

[25] In the 2 foreign phase III studies (ANAM-17-20 and ANAM-17-21), patients with non-small cell lung cancer and cachexia were enrolled, and placebo or anamorelin 100 mg was orally administered once daily for 24 weeks.

significantly, and, though exploratory, anorexia was relieved as compared with the placebo. Therefore, anamorelin was considered to have a certain clinical significance.

(b) LBM results in Japanese clinical studies

The applicant's explanation about LBM results in Japanese clinical studies:

In the Japanese phase II study (ONO-7643-04) conducted in patients with non-small cell lung cancer and cachexia, the least-squares mean [95 % CI] of difference in "mean change from baseline in LBM to Week 12" of the primary endpoint between the anamorelin 100 mg group and the placebo group ([that in the anamorelin 100 mg group] − [that in the placebo group]) was 1.56 [1.11, 2.00] kg, showing a statistically significant difference between the anamorelin 100 mg group and the placebo group (Table 41 in Section 7.2). In the Japanese phase III study (ONO-7643-05) conducted in cachexic patients with colorectal cancer, gastric cancer, or pancreatic cancer, "the percentage of subjects who maintained or gained LBM" of the primary endpoint was 63.3% [48.3%, 76.6%], and the lower limit of the 95% confidence interval exceeded the prespecified threshold responder rate (30.7%), suggesting that anamorelin 100 mg is expected to have efficacy.

The results for LBM by patient characteristics are shown in Table 47, and no trend was seen that the efficacy of anamorelin was lower in any specific population.

Table 47. Efficacy by patient characteristics in the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05) (FAS)

		Japanese phase II study (ONO-7643-04)	Japanese phase III study (ONO-7643-05)
Primary endpoint		Mean change from baseline in LBM to Week 12	Percentage of subjects who maintained or gained LBM
		Difference between anamorelin 100 mg and placebo[a] (kg) [95% CI]	Anamorelin 100 mg (n = 49)
Sex	Male	1.70 [1.15, 2.26] (54 subjects in the placebo group and 49 subjects in the anamorelin 100 mg group)	51.7 (15 of 29 subjects)
	Female	1.35 [0.68, 2.02] (29 subjects in the placebo group and 24 subjects in the anamorelin 100 mg group)	80.0 (16 of 20 subjects)
Age	<65 years	1.61 [0.72, 2.49] (28 subjects in the placebo group and 24 subjects in the anamorelin 100 mg group)	63.2 (12 of 19 subjects)
	≥65 years	1.48 [0.95, 2.02] (55 subjects in the placebo group and 49 subjects in the anamorelin 100 mg group)	63.3 (19 of 30 subjects)
BMI	<20 kg/m^2	1.66 [1.14, 2.17] (51 subjects in the placebo group and 42 subjects in the anamorelin 100 mg group)	67.7 (21 of 31 subjects)
	≥20 kg/m^2	1.72 [0.86, 2.58] (32 subjects in the placebo group and 31 subjects in the anamorelin 100 mg group)	55.6 (10 of 18 subjects)
Body weight loss at baseline	≥5% and ≤10%	1.65 [1.11, 2.19] (49 subjects in the placebo group and 44 subjects in the anamorelin 100 mg group)	57.7 (15 of 26 subjects)
	>10%	1.36 [0.58, 2.14] (34 subjects in the placebo group and 29 subjects in the anamorelin 100 mg group)	69.6 (16 of 23 subjects)
Type of cancer	Colorectal cancer		61.5 (24 of 39 subjects)
	Gastric cancer		40.0 (2 of 5 subjects)
	Pancreatic cancer		100 (5 of 5 subjects)
Use of pharmacotherapy for cancer during the treatment	No	2.62 [1.31, 3.93] (16 subjects in the placebo group and 11 subjects in the anamorelin 100 mg group)	50.0 (4 of 8 subjects)
	Yes	1.53 [1.03, 2.02] (67 subjects in the placebo group and 62 subjects in the anamorelin 100 mg group)	65.9 (27 of 41 subjects)

a) An analysis of covariance with treatment group, time point (week), and degree of body weight loss (≥5% and ≤10% vs. >10%) as factors and their baseline values as covariates

Changes in LBM from baseline at each evaluation time point in the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05) are shown in Figures 1 and 2, respectively. In both studies, LBM started to increase at Week 3 of treatment in the anamorelin 100 mg group, and despite no increase over time, the increased LBM was maintained throughout the treatment period.

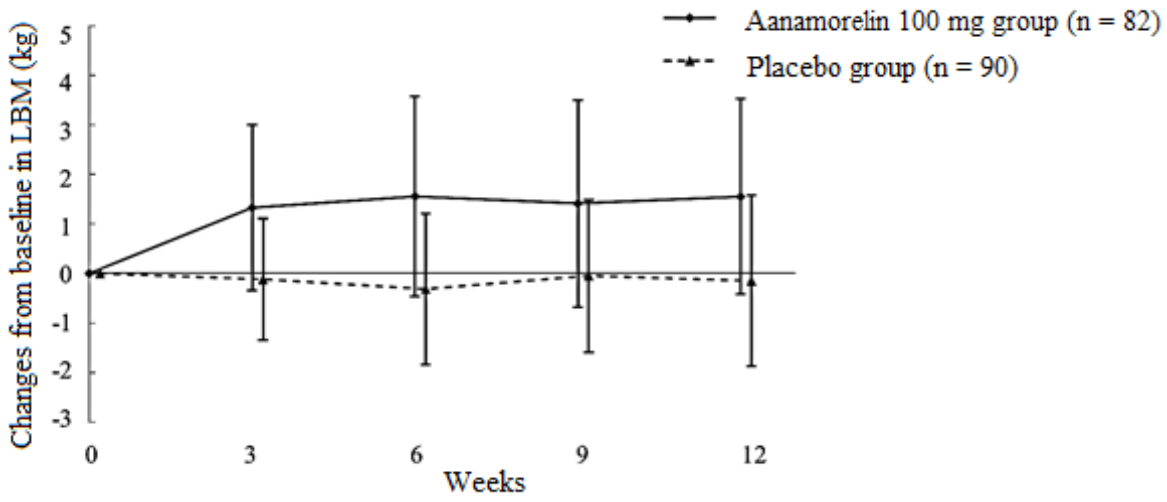

Figure 1. Changes from baseline in LBM at each evaluation point in the Japanese phase II study (ONO-7643-04) (kg) (FAS)

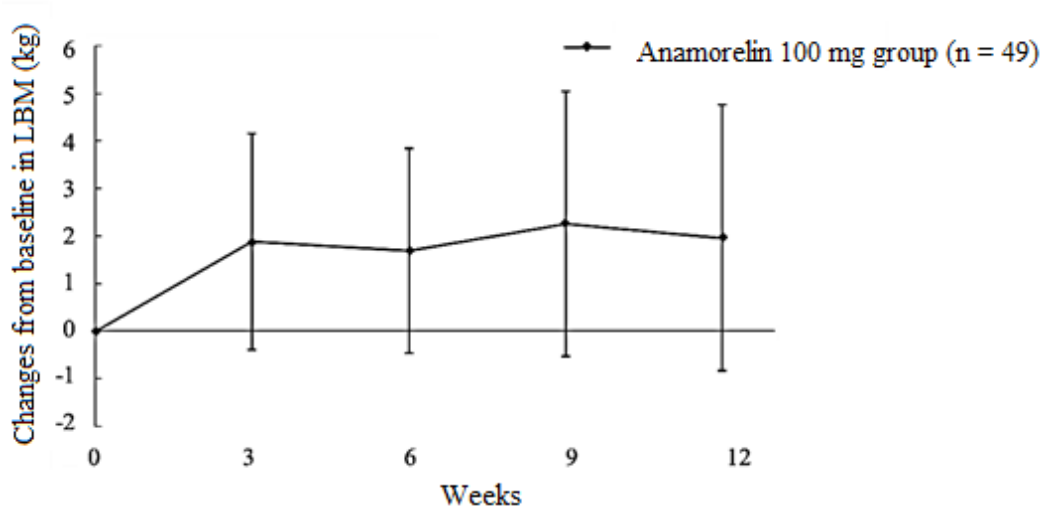

Figure 2. Changes from baseline in LBM at each evaluation point in the Japanese phase III study (ONO-7643-05) (kg) (FAS)

As shown above, the results from the Japanese phase II study (ONO-7643-04) in patients with non-small cell lung cancer and cachexia and the Japanese phase III study (ONO-7643-05) in cachexic patients with colorectal cancer, gastric cancer, or pancreatic cancer demonstrated that treatment with anamorelin increased LBM, indicating a certain clinical significance of anamorelin.

(c) Results for parameters other than LBM in Japanese clinical studies

The applicant's explanation about the results for parameters other than LBM in Japanese clinical studies:

In the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05), quality of life (QOL) was assessed as a secondary endpoint using the QOL Questionnaire for Cancer Patients Treated

with Anticancer Drugs (QOL-ACD)[26]. Mean changes from baseline in the total QOL-ACD scores to Week 12 are shown in Table 48, and no changes from baseline were seen after treatment with anamorelin in either study.

Table 48. Mean change from baseline in total QOL-ACD scores to Week 12 (FAS)

	Japanese phase II study (ONO-7643-04)		Japanese phase III study (ONO-7643-05)
	Placebo (n = 89)	Anamorelin 100 mg (n = 79)	Anamorelin 100 mg (n = 49)
Mean change from baseline to Week 12 (point) (least square mean ± SE)	0.0 ± 1.0	-0.3 ± 1.0	0.0 ± 1.5
Difference from placebo[a] (point) [95% CI]	—	-0.3 [-2.9, 2.3]	

a) An analysis of covariance of repeatedly measured data with treatment group, time point (week), and degree of body weight loss (≥5% and ≤10% vs. >10%) as factors and their baseline values as covariates.

Mean changes from baseline in the appetite-related QOL-ACD question[27] to Week 12 in the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05) are shown in Table 49, and appetite tended to improve in the anamorelin 100 mg group as compared with the placebo group.

Table 49. Mean change from baseline in the appetite-related QOL-ACD question[a] to Week 12 (FAS)

	Japanese phase II study (ONO-7643-04)		Japanese phase III study (ONO-7643-05)
	Placebo (n = 89)	Anamorelin 100 mg (n = 79)	Anamorelin 100 mg (n = 49)
Mean change from baseline to Week 12 (score) (Least square mean ± SE)	0.3 ± 0.1	0.7 ± 0.1	0.6 ± 0.1
Difference from placebo[b] (score) [95% CI]	—	0.4 [0.2, 0.6]	

a) Question 8 "Did you have an appetite?"

b) An analysis of covariance for repeatedly measured data with treatment group, time point (week), and degree of body weight loss (≥5% and ≤10% vs. >10%) as factors and their baseline values as covariates.

At present, there are no Japanese or foreign clinical study data indicating the efficacy of anamorelin for measures other than LBM. A new Japanese phase III study (ONO-7643-06) is currently underway to collect further data on the efficacy. The Japanese phase III study (ONO-7643-06) was designed as an open-label and uncontrolled study in consideration of feasibility and with the same primary endpoints (body weight and appetite) and the same study period (24 weeks) as those used in the new ongoing phase III studies (ANAM-17-20 and ANAM-17-21) conducted outside Japan [see Section 7.R.5]. Results from the Japanese phase III study (ONO-7643-06) will be reported to the PMDA immediately, once available.

In the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05), LBM increased after treatment with anamorelin, and though not fully validated, a tendency toward improvement in appetite-related QOL was seen. In light of these findings, PMDA considers that anamorelin has been demonstrated to have a certain clinical significance in patients with cancer cachexia enrolled in these studies. PMDA also considers that the results from the ongoing Japanese phase III study (ONO-7643-06) should be confirmed after its market launch.

The clinical positioning and intended patients of anamorelin are discussed in Section 7.R.3.

[26] A self-evaluation questionnaire with a total of 22 questions on 4 main domains (functional, physical, mental, and psychosocial) on a scale of 1 to 5 to assess patients' status over the past several days.

[27] Question 8 "Did you have an appetite?" was regarded as a question related to appetite.

7.R.2 Safety

As a result of its review presented in Sections 7.R.2.1 to 7.R.2.3, and in light of the certain clinical significance of anamorelin for cancer cachexia, PMDA considers that the safety of anamorelin is acceptable and also considers that the safety data of anamorelin should be collected via post-marketing surveillance.

7.R.2.1 Occurrence of adverse events

The applicant's explanation about the safety of anamorelin in main clinical studies:

The occurrence of adverse events and relevant events in the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), and the Japanese phase III study (ONO-7643-05) is summarized in Table 50. In the Japanese phase II study (ONO-7643-03) and the Japanese phase II study (ONO-7643-04), the incidence of adverse drug reactions tended to be higher in the anamorelin groups than in the placebo group, but no significant differences were observed for serious adverse drug reactions, adverse drug reactions leading to treatment discontinuation, or deaths. Furthermore, no different tendency in the anamorelin 100 mg group was observed between the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05).

Table 50. Outline of adverse events in main Japanese clinical studies

	Japanese phase II study (ONO-7643-03)			Japanese phase II study (ONO-7643-04)		Japanese phase III study (ONO-7643-05)
	Placebo (n = 58)	Anamorelin 50 mg (n = 65)	Anamorelin 100 mg (n = 55)	Placebo (n = 90)	Anamorelin 100 mg (n = 83)	Anamorelin 100 mg (n = 49)
Adverse events	100 (58)	93.8 (61)	96.4 (53)	81.1 (73)	89.2 (74)	79.6 (39)
Adverse drug reactions	20.7 (12)	38.5 (25)	52.7 (29)	22.2 (20)	41.0 (34)	42.9 (21)
Serious adverse events	50.0 (29)	40.0 (26)	30.9 (17)	8.9 (8)	19.3 (16)	10.2 (5)
Serious adverse drug reactions	6.9 (4)	4.6 (3)	0 (0)	0 (0)	2.4 (2)	4.1 (2)
Adverse events leading to treatment discontinuation	10.3 (6)	21.5 (14)	23.6 (13)	2.2 (2)	3.6 (3)	10.2 (5)
Adverse drug reactions leading to treatment discontinuation	3.4 (2)	6.2 (4)	9.1 (5)	1.1 (1)	2.4 (2)	10.2 (5)
Deaths	20.7 (12)	12.3 (8)	10.9 (6)	12.2 (11)	7.2 (6)	12.2 (6)

Incidence (%) (number of subjects)

7.R.2.2 Safety by patient characteristics

The applicant's explanation about the incidence of adverse drug reactions for individual patient characteristics:

The incidence of adverse drug reactions in the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), and the Japanese phase III study (ONO-7643-05) is shown by patient characteristics in Table 51. Despite the limited number of patients in each group, no particular problematic tendency has been identified.

Table 51. Adverse drug reactions by patient characteristics in main Japanese clinical studies

	Japanese phase II study (ONO-7643-03)			Japanese phase II study (ONO-7643-04)		Japanese phase III study (ONO-7643-05)
	Placebo (n = 58)	Anamorelin 50 mg (n = 65)	Anamorelin 100 mg (n = 55)	Placebo (n = 90)	Anamorelin 100 mg (n = 83)	Anamorelin 100 mg (n = 49)
Sex						
Male	15.8 (6/38)	38.0 (19/50)	48.6 (17/35)	24.6 (14/57)	39.7 (23/58)	48.3 (14/29)
Female	30.0 (6/20)	40.0 (6/15)	60.0 (12/20)	18.2 (6/33)	44.0 (11/25)	35.0 (7/20)
Age						
<65 years	11.5 (3/26)	32.4 (11/34)	39.1 (9/23)	23.3 (7/30)	19.2 (5/26)	47.4 (9/19)
≥65 years	28.1 (9/32)	45.2 (14/31)	62.5 (20/32)	21.7 (13/60)	50.9 (29/57)	40.0 (12/30)
BMI						
<20 kg/m^2	22.9 (8/35)	30.8 (12/39)	48.3 (14/29)	25.0 (14/56)	40.9 (18/44)	38.7 (12/31)
≥20 kg/m^2	17.4 (4/23)	50.0 (13/26)	57.7 (15/26)	17.6 (6/34)	41.0 (16/39)	50.0 (9/18)
Degree of body weight loss at baseline						
≥5% and ≤10%[a)]	22.2 (8/36)	39.5 (15/38)	55.3 (21/38)	19.2 (10/52)	36.0 (18/50)	46.2 (12/26)
>10%[a)]	18.2 (4/22)	37.0 (10/27)	47.1 (8/17)	26.3 (10/38)	48.5 (16/33)	39.1 (9/23)
Cancer therapy during treatment with anamorelin						
No	22.2 (2/9)	38.5 (5/13)	80.0 (8/10)	15.8 (3/19)	66.7 (12/18)	50.0 (4/8)
Yes	20.4 (10/49)	38.5 (20/52)	46.7 (21/45)	23.9 (17/71)	33.8 (22/65)	41.5 (17/41)
Type of cancer						
Colorectal cancer						48.7 (19/39)
Gastric cancer						20.0 (1/5)
Pancreatic cancer						20.0 (1/5)

Incidence, % (number of subjects with adverse events/number of subjects in study population)
a) Classified into ≥5% and <10%, and ≥10% in the Japanese phase II study (ONO-7643-03).

Although it should be noted to the limited number of subjects in individual groups in the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), and the Japanese phase III study (ONO-7643-05), PMDA has confirmed that there was no tendency toward increasing the incidence of adverse drug reactions with anamorelin in a specific patient population. PMDA considers that information should be continuously collected on the safety for individual patient characteristics via post-marketing surveillance.

7.R.2.3 Important adverse events

As shown below, the applicant conducted its review mainly on adverse events of special interest, based on adverse events relatively commonly reported in the clinical studies of anamorelin and data available from the non-clinical pharmacology studies and toxicity studies.

7.R.2.3.1 Effects of anamorelin on cardiac function

The applicant's explanation about the effects of anamorelin on cardiac function:

Since anamorelin inhibits the voltage-sensitive sodium channels, a review was conducted mainly on cardiovascular-related adverse events and abnormal electrocardiography (ECG)-related adverse events in main clinical studies in and outside Japan.

In the Japanese phase II study (ONO-7643-03), cardiovascular-related adverse events were reported in 19.0% (11 of 58) of subjects in the placebo group, 13.8% (9 of 65) of subjects in the anamorelin 50 mg group, and 12.7% (7 of 55) of subjects in the anamorelin 100 mg group. Adverse events reported in ≥2 subjects were oedema peripheral and oedema (3 subjects each) in the anamorelin 50 mg group and oedema peripheral (4 subjects) in the anamorelin 100 mg group. The severity of the event paralysis (1 subject) reported in the anamorelin 50 mg group was assessed as Grade 4 but its causal relationship to anamorelin was denied. The

other adverse events were assessed as Grade ≤2. Cardiovascular-related adverse drug reactions were reported in 1.7% (1 of 58) of subjects in the placebo group, 3.1% (2 of 65) of subjects in the anamorelin 50 mg group, and 0% (0 of 55) of subjects in the anamorelin 100 mg group. There were no cardiovascular-related adverse drug reactions assessed as serious or led to treatment discontinuation. Abnormal ECG-related adverse events were reported in 8.6% (5 of 58) of subjects in the placebo group, 10.8% (7 of 65) of subjects in the anamorelin 50 mg group, and 18.2% (10 of 55) of subjects in the anamorelin 100 mg group. Adverse events reported in ≥2 subjects were palpitations (2 subjects) in the anamorelin 50 mg group and palpitations (3 subjects), tachycardia, ventricular extrasystoles, and atrioventricular block first degree (2 subjects each) in the anamorelin 100 mg group. All of the events were assessed as Grade ≤2 in severity. Abnormal ECG-related adverse drug reactions were reported in 0% (0 of 58) of subjects in the placebo group, 4.6% (3 of 65) of subjects in the anamorelin 50 mg group, and 7.3% (4 of 55) of subjects in the anamorelin 100 mg group. An adverse drug reaction led to treatment discontinuation in 1 subject (tachycardia), and the event resolved without treatment. There were no serious abnormal ECG-related adverse drug reactions.

In the Japanese phase II study (ONO-7643-04), cardiovascular-related adverse events were reported in 2.2% (2 of 90) of subjects in the placebo group and 16.9% (14 of 83) of subjects in the anamorelin 100 mg group. Adverse events reported in ≥2 subjects in the anamorelin 100 mg group were oedema peripheral (10 subjects) and oedema (3 subjects). All of the events were assessed as Grade ≤2 in severity. Cardiovascular-related adverse drug reactions were reported in 0% (0 of 90) of subjects in the placebo group and 6.0% (5 of 83) of subjects in the anamorelin 100 mg group. There were no cardiovascular-related adverse drug reactions assessed as serious or led to treatment discontinuation. Abnormal ECG-related adverse events were reported in 2.2% (2 of 90) of subjects in the placebo group and 12.0% (10 of 83) of subjects in the anamorelin 100 mg group. Adverse events reported in ≥2 subjects in the anamorelin 100 mg group were atrioventricular block first degree (5 subjects), palpitations (2 subjects), and tachycardia (2 subjects). Loss of consciousness (1 subject) in the anamorelin 100 mg group was assessed as Grade 3 in severity and was considered as an adverse drug reaction. The study drug was discontinued in the subject, but the event resolved without treatment. The other adverse events were assessed as Grade ≤2. Abnormal ECG-related adverse drug reactions were reported in 2.2% (2 of 90) of subjects in the placebo group and 9.6% (8 of 83) of subjects in the anamorelin 100 mg group. Except for the event of loss of consciousness in 1 subject, there were no abnormal ECG-related adverse reactions assessed as serious or leading to treatment discontinuation.

In the Japanese phase III study (ONO-7643-05), cardiovascular-related adverse events were reported in 14.3% (7 of 49) of subjects. Cardiovascular-related adverse events reported in ≥2 subjects were oedema peripheral (4 subjects) and oedema (2 subjects). All of these events were assessed as Grade ≤2 in severity. There were no cardiovascular-related adverse drug reactions assessed as serious or leading to treatment discontinuation. Abnormal ECG-related adverse events were reported in 10.2% (5 of 49) of subjects, and all of the events were determined as adverse drug reactions. An abnormal ECG-related adverse event reported in ≥2 subjects was electrocardiogram QRS complex prolonged (3 subjects). All of these events were assessed as Grade ≤2 in severity. Adverse drug reactions led to treatment discontinuation in 2 subjects (electrocardiogram QRS complex prolonged and supraventricular extrasystoles) but resolved without treatment. There were no

abnormal ECG-related adverse drug reactions assessed as serious.

Outside Japan, in the foreign phase I studies (HT-ANAM-112[28)] and HT-ANAM-113), PR interval prolonged and QRS widened were reported after administration of a single dose of anamorelin 300 mg and 400 mg. The events were all transient and were considered to be clinically insignificant.

A pooled analysis of the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302) demonstrated that cardiovascular-related adverse events were reported in 3.7% (12 of 322) of subjects in the placebo group and 6.3% (41 of 650) of subjects in the anamorelin 100 mg group and that cardiovascular-related adverse drug reactions were reported in 0.3% (1 of 322) of subjects in the placebo group and 0.5% (3 of 650) of subjects in the anamorelin 100 mg group. An adverse drug reaction of ischaemic cardiomyopathy in 1 subject in the anamorelin 100 mg group was assessed as Grade 4 in severity and had resolved with sequelae after discontinuation of the study drug. Abnormal ECG-related adverse events were reported in 5.6% (18 of 322) of subjects in the placebo group and 4.3% (28 of 650) of subjects in the anamorelin 100 mg group, and abnormal ECG-related adverse drug reactions were reported with an incidence of 0% (0 of 322) of subjects in the placebo group and 0.2% (1 of 650) of subjects in the anamorelin 100 mg group. Adverse events of atrial fibrillation in 2 subjects and tachycardia paroxysmal in 1 subject in the anamorelin 100 mg group were assessed as Grade 3 in severity and its causal relationship to anamorelin was denied.

As shown above, the incidences of cardiovascular-related adverse events and abnormal ECG-related adverse events were higher in the anamorelin 100 mg group than in the placebo group, but the number of serious adverse drug reactions and adverse drug reactions leading to treatment discontinuation was low. In light of the risk of arrhythmia due to the inhibitory effect of anamorelin on the conduction system, precautionary statements should be included in the package insert in reference to those for class I antiarrhythmic drugs. However, serious cardiovascular risk, as seen with antiarrhythmic drugs, has not been identified in any anamorelin 100 mg group in the Japanese or foreign clinical studies. Therefore, frequent monitoring of patient conditions and hospitalization at the start of treatment, which are described in package inserts of class I antiarrhythmic drugs, are considered unnecessary.

In the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), the Japanese phase III study (ONO-7643-05), and the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302), cardiovascular-related adverse events and abnormal ECG-related adverse events were reported more frequently in the anamorelin 100 mg group than in the placebo group, and serious adverse drug reactions related to cardiovascular events or abnormal ECG were also reported. In light of the risk of arrhythmia due to the inhibitory effect of anamorelin on the conduction system, PMDA considers it appropriate that precautionary statements are included in the package insert of anamorelin in reference to those for class I antiarrhythmic drugs. PMDA also considers that information on the occurrence of adverse events related to cardiac functions in association with the use of anamorelin should be continuously collected via post-marketing surveillance.

[28)] A single oral dose of placebo or anamorelin 150, 200, 300, or 400 mg was administered to evaluate the safety of anamorelin in healthy adults.

7.R.2.3.2 Increase in blood glucose

The applicant's explanation about an increase in blood glucose with treatment with anamorelin:
Since anamorelin is a ghrelin receptor agonist and may cause increases in blood glucose, adverse events related to increased blood glucose were examined with a focus on main Japanese and foreign clinical studies.

Changes in blood glucose levels over time in the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), and the Japanese phase III study (ONO-7643-05) are shown in Table 52. In the Japanese phase II study (ONO-7643-03) and the Japanese phase II study (ONO-7643-04), fasting blood glucose levels tended to increase in the anamorelin groups as compared with the placebo group. Also in the Japanese phase III study (ONO-7643-05), fasting blood glucose tended to increase with the administration of anamorelin.

Table 52. Changes in fasting blood glucose levels (mg/dL) in main Japanese clinical studies

	Japanese phase II study (ONO-7643-03)			Japanese phase II study (ONO-7643-04)		Japanese phase III study (ONO-7643-05)
	Placebo (n = 58)	Anamorelin 50 mg (n = 65)	Anamorelin 100 mg (n = 55)	Placebo (n = 90)	Anamorelin 100 mg (n = 83)	Anamorelin 100 mg (n = 49)
Baseline	100.6 ± 15.7 (56)	102.6 ± 16.6 (65)	105.0 ± 22.8 (55)	99.2 ± 13.6 (89)	99.3 ± 19.4 (83)	106.0 ± 21.3 (48)
Week 3	—	—	—	99.3 ± 15.7 (87)	114.4 ± 31.5 (76)	129.1 ± 54.4 (45)
Week 4	100.3 ± 14.5 (54)	110.3 ± 24.6 (57)	122.0 ± 51.6 (49)	—	—	—
Week 6	—	—	—	101.1 ± 20.8 (76)	110.5 ± 27.5 (71)	121.6 ± 38.8 (41)
Week 8	103.4 ± 20.1 (47)	113.0 ± 30.7 (46)	112.0 ± 24.5 (36)	—	—	—
Week 9	—	—	—	102.7 ± 22.3 (71)	109.4 ± 23.3 (62)	121.0 ± 32.9 (35)
Week 12	105.2 ± 23.3 (42)	107.9 ± 27.1 (37)	102.6 ± 18.4 (30)	97.5 ± 17.5 (64)	108.9 ± 30.9 (58)	111.0 ± 21.5 (31)

Mean ± SD, (number of subjects at each time point)

In the Japanese phase II study (ONO-7643-03), adverse events related to increased blood glucose were reported in 20.7% (12 of 58) of subjects in the placebo group, 24.6% (16 of 65) of subjects in the anamorelin 50 mg group, and 30.9% (17 of 55) of subjects in the anamorelin 100 mg group. The following adverse events were reported in ≥2 subjects: glycosylated haemoglobin increased, hyperglycaemia (4 subjects each), blood glucose increased, blood triglycerides increased, dehydration (3 subjects each), diabetes mellitus, and blood cholesterol increased (2 subjects each) in the anamorelin 50 mg group; and glycosylated haemoglobin increased (11 subjects), blood glucose increased (10 subjects), glucose urine present (5 subjects), hyperglycaemia, and diabetes mellitus (3 subjects each) in the anamorelin 100 mg group. The following events were assessed as Grade 3 in severity: hyperglycaemia, blood glucose increased, and dehydration (1 subject each) in the anamorelin 50 mg group, and hyperglycaemia (3 subjects) and blood glucose increased (1 subject) in the anamorelin 100 mg group. The remaining adverse events were Grade ≤2 in severity. Adverse drug reactions related to increased blood glucose were reported in 1.7% (1 of 58) of subjects in the placebo group, 10.8% (7 of 65) of subjects in the anamorelin 50 mg group, and 23.6% (13 of 55) of subjects in the anamorelin 100 mg group. Hyperglycaemia and dehydration (1 subject each) in the anamorelin 50 mg group were assessed as serious adverse drug reactions. Adverse drug reactions led to treatment discontinuation in 1 subject (dehydration) in the anamorelin 50 mg group and 3 subjects (hyperglycaemia [2 subjects], type 2 diabetes mellitus [1 subject], and blood cholesterol increased [1 subject]; 1 subject had more than 1 event) in the anamorelin 100 mg group. The outcome was reported as "recovered" for all but one case of recovering.

In the Japanese phase II study (ONO-7643-04), adverse events related to increased blood glucose were reported in 6.7% (6 of 90) of subjects in the placebo group and 16.9% (14 of 83) of subjects in the anamorelin 100 mg group. In the anamorelin 100 mg group, the following adverse events were reported in ≥2 subjects; diabetes mellitus (4 subjects), hyperglycaemia (3 subjects), glycosylated haemoglobin increased, and glucose tolerance impaired (2 subjects each). Loss of consciousness, hyperglycaemia, and glucose tolerance impaired (1 subject each) were assessed as Grade 3 in severity. The remaining adverse events were assessed as Grade ≤2. Adverse drug reactions related to increased blood glucose were reported in 3.3% (3 of 90) of subjects in the placebo group and 12.0% (10 of 83) of subjects in the anamorelin 100 mg group. A serious adverse drug reaction were reported in 1 subject (loss of consciousness) in the anamorelin 100 mg group. The study treatment was discontinued, and the event resolved without treatment.

In the Japanese phase III study (ONO-7643-05), adverse events related to increased blood glucose were reported in 14.3% (7 of 49) of subjects and were all assessed as adverse drug reactions. The following adverse events related to increased blood glucose were reported in ≥2 subjects: hyperglycaemia (3 subjects) and diabetes mellitus (2 subjects). Diabetes mellitus (2 subjects) and type 2 diabetes mellitus (1 subject) were assessed as Grade 3 in severity. The remaining adverse events were assessed as Grade ≤2. A serious adverse drug reaction was reported in 1 subject (type 2 diabetes mellitus). The study treatment was discontinued, and the event resolved with insulin.

The pooled analysis of the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302) demonstrated that adverse events related to increased blood glucose were reported in 8.1% (26 of 322) of subjects in the placebo group and 16.2% (105 of 650) of subjects in the anamorelin 100 mg group, and that adverse drug reactions related to increased blood glucose were reported in 3.4% (11 of 322) of subjects in the placebo group and 6.5% (42 of 650) of subjects in the anamorelin 100 mg group. An adverse drug reaction hypertriglyceridaemia (1 subject) in the anamorelin 100 mg group was assessed as Grade 4 in severity, and hyperglycaemia (5 subjects), blood glucose increased, diabetes mellitus, and diabetes mellitus inadequate control (1 subject each) were assessed as Grade 3 in severity. These events resolved after discontinuation of the study treatment or treatment with oral hypoglycemic agents.

As shown above, since adverse drug reactions related to increased blood glucose have occurred, precautionary statements should be included in the package insert to administer anamorelin with caution in patients with poorly controlled diabetes mellitus and to measure blood and urine glucose.

PMDA's view:
PMDA confirmed the following: in the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), the Japanese phase III study (ONO-7643-05), and the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302), the incidence of adverse events related to increased blood glucose tended to be higher in the anamorelin 100 mg group than in the placebo group, and adverse drug reactions of Grade ≥3 and serious adverse drug reactions occurred. PMDA considers that patients should be carefully monitored by blood glucose measurements. If any abnormalities are observed, administration of anamorelin should be discontinued

and appropriate measures should be taken. PMDA also considers that information on adverse events related to increased blood glucose in association with the use of anamorelin should be continuously collected via post-marketing surveillance.

7.R.2.3.3 Effects of anamorelin on liver function

The applicant's explanation about hepatic dysfunction associated with treatment with anamorelin:
In the Japanese phase II study (ONO-7643-03), hepatic dysfunction-related adverse events were reported in 27.6% (16 of 58) of subjects in the placebo group, 16.9% (11 of 65) of subjects in the anamorelin 50 mg group, and 25.5% (14 of 55) of subjects in the anamorelin 100 mg group. Hepatic dysfunction-related adverse events reported in ≥2 subjects were AST increased, ALT increased (8 subjects each), γ-GTP increased (6 subjects), and blood alkaline phosphatase increased (3 subjects) in the anamorelin 50 mg group; γ-GTP increased (10 subjects), blood alkaline phosphatase increased (7 subjects), AST increased, ALT increased (6 subjects each), and blood bilirubin increased (2 subjects) in the anamorelin 100 mg group. AST increased and ALT increased (1 subject each) in the anamorelin 50 mg group, and γ-GTP increased (2 subjects) and ALT increased (1 subject) in the anamorelin 100 mg group were assessed as Grade 3 in severity. Gamma (γ)-GTP increased and ALT increased (1 subject each) in the anamorelin 100 mg group were assessed as hepatic dysfunction-related adverse drug reactions. The other adverse events were assessed as Grade ≤2. Hepatic dysfunction-related adverse drug reactions were reported in 3.4% (2 of 58) of subjects in the placebo group, 4.6% (3 of 65) of subjects in the anamorelin 50 mg group, and 9.1% (5 of 55) of subjects in the anamorelin 100 mg group. There were no serious hepatic dysfunction-related adverse drug reactions.

In the Japanese phase II study (ONO-7643-04), hepatic dysfunction-related adverse events were reported in 4.4% (4 of 90) of subjects in the placebo group and 10.8% (9 of 83) of subjects in the anamorelin 100 mg group. Hepatic dysfunction-related adverse events reported in ≥2 subjects in the anamorelin 100 mg group were γ-GTP increased (5 subjects) and hepatic function abnormal (3 subjects). All of the events were assessed as Grade ≤2 in severity. Hepatic dysfunction-related adverse drug reactions were reported in 1.1% (1 of 90) of subjects in the placebo group and 3.6% (3 of 83) of subjects in the anamorelin 100 mg group. There were no hepatic dysfunction-related serious adverse drug reactions or those leading to treatment discontinuation.

In the Japanese phase III study (ONO-7643-05), hepatic dysfunction-related adverse events were reported in 10.2% (5 of 49) of subjects, and hepatic dysfunction-related adverse drug reactions were reported in 8.2% (4 of 49) of subjects. An adverse event related to hepatic dysfunction and reported in ≥2 subjects was γ-GTP increased (4 subjects). Gamma (γ)-GTP increased (1 subject) was assessed as Grade 3 in severity but resolved without treatment. The other adverse events were assessed as Grade ≤2. There were no hepatic dysfunction-related adverse drug reactions or those leading to treatment discontinuation.

The pooled analysis of foreign phase III studies (HT-ANAM-301 and HT-ANAM-302) demonstrated that adverse events related to hepatic dysfunction were reported in 10.9% (35 of 322) of subjects in the placebo group and 13.7% (89 of 650) of subjects in the anamorelin 100 mg group, and that adverse drug reactions related to hepatic dysfunction were reported in 1.2% (4 of 322) of subjects in the placebo group and 0.8% (5

of 650) of subjects in the anamorelin 100 mg group. AST increased (7 subjects), γ-GTP increased (2 subjects), ALT increased, INR increased, and blood alkaline phosphatase increased (1 subject each) in the anamorelin 100 mg group were assessed as Grade 3 in severity.

PMDA's view:
PMDA confirmed the following: in the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), the Japanese phase III study (ONO-7643-05), and the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302), there were no serious adverse drug reactions related to hepatic dysfunction or no adverse drug reactions related to hepatic dysfunction leading to treatment discontinuation. However, in the Japanese phase II study (ONO-7643-03) and the Japanese phase II study (ONO-7643-04), adverse drug reactions related to hepatic dysfunction tended to occur more frequently in the anamorelin group than in the placebo group, and hepatic dysfunction-related adverse drug reactions of Grade 3 (ALT increased and γ-GTP increased) were reported in 2 subjects receiving anamorelin in the Japanese phase II study (ONO-7643-03). Therefore, PMDA considers that precautionary statements for hepatic dysfunction should be included in the package insert and that information should be continuously collected on the occurrence of adverse events related to hepatic dysfunction in association with the use of anamorelin via post-marketing surveillance.

7.R.2.3.4 Edema

The applicant's explanation about edema that were commonly observed in the clinical studies:
In the Japanese phase II study (ONO-7643-03), edema-related adverse events were reported in17.2% (10 of 58) of subjects in the placebo group, 10.8% (7 of 65) of subjects in the anamorelin 50 mg group, and 12.7% (7 of 55) of subjects in the anamorelin 100 mg group. Edema-related adverse events reported in ≥2 subjects were oedema peripheral, oedema (3 subjects each), and pleural effusion (2 subjects) in the anamorelin 50 mg group and oedema peripheral (4 subjects) and lymphoedema (2 subjects) in the anamorelin 100 mg group. Pericardial effusion and pleural effusion (1 subject each) in the anamorelin 50 mg group were assessed as Grade 5 in severity, and lymphoedema (1 subject) in the anamorelin 100 mg group was assessed as Grade 3. The causal relationship to anamorelin was denied for these events. The other adverse events were assessed as Grade ≤2 in severity. Edema-related adverse drug reactions occurred in 0% (0 of 58) of subjects in the placebo group, 1.5% (1 of 65) of subjects in the anamorelin 50 mg group, and 0% (0 of 55) of subjects in the anamorelin 100 mg group. There were no serious adverse drug reactions related to edema or edema-related adverse drug reactions leading to discontinuation of the study drug.

In the Japanese phase II study (ONO-7643-04), edema-related adverse events were reported in 1.1% (1 of 90) of subjects in the placebo group and 16.9% (14 of 83) of subjects in the anamorelin 100 mg group. Edema-related adverse events reported in ≥2 subjects in the anamorelin 100 mg group were oedema peripheral (10 subjects) and oedema (3 subjects). All of the events were assessed as Grade ≤2 in severity. Edema-related adverse drug reactions were reported in 0% (0 of 90) of subjects in the placebo group and 6.0% (5 of 83) of subjects in the anamorelin 100 mg group. There were no serious adverse drug reactions related to edema, and none of the edema-related adverse drug reactions led to treatment discontinuation.

In the Japanese phase III study (ONO-7643-05), edema-related adverse events were reported in 12.2% (6 of 49) of subjects. Edema-related adverse events reported in ≥2 subjects were oedema peripheral (4 subjects) and oedema (2 subjects). All of the events were assessed as Grade ≤2 in severity, and no events were assessed as adverse drug reactions.

The pooled analysis of foreign phase III studies (HT-ANAM-301 and HT-ANAM-302) demonstrated that edema-related adverse events occurred in 3.7% (12 of 322) of subjects in the placebo group and 5.2% (34 of 650) of subjects in the anamorelin 100 mg group and that edema-related adverse drug reactions occurred in 0.3% (1 of 322) of subjects in the placebo group and 0.5% (3 of 650) of subjects in the anamorelin 100 mg group. Pericardial effusion (2 subjects) and oedema peripheral (1 subject) in the anamorelin 100 mg group were assessed as Grade 3 in severity but their causal relationship to anamorelin were denied.

PMDA's view:
PMDA confirmed the following: in the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), the Japanese phase III study (ONO-7643-05), and the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302), the number of serious edema-related adverse events was small, and none of the edema-related adverse events were clinically significant. However, since the incidence of edema-related adverse events was higher in the anamorelin groups than in the placebo group in the Japanese phase II study (ONO-7643-04), and patients were excluded from the clinical studies if they had ascites, pleural effusion, or pericardial effusion requiring drainage, required attention to edema, or required diuretics, PMDA considers that attention should be paid to the occurrence of edema and that information on edema should be continuously collected via post-marketing surveillance.

7.R.2.3.5 Effects of anamorelin on tumors

The applicant's explanation about the effects of anamorelin on tumors:
Reportedly, anamorelin increases IGF-1, which, in turn, facilitates tumor proliferation [see Section 3.R.2]. In the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), and the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302), the percentage of patients with tumor progression[29)] after 12-week oral administration of anamorelin in the overall response is shown in Table 53, and anamorelin did not cause tumor progression.

Table 53. Percentage of patients with tumor progression after 12-week oral administration of anamorelin in overall response[a)]

Japanese phase II study (ONO-7643-03)		Japanese phase II study (ONO-7643-04)		Foreign phase III study (HT-ANAM-301)		Foreign phase III study (HT-ANAM-302)	
Placebo (n = 58)	Anamorelin 100 mg (n = 55)	Placebo (n = 90)	Anamorelin 100 mg (n = 83)	Placebo (n = 161)	Anamorelin 100 mg (n = 320)	Placebo (n = 161)	Anamorelin 100 mg (n = 330)
42.1 (24/57)	41.8 (23/55)	63.5 (47/74)	56.7 (38/67)	20.9 (14/67)	24.5 (35/143)	32.6 (14/43)	24.8 (26/105)

a) The percentage (%) of patients with progressive disease (PD) according to the category classification of the RECIST (number of patients meeting the criteria/number of patients evaluated)

[29)] The percentage of patients with progressive disease (PD) evaluated by oncologists according to the category classification of the RECIST.

PMDA confirmed that anamorelin have no effects on tumor progression in the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), and the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302).

7.R.2.4 Safety of anamorelin in patients with hepatic impairment

The applicant's explanation about the safety of anamorelin in patients with hepatic impairment:

In the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), the Japanese phase III study (ONO-7643-05), and the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302), adverse events were reported after multiple oral doses of anamorelin 100 mg once daily in 80.1% (545 of 680) of patients with normal hepatic function (Grade 3 in 20.9%, Grade 4 in 4.4%, and Grade 5 in 13.4%); 82.7% (124 of 150) of patients with mild hepatic impairment (Grade 3 in 21.3%, Grade 4 in 7.3%, and Grade 5 in 14.7%); and 50.0% (3 of 6) of patients with moderate hepatic impairment (Grade 3 in 33.3%, Grades 4 and 5 in 0%). Adverse drug reactions were reported in 20.9% (142 of 680) of patients with normal hepatic function (Grade 3 in 4.0%, Grade 4 in 0.3%, and Grade 5 in 0.1%); 26.0% (39 of 150) of patients with mild hepatic impairment (Grade 3 in 0.7%, and Grades 4 and 5 in 0%); and 16.7% (1 of 6) of patients with moderate hepatic impairment (Grades 3, 4, and 5 with 0%). Anamorelin was not administered to patients with severe hepatic impairment. No marked differences in the incidence of adverse drug reactions were observed between patients with hepatic impairment and patients with normal hepatic function at present. No trend was identified in which adverse events or adverse drug reactions were more severe with the severity of hepatic impairment.

However, no pharmacokinetic studies have been conducted in subjects with hepatic impairment, and the liver mainly contributes to the elimination of anamorelin *in vivo*. In light of the above, the possibility cannot be ruled out that the plasma concentration of anamorelin may increase in patients with hepatic impairment. Therefore, it is considered appropriate that patients with moderate to severe hepatic impairment are listed in the Careful Administration section of the package insert to call attention.

PMDA's view:

PMDA considers it appropriate that patients with moderate to severe hepatic impairment are listed in the Careful Administration section of the package insert to call attention. PMDA also considers that information on the safety of anamorelin in patients with hepatic impairment should be continuously collected via post-marketing surveillance in light of the limited number of such patients evaluated in the clinical studies.

7.R.2.5 Safety of anamorelin in patients with renal impairment

The applicant's explanation about the safety of anamorelin in patients with renal impairment:

In the Japanese phase II study (ONO-7643-03), the Japanese phase II study (ONO-7643-04), the Japanese phase III study (ONO-7643-05), and the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302), adverse events were reported after multiple oral doses of anamorelin 100 mg once daily in 81.0% (255 of 315) of patients with normal renal function (Grade 3 in 18.1%, Grade 4 in 4.8%, and Grade 5 in 16.8%); 80.1% (297 of 371) of patients with mild renal impairment (Grade 3 in 22.1%, Grade 4 in 5.1%, and Grade 5 in 10.2%); 79.4% (112 of 141) of patients with moderate renal impairment (Grade 3 in 24.1%, Grade 4 in 5.7%, and Grade

5 in 13.5%); and 90.0% (9 of 10) of patients with severe renal impairment (Grade 3 in 30.0% and Grades 4 and 5 with 0%). Adverse drug reactions were reported in 21.3% (67 of 315) of patients with normal renal function (Grade 3 in 1.9% and Grades 4 and 5 in 0%); 21.6% (80 of 371) of patients with mild renal impairment (Grade 3 in 4.3%, Grade 4 in 0.5%, and Grade 5 in 0.3%); and 22.7% (32 of 141) patients with moderate renal impairment (Grade 3 in 3.5% and Grades 4 and 5 in 0%). Although the number of patients was limited, adverse drug reactions were reported in 30.0% (3 of 10) of patients with severe renal impairment (Grade 3 in 10.0% and Grades 4 and 5 with 0%). No marked differences in the incidence of adverse drug reactions were observed between patients with renal impairment and patients with normal renal function at present. No trend was identified in which severity of adverse events or adverse drug reactions increases with the severity of renal impairment.

No pharmacokinetic study was conducted in subjects with renal impairment. However, the urinary excretion rate of anamorelin after oral administration was low [see Sections 6.2.1 and 6.2.3], and the extent of urinary excretion in the elimination of anamorelin from the body is small. In light of these findings, the plasma concentration of anamorelin is considered unlikely to elevate due to decreased renal function.

PMDA's view:
Although the number of patients with moderate or severe renal impairment was limited in the clinical studies, PMDA confirmed that no significant problems have been identified. Because of the limited number of patients evaluated in the clinical studies, PMDA considers that information on the safety of anamorelin in patients with renal impairment should be continuously collected via post-marketing surveillance.

7.R.3 Indication

The applicant's explanation about the indication of anamorelin:
The results of the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05) demonstrate a certain clinical significance of anamorelin in patients with cancer cachexia, and the safety of anamorelin is acceptable. Patients with radically unresectable, radical irradiation-unfeasible advanced cancer (mainly stage IV, including postoperative recurrent cancer) were enrolled in the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05), and patients with cancer cachexia in these stages are expected to receive anamorelin in clinical practice.

In the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05), cachexic patients with non-small cell lung cancer, colorectal cancer, gastric cancer, or pancreatic cancer were enrolled, and it was confirmed that types of cancer had no effects on the efficacy and safety of anamorelin. Also, in the foreign phase II exploratory studies (RC-1291-203 and RC-1291-205) enrolling patients with various types of cancer, the types of cancer had no remarkable effects on the efficacy of anamorelin for cancer cachexia. Therefore, the types of cancer seem to be unlikely to affect the efficacy of anamorelin for cancer cachexia. Meanwhile, information on the safety and efficacy of anamorelin in cachexic patients with types of cancer that have not been investigated in clinical studies in Japan is planned to be collected via post-marketing surveillance.

The disease term is specified as “cancer cachexia” in the treatment guidelines of the European Palliative Care Research Collaborative (EPCRC). Also, in Japan, the term “cancer cachexia” is used by associations including the Japanese Society for Parenteral and Enteral Nutrition and the Japanese Society for Palliative Medicine, indicating the term “cancer cachexia” is widely used in clinical practice in Japan.

PMDA’s view:
In the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05), anamorelin has been demonstrated to increase LBM and improve appetite-related QOL in the enrolled patients with cancer cachexia. In light of the above, PMDA considers that anamorelin is of a certain clinical significance in patients with cancer cachexia. Therefore, PMDA considers that anamorelin can be approved for use in patients with “cancer cachexia.” However, the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05) were conducted in patients who had no indication of surgery, had body weight loss, decreased appetite, or poor nutrition condition to a certain extent, had a performance status of ≤2, and were expected to survive at least 4 months (Tables 31, 38, and 43). Accordingly, the efficacy of anamorelin was not evaluated in patients with cachexia in the early- or end-stage of cancer in these studies. Also, the safety and efficacy of anamorelin have not been evaluated in cachexic patients with cancer other than non-small cell lung cancer, or gastrointestinal cancer (colorectal cancer, gastric cancer, or pancreatic cancer). PMDA considers that physicians should appropriately select patients for treatment of anamorelin with a full understanding of the efficacy and safety of anamorelin on the basis of information on the enrolled patients and results of the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05).

7.R.4 Dosage and administration

The applicant’s explanation about the dosage and dosing regimen of anamorelin:
Since anamorelin is affected by food as seen in the Japanese phase I study (ONO-7643-02) in healthy adults, anamorelin was administered in a fasted state, and subjects were instructed not to eat for at least 1 hour after taking anamorelin in the subsequent clinical studies. Following multiple oral doses of anamorelin 50 to 150 mg, once daily, in a fasted state for 7 days, the incidences of adverse events, especially hepatic function-related adverse events, increased in the anamorelin 150 mg group than in other dose groups. Meanwhile, the GH secretagogue action, which was used as a measure of the pharmacological action, was comparable between the anamorelin 100 mg and 150 mg groups (the maximum level on Day 7 of administration, 12.97 ng/mL in the anamorelin 100 mg group and 12.84 ng/mL in the anamorelin 150 mg group). In the Japanese phase II study (ONO-7643-03) in patients with non-small cell lung cancer and cachexia, the “mean change from baseline in LBM to Week 12” tended to be higher in the anamorelin 100 mg group than in the anamorelin 50 mg group.

On the basis of the above, the dosage and dosing regimen of anamorelin was decided to be administered at 100 mg, once daily, in a fasted state in the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05). The results of the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05) demonstrated a certain level of the clinical significance of anamorelin [see Section 7.R.1] and suggested that the safety of anamorelin is acceptable in light of its benefit [see Section 7.R.2].

Accordingly, the proposed dosage and dosing regimen of anamorelin were determined based on the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05).

PMDA's view:

PMDA considers it acceptable that the dosage and dosing regimen of anamorelin was determined based on the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05). PMDA also considers that the following information should be provided: study data on anamorelin for ≥12 weeks are unavailable, and anamorelin has not been evaluated for improvement in response to cancer therapy or prolongation of patient survival.

7.R.5 Post-marketing investigations

The applicant is currently conducting the Japanese phase III study (ONO-7643-06) shown in Table 54 to further clarify the clinical significance of anamorelin. The study will be continued as a post-marketing clinical study after the approval. The post-marketing surveillance shown in Table 55 is planned.

Table 54. Outline of the Japanese phase III study (ONO-7643-06)

Objective	**To confirm the efficacy and safety of anamorelin in patients with cancer cachexia**
Study design	**A multicenter, open-label, uncontrolled study (Including an observation period up to 4 weeks, a 24-week treatment period, and a 2-week follow-up period after the end of the study treatment)**
Population	**Cachexic patients with non-small cell lung cancer, colorectal cancer, gastric cancer, or pancreatic cancer.**
Target sample size	**100 patients (patients with non-small cell lung cancer and cachexia, [redacted]; and cachexic patients with colorectal cancer, gastric cancer, or pancreatic cancer, [redacted])**
Duration of treatment with anamorelin	**24 weeks**
Dosage and dosing regimen	**Anamorelin 100 mg, orally administered once daily in a fasted state**
Primary endpoint	**Proportion of patients meeting the following criteria: • a ≥5% body weight gain from baseline to Week 9 of the treatment period • increase in the total score of ≥2 points in the 5-item Functional Assessment of Anorexia/Cachexia Treatment (FAACT) from baseline at Week 9 of the treatment period * Patients are evaluated if they are confirmed to survive until Day 64 to conservatively handle missing values for patients who die before Week 9.**
Secondary endpoints	**• Change from baseline in body weight to Week 9 of the treatment period • Change from baseline in total score of patient-reported anorexia symptoms to Week 9 of the treatment period as measured by the 5-item FAACT • Change from baseline in FAACT total score to Week 9 of the treatment period**

Table 55. Outline of the general drug use-results survey (draft)

Objective	**To evaluate and review the safety of anamorelin in patients with cancer cachexia in clinical practice**
Study method	**Central registration**
Population	**Cachexic patients with non-small cell lung cancer, gastrointestinal cancer, or other cancer**
Target sample size	**300 patients**
Observation period	**12 weeks**
Main survey items	**• Patient characteristics (e.g., age, sex, body weight, types, stage, and duration of cancer, stage of cancer cachexia, laboratory data within 2 weeks of the start of the treatment with anamorelin, concurrent conditions), previous treatment of cancer, etc. • Treatment with anamorelin (including treatment duration, dosage, and reason for discontinuation) • Concomitant drugs and therapies • Adverse events (e.g., onset date, seriousness, outcome, discontinuation or continuation of anamorelin, and a causal relationship with anamorelin)**

PMDA considers that the following should be evaluated in the post-marketing setting:

- Cancer therapies during the treatment with anamorelin (including pharmacotherapy [e.g., drug name,

dosage and dosing regimen] and radiotherapy);

- Safety by type of cancer;
- Drug name, dosage and dosing regimen, and other relevant information of pharmacotherapy, if any, for concurrent condition during the treatment with anamorelin;
- Safety in patients with hepatic impairment;
- Safety in patients with renal impairment;
- Safety of a combined use of anamorelin and moderately potent CYP3A4 inhibitors;
- Safety of a combined use of anamorelin and CYP3A4 inducers;
- Safety of a combined use of anamorelin and P-gp inhibitors;
- Safety of a combined use of anamorelin and OATP1B3 inhibitors; and
- Safety of a combined use of anamorelin and drugs with MATE1 as a substrate.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1-2, CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. The inspection indicated that the clinical studies were generally conducted in accordance with GCP. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following issues at some study sites, although the issues had no significant impact on the overall assessment of the studies. The heads of the relevant medical institutions were notified of these issues as the findings requiring improvement.

Findings requiring improvement
Study sites

- Failure to retain some source data (records on the time of blood sampling).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that anamorelin has efficacy in the treatment of cancer cachexia, and that anamorelin has acceptable safety in view of its benefit.

PMDA has concluded that anamorelin may be approved if anamorelin is not considered to have any particular

problems based on comments from the Expert Discussion.

Review Report (2)

August 9, 2019

Product Submitted for Approval

Brand Name	Adlumiz Tablets 50 mg
Non-proprietary Name	Anamorelin Hydrochloride
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	November 27, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy, clinical significance, and safety

At the Expert Discussion, the expert advisors supported the PMDA's conclusion on issues presented in the Sections "7.R.1 Efficacy and clinical significance of anamorelin" and "7.R.2 Safety" in the Review Report (1). The following comments were raised from the expert advisors:

- Since anamorelin was confirmed to show a tendency toward increase in LBM and improvement in appetite, anamorelin has been demonstrated to be effective for cancer cachexia to a certain extent.
- The profiles of anamorelin, including its efficacy and safety, should be confirmed when data become available from the currently ongoing Japanese phase III study (ONO-7643-06) and the foreign phase III studies (ANAM-17-20 and ANAM-17-21) which were started after the approval of anamorelin in Japan. Meanwhile, in light of the current status including the treatment environment for cancer cachexia in Japan, it is considered meaningful to make anamorelin available in routine clinical practice based on the data currently available from the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05).

In view of the comments from the Expert Discussion, PMDA considers that the efficacy and safety of anamorelin, including its ethnic differences, should be confirmed for the data from the ongoing Japanese phase III study (ONO-7643-06) and the foreign phase III studies (ANAM-17-20 and ANAM-17-21) and that information thereof should be provided appropriately to healthcare professionals in clinical practice. PMDA thus asked the applicant to report these clinical study data to PMDA as soon as they are available, and the

applicant accepted it.

1.2 Indication

At the Expert Discussion, the expert advisors supported the PMDA's conclusion on issues presented in the Section "7.R.3 Indication" in the Review Report (1). The following comments were raised from the expert advisors:

- Under the current circumstances, a common view on the treatment of cancer cachexia has not been sufficiently shared in clinical practice. In addition, steroids are often used for patients with irreversible pathological conditions in current clinical practice, whereas patients enrolled in the clinical studies were those who were not in an irreversible condition. There is a concern that the patients' conditions may be different between the patients enrolled in the clinical studies and the image of patient portrayed by physicians in clinical practice. Therefore, in order to call attention, intended patients for anamorelin should be specifically described in the package insert based on the clinical studies, and such information should be provided to healthcare professionals in clinical practice in cooperation with organizations including relevant academic societies.

PMDA's view:

At present, data from the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05) serve as the only rationale for selecting patients for treatment with anamorelin. Therefore, the patient selection conditions should be specifically described in the Precautions Concerning Indications section of the package insert by referring to the inclusion and exclusion criteria in the Japanese clinical studies. On the basis of the precautions, the applicant should provide information on intended patients for anamorelin to healthcare professionals in clinical practice in cooperation with organizations such as relevant academic societies. In addition, the precautions should include that anamorelin should be administered to patients who had inadequate response to previously received basic cancer cachexia treatments with nutrition and exercise therapies.

Since the expert advisors supported the above PMDA's conclusion, PMDA has concluded that the package insert of anamorelin should include the following statements in the Indication and Precautions Concerning Indications sections.

Indication

Cancer cachexia

Precautions Concerning Indications

1. Anamorelin should be used in patients with cancer cachexia with inadequate response to therapies such as nutrition.
2. Anamorelin should be used in patients with a loss of ≥5% of body weight over the preceding 6 months and anorexia, and at least 2 of the following 3 conditions (a) to (c):
   (a) Fatigue or malaise; (b) Generalized muscle weakness; and (c) At least 1 of the following laboratory values: CRP >0.5 mg/dL, hemoglobin <12 g/dL; or albumin <3.2 g/dL.

3. Anamorelin should not be used in patients who have difficulty with oral intake of food or poor digestion and absorption of food.
4. Before selecting patients to be treated with anamorelin, physicians should read carefully and understand thoroughly the content described in the Clinical Studies section and fully understand the characteristics, e.g., cancer type and disease stage of patients enrolled in the clinical studies, and the efficacy and safety of anamorelin.

1.3 Dosage and administration

At the Expert Discussion, the expert advisors supported the PMDA's conclusion on issues presented in the Section "7.R.4 Dosage and administration" of the Review Report (1). The following comments were raised from the expert advisors:

- Discontinuation of the treatment should be considered when no therapeutic effects are observed after the start of anamorelin.
- Even in patients who respond well to anamorelin, physicians should be advised to periodically review the need to continue treatment to prevent unnecessary long-term treatment with anamorelin.

PMDA's view:

In the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05), LBM increased until Week 3 of the treatment with anamorelin and then remained at a certain level until Week 12 (Figures 1 and 2), and there is no information on the use of anamorelin for >12 weeks. Therefore, PMDA considers that physicians should determine the effect of anamorelin within 3 weeks after the start of the treatment and that physicians should periodically review the need to continue treatment after a certain period.

Since the expert advisors supported the above PMDA's conclusion, PMDA has concluded that the sections Dosage and Administration and Precautions Concerning Dosage and Administration of the package insert of anamorelin should include the following statements.

Dosage and Administration

The usual adult dosage is 100 mg of anamorelin hydrochloride administered orally once daily in a fasted state.

Precautions Concerning Dosage and Administration

1. Patients should be instructed to take anamorelin in a fasted state and not to eat for at least 1 hour after taking anamorelin to avoid the food effect.
2. If no effect is observed within 3 weeks after the start of anamorelin, physicians should consider discontinuation of anamorelin.
3. Because anamorelin has not been used for >12 weeks, physicians should periodically review the need to continue the treatment.

1.4 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusion on issues presented in the

Section “7.R.5 Post-marketing investigations” in the Review Report (1). The following comments were raised from the expert advisors:

- In clinical practice, anamorelin is expected to be used in cachexic patients with cancer other than non-small cell lung cancer or gastrointestinal cancer evaluated in the Japanese phase II study (ONO-7643-04) and the Japanese phase III study (ONO-7643-05). Therefore, it is important to promptly provide the information on the profiles including the safety of anamorelin noted in clinical practice to healthcare professionals in clinical practice.

In view of the discussion at the Expert Discussion, PMDA considered that post-marketing surveillance should be conducted in all patients treated with anamorelin to immediately collect data including the efficacy and safety of anamorelin in clinical practice and to take measures for the proper use of anamorelin without delay. PMDA thus asked the applicant to review the post-marketing surveillance plan, and the applicant responded as follows. PMDA accepted the applicant’s response.

- The post-marketing surveillance will be conducted in all patients treated with anamorelin. The sample size of the surveillance is planned to be 5,000 patients with an observation period of 1 year.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for anamorelin should include the safety and efficacy specifications presented in Table 56 and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Table 57, and a specified use-results survey presented in Table 58.

The outlines of the ongoing Japanese phase III study (ONO-7643-06) and the foreign phase III studies (ANAM-17-20 and ANAM-17-21) have been submitted (Tables 59 and 60, respectively).

PMDA instructed the applicant to promptly disclose the data from the clinical studies presented in the risk management plan (draft) as soon as they become available. In response to that, the applicant answered to take appropriate actions in confirming the efficacy and safety profiles of anamorelin, including ethnic differences. PMDA accepted it.

Table 56. Safety and efficacy specifications in the risk management plan (draft)

Safety specifications		
Important identified risks	**Important potential risks**	**Important missing information**
• **Hepatic function disorders** • **Inhibition of conduction system** • **Hyperglycaemia**	• **Tumor progression** • **Interaction with moderately potent CYP3A4 inhibitors**	• **Not applicable**
Efficacy specification		
• **Effects of increases in body weight gain and improvement in appetite**		

Table 57. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey	• Post-marketing clinical study (from the Japanese phase III study [ONO-7643-06]) • Foreign phase III studies (ANAM-17-20 and ANAM-17-21)	• Provision of information obtained in the early post-marketing phase vigilance. • Organize and disseminate information for healthcare professionals. • Organize and disseminate information for patients.

Table 58. Outline of the specified use-results survey (draft)

Objective	To assess and review the profiles including safety of anamorelin in patients with cancer cachexia in clinical practice
Survey method	All-case surveillance
Population	Cachexic patients with non-small cell lung cancer, gastrointestinal cancer, and other cancer
Planned sample size	All patients treated with anamorelin (planned sample size of 5,000 patients)
Observation period	1 year
Main survey items	• Patient characteristics (e.g., age; sex; body weight; types, stage, and duration of cancer; PS; stage of cancer cachexia, laboratory data within 2 weeks of the start of anamorelin treatment; concurrent conditions), prior cancer treatments (surgery, use of antineoplastic drugs), etc. • Treatment with anamorelin (including treatment duration, dosage, and reason for discontinuation) • Treatment of cancer during anamorelin treatment (including pharmacotherapy [e.g., drug name and dosing regimen] and radiotherapy) • Concomitant drugs and therapies • Efficacy (e.g., body weight and appetite over time) • Adverse events (e.g., onset date, seriousness, outcome, discontinuation or continuation of anamorelin, and a causal relationship with anamorelin)

Table 59. Outline of the post-marketing clinical study (from the Japanese phase III study [ONO-7643-06])

Objective	To confirm the efficacy and safety of anamorelin in the treatment of cancer cachexia
Study design	A multicenter, open-label, uncontrolled study (Including an observation period up to 4 weeks, a 24-week treatment period, and a 2-week follow-up period after the end of the study treatment)
Population	Cachexic patients with non-small cell lung cancer, colorectal cancer, gastric cancer, or pancreatic cancer
Planned sample size	100 patients ([redacted] patients with non-small cell lung cancer and cachexia; [redacted] cachexic patients with colorectal cancer, gastric cancer, or pancreatic cancer)
Duration of treatment with anamorelin	24 weeks
Dosing regimen	Anamorelin 100 mg is administered orally, once daily, in a fasted state.
Primary endpoint	Percentage of patients meeting the following criteria: A ≥ 5% body weight gain from baseline to Week 9 ≥2 points increase in the total score of anorexia symptoms from baseline to Week 9 as measured by the 5-item Anorexia Symptom Scale of FAACT * Patients are evaluated if they are confirmed to survive until Day 64 to conservatively handle missing values for patients who die before Week 9.
Secondary endpoints	Change from baseline in body weight to Week 9 Change from baseline in the total score of anorexia symptoms to Week 9 as measured by the 5-item Anorexia Symptom Scale of FAACT Change from baseline in FAACT total score to Week 9

Table 60. Outline of foreign phase III studies (ANAM-17-20 and ANAM-17-21)

Objective	**To confirm the efficacy and safety of anamorelin for cancer cachexia**
Study design	**Multicenter, double-blind, placebo-controlled studies** **(Including an observation period up to 4 weeks, a 24-week treatment period, and a 2-week follow-up period after the end of the study treatment)**
Population	**Patients with non-small cell lung cancer and cachexia**
Planned sample size	**316 patients (158 patients in the placebo group; 158 patients in the anamorelin 100 mg group)**
Duration of treatment with anamorelin	**24 weeks**
Dosing regimen	**Anamorelin 100 mg is administered orally, once daily, in a fasted state.**
Primary endpoint	**Percentage of patients meeting the following criteria:** **• A ≥ 5% body weight gain from baseline to Week 9** **• ≥2 points increase in the total score in the 5-itemFAACT from baseline to Week 9** *** Patients are evaluated if they are confirmed to survive until Day 64 to conservatively handle missing values for patients who die before Week 9.**
Secondary endpoints	**• Change from baseline in body weight to Week 9** **• Change from baseline in the total score of anorexia symptoms to Week 9 as measured by the 5-item Anorexia Symptom Scale of FAACT** **• Change from baseline in FAACT total score to Week 9**

2. Overall Evaluation

As a result of the above 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. As the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Cancer cachexia

Dosage and administration

The usual adult dosage is 100 mg of anamorelin hydrochloride administered orally once daily in a fasted state.

Approval conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is also required to conduct a drug use-results survey involving all patients treated with the product until data from a certain number of patients have been accumulated in the post-marketing setting in order to collect the safety and efficacy data on the product without delay and to take necessary measures to facilitate the proper use of the product.

Appendix

List of abbreviations

ADR	Adverse drug reaction (an adverse event for which a causal relationship with the study drug cannot be ruled out)
ALT	Alanine aminotransferase
Anamorelin	Anamorelin hydrochloride
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
BCRP	Breast cancer resistance protein
BSEP	Bile salt export pump
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
C_{max}	Maximum concentration
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTD	Common technical document
CYP	Cytochrome P450
DEXA	Dual energy X-ray absorptiometry
EC_{50}	Half maximal effective concentration
ECOG	Eastern cooperative oncology group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EPCRC	European palliative care research collaborative
FAACT	Functional Assessment of Anorexia/Cachexia Treatment
FAS	Full analysis set
FDA	Food and Drug Administration
GC	Gas chromatography
GCP	Good clinical practice
GH	Growth hormone
GHS-R_{1a}	Growth hormone secretagogue receptor 1a
γ-GTP	γ-Glutamyltransferase
Hb	Hemoglobin
hERG	Human ether-a-go-go related gene
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
ICH Q1E guideline	Evaluation of Stability Data (Notification No.0603004, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare, dated June 3, 2003)
ICR	Institute of cancer research
IGF-1	Insulin-like growth factor-1

INR	International normalised ratio
IR	Infrared spectroscopy
JCOG	Japan Clinical Oncology Group
LBM	Lean body mass
LC/MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
M4	Metabolite 4, a monooxidized form of anamorelin
M6	Metabolite 6, an *N*-demethylated form of anamorelin
MATE	Multidrug and toxin extrusion
MDCKII	Madin-Darby canine kidney cell-II
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
mRNA	Messenger RNA
MRP	Multidrug resistance-associated protein
MS	Mass spectrum
NAG	*N*-acetyl-β-$_D$-glucosaminidase
NCI	National Cancer Institute
NK_2	Neurokinin 2
NMR	Nuclear magnetic resonance spectrum
NZW	New Zealand white
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per protocol set
the product	Adlumiz Tablets 50 mg
PS	Performance status
PTP	Press through packaging
QOL	Quality of life
QOL-ACD	The QOL questionnaire for cancer patients treated with anticancer drugs
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
Radio-HPLC	High-performance liquid chromatography equipped with a radioactivity detector
RECIST	Response evaluation criteria in solid tumors
RH	Relative humidity
S9	S9 fraction: supernatant fraction obtained from liver homogenate by centrifuging at 9,000 g.
SD	Sprague-Dawley
SDH	Sorbitol dehydrogenase
$t_{1/2}$	Elimination half life
t_{max}	Time to reach maximum concentration
UICC-TNM Classification	Tumor, node, metastasis classification of the International Union Against Cancer

UV	Ultraviolet spectrum
UV/VIS	Ultraviolet-visible spectrum
WBP	Whole body plethysmography
ΔΔQTcF	Difference in placebo-adjusted change from baseline in QTcF

Second Review Report

November 16, 2020
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Adlumiz Tablets 50 mg
Non-proprietary Name	Anamorelin Hydrochloride
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	November 27, 2018
Dosage Form/Strength	Tablet: Each film-coated tablet contains 50 mg of anamorelin hydrochloride.
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the deliberation by the First Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council held on August 29, 2019, and the data submitted in the new drug application, including additional data submitted by the applicant, PMDA has concluded that the product has efficacy in the treatment of cancer cachexia in patients with non-small cell lung cancer, gastric cancer, pancreatic cancer, and colorectal cancer and that the product has acceptable safety in view of its benefit. As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

Indication

Cancer cachexia in patients with the following malignancies:
Non-small cell lung cancer, gastric cancer, pancreatic cancer, and colorectal cancer.

Dosage and administration

The usual adult dosage is 100 mg of anamorelin hydrochloride administered orally once daily in a fasted state.

Approval conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is also required to conduct a drug use-results survey involving all patients treated with the product until data from a certain number of patients have been accumulated in the post-marketing setting in order to collect the safety and efficacy data on the product without delay and to take necessary measures to facilitate the proper use of the product.

1. Review process and response details

On the basis of clinical data from studies including the Japanese clinical studies (ONO-7643-04 and ONO-7643-05) in patients with cancer cachexia, PMDA has concluded that the product has efficacy in the treatment of cancer cachexia and that the product has acceptable safety in view of its benefits (See the Review Report for Adlumiz Tablets 50 mg [August 20, 2019]). On the basis of the results of the review conducted by PMDA, the Ministry of Health, Labour and Welfare consulted the Pharmaceutical Affairs and Food Sanitation Council on the appropriateness of approval decision of the product. In response, the product was reviewed at a meeting of the First Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as "the First Committee on New Drugs") held on August 29, 2019.

At the First Committee on New Drugs, it was recommended that the data available from the completed clinical studies should be reorganized for the benefit and risk of anamorelin demonstrated in the Japanese and foreign studies and the intended patients of anamorelin before deliberating the appropriateness of approval decision of anamorelin. In light of the recommendation, PMDA decided to review the proper use of anamorelin after further scrutinizing the benefit and risk profiles of anamorelin.

The review at the Expert Discussion and the subsequent review by PMDA are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

Among the clinical studies conducted in Japan before the application for approval, 2 studies were conducted in the late stage of the development: Study ONO-7643-04 in patients with non-small cell lung cancer and cachexia and Study ONO-7643-05 in cachexic patients with gastric cancer, pancreatic cancer, or colorectal cancer. In the Second Review Report, Study ONO-7643-04 and Study ONO-7643-05 are abbreviated as "Study 04" and "Study 05," respectively.

1.1 Safety of anamorelin

PMDA drew a conclusion on the safety of anamorelin based on the adverse events observed in the Japanese and foreign clinical studies and data from the nonclinical studies (See the Review Report for Adlumiz Tablets 50 mg [August 20, 2019], hereinafter referred to as "the Review Report"). During the deliberation in the First Committee on New Drugs, the following comments were raised for the safety of anamorelin.

(a) Plasma concentrations of unchanged anamorelin substantially vary among individuals after administration of anamorelin 100 mg once daily in patients with cancer cachexia. In addition, since anamorelin is a drug metabolized by the liver, the expose to anamorelin may be higher in patients with hepatic impairment. In the foreign thorough QT/QTc study in healthy adults, QRS widened was reported in 1 of 7 patients who received anamorelin 400 mg as the highest dose, for which the study was once interrupted and resumed at the reduced dose of 300 mg (See Section 6.2.10 of the Review Report). The safety of anamorelin should

be carefully evaluated in full consideration of the safety profiles observed in the foreign thorough QT/QTc study.

(b) In the foreign clinical studies of anamorelin, adverse events that correspond to torsade de pointes/QT prolongation (SMQ) were reported in 3 of approximately 900 subjects. In the assessment report prepared by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), a concern was raised for the appropriateness of safety assessment, including the frequency of electrocardiographic monitoring. Taking account of such concern, the effects of anamorelin on cardiac functions should be carefully reviewed.

(c) Cetuximab (genetical recombination), an antineoplastic drug that may be used concurrently with anamorelin, is known to cause electrolyte abnormalities including hypomagnesaemia. The combined use of anamorelin with antineoplastics that potentially affect the cardiac functions or electrolytes may result in an increase in cardiac-related events even in patients without evident cardiac failure or arrhythmia. It is recommended that the safety in patients receiving anamorelin in combination with antineoplastics in the clinical studies should be reorganized and that appropriate measures should be taken, including the collection of information on concomitantly used drugs and the revision of the package insert, if necessary, in the post-marketing setting.

The contents of the PMDA's review based on the comments raised from the First Committee on New Drugs are summarized below.

(a) Pharmacokinetics and safety of anamorelin in patients with cancer cachexia

PMDA asked the applicant to explain the estimated maximum exposure and safety profiles of anamorelin when patients with cancer cachexia received oral doses of anamorelin 100 mg once daily, in consideration of the interindividual variability of plasma concentrations of unchanged anamorelin and factors affecting the pharmacokinetics of anamorelin.

The applicant's answer:

In a population pharmacokinetic (PPK) analysis, body weight and α1-acid glycoprotein (AGP) concentration were identified as covariates affecting the plasma concentrations of unchanged anamorelin. Accordingly, the use of the 5th percentile value of body weight (38.6 kg) and the 95th percentile value of AGP concentrations in the population of patients with cancer cachexia in the PPK analysis should allow the estimation of maximum exposure of anamorelin based on interindividual variability. The steady-state C_{max} and AUC_{τ} after oral doses of anamorelin once daily in patients with cancer cachexia and normal hepatic function were estimated. Then, in consideration of the severity of hepatic impairment and concomitant use of CYP3A4 inhibitors that might affect the pharmacokinetics of anamorelin, the estimated exposure of unchanged anamorelin in plasma after oral doses of anamorelin 100 mg once daily in patients with cancer cachexia was calculated by using a physiologically based pharmacokinetic (PBPK) analysis model (Table 1).

Table 1. Estimated maximum exposure of unchanged anamorelin in plasma after oral doses of anamorelin 100 mg once daily in patients with cancer cachexia

Subject characteristics possibly increasing the anamorelin exposure		C_{max}		AUC_{τ}	
Severity of hepatic impairment	Concomitant use of moderately potent CYP3A4 inhibitors[a)]	Fold-increase[b)]	Estimated steady-state value[c)] (ng/mL)	Fold-increase[b)]	Estimated steady-state value[c)] (ng·h/mL)
Normal hepatic function	No	—	2,300[d)]	—	6,820[d)]
Mild	No	1.0	2,300	1.3	8,870
	Yes	1.4	3,220	2.0	13,600
Moderate	No	1.6	3,680	2.3	15,700
	Yes	2.0	4,600	3.2	21,800
Severe	No	1.8	4,140	3.0	20,500
	Yes	2.1	4,830	3.9	26,600

a) Since the concomitant use of potent CYP3A4 inhibitors is contraindicated, the concomitant use of moderate CYP3A4 inhibitors were evaluated.
b) Fold-increase on the estimated exposure (C_{max} and AUC) of anamorelin in patients with cancer cachexia was estimated by the PBPK model.
c) Calculated by multiplying the estimated maximum exposure in patients with cancer cachexia and normal hepatic function by the fold-increase estimated by the PBPK model.
d) Estimated maximum exposure based on the interindividual variability. C_{max} and AUC_{τ} at steady state in patients with cancer cachexia were estimated with the use of body weight and AGP concentrations identified as covariates by the PPK analysis (body weight of 38.6 kg and AGP concentration of 242 mg/dL, which represent the 5th percentile value and the 95th percentile value, respectively, in the patient population of the PPK analysis).

The QRS widened observed in a foreign thorough QT/QTc study is thought to be mediated by the inhibition of sodium channel current (See Section 3.R.3 of the Review Report). In general, the inhibition of a channel depends on the concentrations of the inhibiting test substance. Actually, in the foreign thorough QT/QTc study, the QRS widened occurred after the administration of anamorelin in some cases, but the electrocardiographic abnormalities were relieved with decreases in the plasma concentrations of unchanged anamorelin and had resolved to baseline at 24 hours postdose in these cases. These findings suggested that the maximum plasma concentration (C_{max}) of unchanged anamorelin was appropriate as an index for the exposure for the evaluation of the effects on QRS width. In the foreign thorough QT/QTc study, the events observed after the single dosing of anamorelin 400 mg, i.e., electrocardiogram QRS complex prolonged (C_{max} of 3,360 ng/mL) and ventricular extrasystoles (C_{max} of 3,830 ng/mL), were both mild in severity and had resolved without treatment at 6 hours postdose, and the C_{max} level of anamorelin where concerns are raised for the effects on cardiac functions was estimated to be around 3,360 ng/mL.

In the Japanese and foreign clinical studies in which anamorelin 100 mg was orally administered once daily in patients with cancer cachexia, the maximum exposure of unchanged anamorelin in plasma (C_{max} and AUC_{τ}) were estimated to be 3,670 ng/mL and 14,100 ng·h/mL, respectively, and the estimated maximum exposures of C_{max} and AUC_{τ} in patients with cancer cachexia and moderate or severe hepatic impairment were higher as shown in Table 1. The safety of anamorelin at these exposure has not been fully evaluated in clinical studies so far, and the effects on cardiac functions are also concerned. Therefore, it was decided to newly add patients with moderate or severe hepatic impairment to the list of contraindications.

PMDA has confirmed that no tendency was identified where adverse events or adverse drug reactions became more severe with the severity of hepatic impairment in the Japanese and foreign clinical studies (See Section 7.R.2.4 of the Review Report). However, based on the following reasons, PMDA considers that the applicant's response to add patients with moderate or severe hepatic impairment to the list of contraindications is

acceptable.

- The liver is considered to be mainly involved in the elimination of anamorelin from the body (See Section 6.2.3 of the Review Report), and the plasma concentrations of unchanged anamorelin may increase in patients with hepatic impairment.
- In patients with hepatic impairment, the use of anamorelin in combination with moderately potent CYP3A4 inhibitors may further increase the plasma concentration of unchanged anamorelin.
- The data from the foreign thorough QT/QTc study suggest that the QRS widened observed after the administration of anamorelin may be enhanced in a manner dependent to the plasma concentration of unchanged anamorelin.
- The exposure of unchanged anamorelin in patients with cancer cachexia substantially varies among individuals (See Sections 6.2.4 to 6.2.6 of the Review Report).
- The estimated exposure (C_{max}) of unchanged anamorelin in patients with cancer cachexia and moderate or severe hepatic impairment with a body weight of 38.6 kg and AGP concentration of 242 ng/mL (the 5th and 95the percentile values, respectively, of the patient population in the PPK analysis) was higher than the C_{max} of anamorelin at which QRS widened was observed in the clinical studies and C_{max} of anamorelin in the Japanese and foreign clinical studies in which oral doses of anamorelin 100 mg was administered once daily in patients with cancer cachexia.

The C_{max} of unchanged anamorelin in patients with mild hepatic impairment does not exceed the C_{max} after administration of anamorelin 400 mg at which QRS widened was observed in the foreign thorough QT/QTc study or the C_{max} of anamorelin in the Japanese or foreign clinical studies in patients with cancer cachexia where anamorelin 100 mg was orally administered once daily. However, the estimated maximum exposure of unchanged anamorelin after coadministration of moderately potent CYP3A4 inhibitors was close to 3,360 ng/mL (See Table 1), and the risk of QRS widened could not be ruled out. Therefore, PMDA has concluded that patients with mild hepatic impairment should be listed in the Careful Administration section of the package insert to call attention.

At the Expert Discussion, the expert advisors made the following comments and supported the PMDA's conclusion.

- The following PMDA's conclusions are considered appropriate: Anamorelin should be contraindicated in patients with moderate or severe hepatic impairment with an emphasis on the safety; anamorelin should be carefully administered to patients with mild renal impairment; and patients should be closely monitored for safety during the treatment.

In view of the discussion at the Expert Discussion, PMDA has reached the following conclusions: Anamorelin should be contraindicated in patients with moderate or severe hepatic impairment; patients with mild hepatic impairment should be listed in the Careful Administration section of the package insert; a precautionary statement should be included in the package insert to the effect that caution should be exercised when anamorelin is used especially in combination with moderately potent CYP3A4 inhibitors; and a precautionary statement should be included in the Important Precautions section of the package insert to the effect that hepatic

function should be tested on a regular basis before and during treatment with anamorelin. PMDA instructed the applicant to take actions on these conclusions. The applicant took appropriate actions, and PMDA accepted them.

(b) Effects of anamorelin on cardiac functions and monitoring of the effects

In non-clinical studies, anamorelin inhibited the sodium channel. In Japanese and foreign clinical studies, the incidence of cardiovascular-related adverse events and abnormal ECG-related adverse events tended to be higher in the anamorelin 100 mg group than in the placebo group, and serious adverse drug reactions occurred. Thus, PMDA concluded that precautions should be provided in the package insert of anamorelin for electrocardiographic abnormalities due to the inhibitory effects of anamorelin on the conduction system. PMDA also concluded that precautions should be provided in the package insert stating that electrocardiography should be performed regularly during the clinical use of anamorelin and that appropriate measures, including interruption and discontinuation of anamorelin, should be chosen if PR interval is prolonged or QRS widened (See Sections 3.R.3 and 7.R.2.3.1 of the Review Report).

The CHMP of the EMA reported in its assessment report that the inspections revealed several flawed administrative GCP findings (i.e., availability of source data at the study sites and collection of safety data) in the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302) in patients with non-small cell lung cancer and cachexia, indicating underestimation of the safety.

The applicant's explanation about the issues:

- The CHMP indicated the following: GCP inspections performed at [redacted], a contract research organization of the clinical study, revealed that chemotherapy had been performed elsewhere in some study sites (13 of 93 study sites) in the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302), and therefore, all medical records could not be accessed in these study sites, which raised a concern that adverse events occurring in subjects might not have been reported appropriately. The CHMP pointed out that the number and details of adverse events and the proportion of subjects with the use of concomitant corticosteroids, which were specified to be used only before and after chemotherapy, had to be compared between study sites that could access all source data and study sites that could not. In response to the comments from the CHMP, Helsinn, a licenser of anamorelin, and [redacted] checked and found that all accessible information from medical records was appropriately collected with no omission of a report of adverse events in the study sites where the GCP inspections were performed. In addition, the details and incidence of Grade ≥3 adverse events were similar between subjects who received chemotherapy at their study sites and subjects who did not (among 13 study sites where chemotherapy was performed elsewhere, all source data were accessible in 3 study sites and not accessible in 10 study sites). Although the incidence of Grade ≤2 adverse events tended to be lower in patients who underwent chemotherapy elsewhere, the incidence of reported adverse events was the lowest in the 3 study sites where all source data were accessible, indicating that it could not be concluded that the difference in the accessibility to source data was related to the incidence of adverse events. Also, corticosteroids were used concomitantly in many subjects, regardless of the accessibility to the source data. Therefore, although the CHMP

indicated the possibility of insufficient collection of information on adverse events and concomitant therapies, it is considered that there is no influence on the assessment of the safety of anamorelin.

PMDA's view:

Since all source data were accessible only in 3 of the 13 study sites where chemotherapy was performed elsewhere, sufficient information on concomitant therapies might not have been collected. However, PMDA considers the applicant's explanation to be reasonable to a certain extent that the influence was not significant. However, while the safety data from the foreign clinical studies should be used as reference data because of the possibility of underestimation, the safety of anamorelin should be evaluated based on the data from the Japanese clinical studies.

At the meeting of the First Committee on New Drugs, it was pointed out that 3 cases of adverse events corresponding to torsade de pointes/QT prolongation (SMQ) in foreign clinical studies have not been mentioned in the Review Report. In response to that, the occurrence of torsade de pointes in the Japanese and foreign studies is described below.

- The 3 events (PTs) that correspond to torsades de pointes/QT prolongation (SMQ) observed in the foreign clinical studies are ventricular tachycardia in 2 subjects[1)2)], and QT prolonged in 1 subject[3)]. Although the event ventricular tachycardia in 1 subject was assessed as serious, the causal relationship to anamorelin was denied in all 3 events, and treatment with anamorelin was continued in all of 3 cases.
- Studies 04 and 05 were started in Japan after major foreign clinical studies were completed. In Studies 04 and 05, the following safety measures were taken based on the available information on the occurrence of adverse events obtained from previous Japanese and foreign clinical studies, including the foreign thorough QT/QTc study.
  - i) Patients with angina pectoris or myocardial infarction and patients at higher risk of widened QRS (QRS width of ≥110 ms) were excluded.
  - ii) The regular visit interval was shorter than that in Study ONO-7643-03 which had been conducted in Japan previously.
  - iii) Criteria for treatment interruption based on findings from 12-lead electrocardiography, changes in blood pressure over time, and subjective symptoms were newly added in addition to criteria for treatment discontinuation specified in Study ONO-7643-03.
  - iv) 12-lead electrocardiography was specified as a mandatory test to be performed before the start of treatment with anamorelin and at each regular visit in Study ONO-7643-03. In Studies 04 and 05, the frequency of electrocardiographic measurements during the study period was increased with the shortened intervals between regular visits. In addition, it was additionally specified that if anamorelin was interrupted on the basis of electrocardiographic findings, 12-lead electrocardiography and vital signs (blood pressure and pulse rate) should be checked before and after the administration of the

[1)] In the foreign phase II study (RC-1291-205), an 8[redacted]-year-old male experienced the event on Day 8 of the treatment with anamorelin 50 mg administered once daily.
[2)] In the foreign phase III study (HT-ANAM-301), a 6[redacted]-year-old male experienced the event on Day 75 of the treatment with anamorelin 100 mg administered once daily.
[3)] In the foreign phase II study (ST-ANAM-207), a 5[redacted]-year-old female experienced the event on Day 85 of the treatment with anamorelin 100 mg administered once daily.

study drug at the following visit to determine whether the study treatment could be continued.

v) Criteria based on the risk of inhibitory effects on the conduction system were added to the discontinuation criteria.

vi) The criteria for precautions for cardiac functions used in Study ONO-7643-03 were also specified in Studies 04 and 05.

- In Study 04 where the above safety measures were taken, 1 patient (1.2%) in the anamorelin 100 mg group and 1 patient (1.1%) in the placebo group met the cardiac function-related criteria for treatment discontinuation, such as 12-lead electrocardiography findings, blood pressure, or arrhythmia; 3 patients (3.6%) in the anamorelin 100 mg group and 2 patients (2.2%) in the placebo group met the criteria for treatment interruption; and 14 patients (16.9%) in the anamorelin 100 mg group and 4 (4.4%) in the placebo group met the criteria for precautions. In Study 05, an uncontrolled study, no patient (0%), 3 patients (6.1%), and 6 patients (12.2%) met the cardiac function-related criteria for treatment discontinuation, treatment interruption, and precautions, respectively.
- No case of torsade de pointes has been reported in association with the use of anamorelin in the Japanese and foreign clinical studies.

PMDA's view:

PMDA confirmed that a causal relationship of torsades de pointes/QT prolongation (SMQ) to anamorelin was denied in the 3 patients in the foreign clinical studies, and treatment with anamorelin was continued. PMDA also confirmed that the Japanese clinical studies were conducted with new safety measures based on the foreign clinical studies and that no clinically significant events occurred in the Japanese clinical studies. PMDA has reached the same conclusion as the conclusion, which was drawn at the previous meeting of the First Committee on New Drug, that in light of the effects of anamorelin on cardiac functions, precautions should be included in the Important Precautions section of the package insert that examinations including electrocardiography should be performed regularly during treatment with anamorelin and that appropriate measures including treatment discontinuation should be taken if any abnormalities are observed. However, in order to manage the risk of inhibition of the conduction system by anamorelin, it is also important to take safety measures similar to those specified in Studies 04 and 05 even after the market launch of anamorelin. Therefore, information on the cardiac function-related criteria for treatment discontinuation, treatment interruption, and precautions as well as occurrences of events in patients who meet these criteria in Studies 04 and 05 should be provided in the Clinical Studies section of the package insert and materials for healthcare professionals. In addition, precautions should be thoroughly disseminated. More specifically, the conditions of patients should be monitored before and during treatment with anamorelin on a regular basis with the reference to the frequency of electrocardiography and other examinations in Studies 04 and 05, and appropriate measures, including discontinuation of treatment with anamorelin, should be taken if any abnormalities are seen.

At the Expert Discussion, the above PMDA's conclusion was supported.

(c) Concomitant use with antineoplastics

PMDA reviewed the appropriateness of the concomitant use of anamorelin with cardiotoxic drugs, e.g., antineoplastics, and the need for precautions again.

Of subjects who received anamorelin 100 mg orally once daily, 79.1% (148 of 187) of subjects were concomitantly treated with antineoplastics in the Japanese clinical studies (Studies ONO-7643-03, 04, and 05), (i.e., 78.2% [43 of 55] of subjects in Study ONO-7643-03; 77.1% [64 of 83] of subjects in Study 04; and 83.7% [41 of 49] of subjects in Study 05). Antineoplastics concomitantly used are shown in Table 2.

Table 2. Concomitant antineoplastics (Studies ONO-7643-03, 04, and 05)

Concomitant drugs	Study ONO-7643-03		Study 04	Study 05
	Anamorelin 50 mg (n = 65)	Anamorelin 100 mg (n = 55)	Anamorelin 100 mg (n = 83)	Anamorelin 100 mg (n = 49)
Concomitant antineoplastics	78.5% (51 subjects)	78.2% (43 subjects)	77.1% (64 subjects)	83.7% (41 subjects)
Paclitaxel	9.2% (6 subjects)	12.7% (7 subjects)	18.1% (15 subjects)	8.2% (4 subjects)
Carboplatin	18.5% (12 subjects)	23.6% (13 subjects)	16.9% (14 subjects)	0% (0 subjects)
Bevacizumab (genetical recombination)	21.5% (14 subjects)	18.2% (10 subjects)	14.5% (12 subjects)	30.6% (15 subjects)
Pemetrexed	21.5% (14 subjects)	23.6% (13 subjects)	13.3% (11 subjects)	0% (0 subjects)
Erlotinib	15.4% (10 subjects)	14.5% (8 subjects)	13.3% (11 subjects)	0% (0 subjects)
Docetaxel	12.3% (8 subjects)	12.7% (7 subjects)	10.8% (9 subjects)	0% (0 subjects)
Tegafur/gimeracil/oteracil potassium	15.4% (10 subjects)	9.1% (5 subjects)	10.8% (9 subjects)	14.3% (7 subjects)
Gefitinib	4.6% (3 subjects)	10.9% (6 subjects)	7.2% (6 subjects)	0% (0 subjects)
Afatinib	0% (0 subjects)	0% (0 subjects)	7.2% (6 subjects)	0% (0 subjects)
Gemcitabine	10.8% (7 subjects)	5.5% (3 subjects)	4.8% (4 subjects)	6.1% (3 subjects)
Cisplatin	1.5% (1 subject)	0% (0 subjects)	4.8% (4 subjects)	2.0% (1 subject)
Vinorelbine	12.3% (8 subjects)	9.1% (5 subjects)	2.4% (2 subjects)	0% (0 subjects)
Irinotecan	1.5% (1 subject)	0% (0 subjects)	2.4% (2 subjects)	38.8% (19 subjects)
Amrubicin[a)]	1.5% (1 subject)	3.6% (2 subjects)	1.2% (1 subject)	0% (0 subjects)
Lentinan	0% (0 subjects)	0% (0 subjects)	1.2% (1 subject)	0% (0 subjects)
Fluorouracil	0% (0 subjects)	0% (0 subjects)	0% (0 subjects)	34.7% (17 subjects)
Levofolinate	0% (0 subjects)	0% (0 subjects)	0% (0 subjects)	34.7% (17 subjects)
Ramucirumab (genetical recombination)	0% (0 subjects)	0% (0 subjects)	0% (0 subjects)	18.4% (9 subjects)
Oxaliplatin	0% (0 subjects)	0% (0 subjects)	0% (0 subjects)	12.2% (6 subjects)
Trifluridine/tipiracil	0% (0 subjects)	0% (0 subjects)	0% (0 subjects)	12.2% (6 subjects)
Capecitabine	0% (0 subjects)	0% (0 subjects)	0% (0 subjects)	8.2% (4 subjects)
Cetuximab (genetical recombination)	0% (0 subjects)	0% (0 subjects)	0% (0 subjects)	6.1% (3 subjects)
Panitumumab (genetical recombination)	0% (0 subjects)	0% (0 subjects)	0% (0 subjects)	4.1% (2 subjects)
Regorafenib	0% (0 subjects)	0% (0 subjects)	0% (0 subjects)	4.1% (2 subjects)
Aflibercept	0% (0 subjects)	0% (0 subjects)	0% (0 subjects)	2.0% (1 subject)
Trastuzumab (genetical recombination)	0% (0 subjects)	0% (0 subjects)	0% (0 subjects)	2.0% (1 subject)

a) Three subjects in Study ONO-7643-03 received the drug after the completion of the treatment with anamorelin. A subject in Study 04 received the drug in combination with anamorelin at the direction of the physician, and anamorelin was discontinued on the following day.

As for cardiotoxic antineoplastics that were concomitantly used with anamorelin in these Japanese clinical studies,[4)] the incidence of adverse events and adverse drug reactions were compared between subjects with the concomitant use of these antineoplastics (247 subjects: 85 subjects in the placebo group; 41 subjects in the anamorelin 50 mg group; and 121 subjects in the anamorelin 100 mg group) and subjects without the concomitant use (553 subjects: 211 subjects in the placebo group; 89 subjects in the anamorelin 50 mg group; and 253 subjects in the anamorelin 100 mg group).

[4)] With reference to precautionary statements in the package inserts of anti-neoplastic drugs, the applicant selected the following drugs in addition to anthracycline anti-neoplastic drugs: irinotecan, fluorouracil, levofolinate, ramucirumab (genetical recombination), oxaliplatin, capecitabine, cetuximab (genetical recombination), aflibercept (genetical recombination), carboplatin, bevacizumab (genetical recombination), docetaxel, paclitaxel, tegafur/gimeracil/oteracil potassium, vinorelbine, gemcitabine, cisplatin, tegafur/uracil, afatinib, regorafenib, and trastuzumab (genetical recombination).

The adverse event that corresponds to cardiac failure (SMQ narrow search) was cardiac failure congestive in 1 patient in the anamorelin 100 mg group (without concomitant use of cardiotoxic antineoplastics) but its causal relationship to anamorelin was denied. There was no adverse events that correspond to cardiac failure (SMQ narrow search) reported in subjects with concomitant use of cardiotoxic antineoplastics. The incidence of adverse events and adverse drug reactions corresponding to inhibition of the conduction system is shown in Table 3.

Table 3. Averse events and adverse drug reactions corresponding to inhibition of the conduction system in association with anamorelin with and without cardiotoxic antineoplastics (Studies ONO-7643-03, 04, and 05)

	Placebo group		Anamorelin 50 mg group		Anamorelin 100 mg group	
	With concomitant use (n = 85)	Without concomitant use (n = 211)	With concomitant use (n = 41)	Without concomitant use (n = 89)	With concomitant use (n = 121)	Without concomitant use (n = 253)
Adverse events	**8.2 (7 subjects)**	**10.0 (21 subjects)**	**19.5 (8 subjects)**	**11.2 (10 subjects)**	**14.9 (18 subjects)**	**19.8 (50 subjects)**
Adverse drug reactions	**2.4 (2 subjects)**	**1.9 (4 subjects)**	**9.8 (4 subjects)**	**4.5 (4 subjects)**	**9.1 (11 subjects)**	**11.5 (29 subjects)**

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As shown above, no clinically relevant differences were observed for adverse events and adverse drug reactions corresponding to cardiac failure (SMQ narrow search) or inhibition of the conduction system between subjects with or without concomitant use of cardiotoxic antineoplastics.

Although no clinically relevant effects on the safety of anamorelin were observed between subjects with or without concomitant use of cardiotoxic antineoplastics in the Japanese clinical studies, PMDA considers that cardiotoxic antineoplastics should be listed in the Precautions Concerning Concomitant Use because concomitant use of anamorelin and cardiotoxic antineoplastics may increase the adverse effects on cardiac function.

Regardless of the concomitant use of antineoplastics, the possibility of increased risk in inhibition of the conduction system cannot be ruled out when anamorelin is administered to patients with electrolyte abnormality. Therefore, PMDA considers appropriate that patients with electrolyte abnormality such as hypomagnesaemia should be newly added in the Careful Administration section of the package insert and that precautions should be additionally included in the Important Precautions section stating that electrolyte examinations should be performed on a regular basis before and during treatment with anamorelin. Furthermore, PMDA considers that information on the treatment of cancer (e.g., pharmacotherapy [drug names, dosage, and dosing regimens] and radiotherapy) and the safety should be collected in the post-marketing setting.

No adverse events related to electrolyte abnormalities or inhibition of the conduction system occurred in 5 subjects receiving anamorelin in combination with cetuximab (genetical recombination) or panitumumab (genetical recombination). Nevertheless, information should be collected on the occurrence of the inhibition of the conduction system in patients receiving anamorelin in combination with antineoplastics that are known to cause electrolyte abnormalities in the post-marketing setting. In addition, only limited types of antineoplastics were concomitantly used with anamorelin in the clinical studies, and anamorelin may be used in combination with other types of antineoplastics in the post-marketing setting. Therefore, PMDA considers that information

on antineoplastics used concomitantly with anamorelin in its clinical studies should be provided in materials for healthcare professionals. PMDA considers it appropriate to thoroughly inform that patients should be monitored more closely during treatment with anamorelin until a certain level of experience and safety information becomes available in the postmarketing setting when anamorelin is used in combination with antineoplastics that have not or have rarely used in the clinical studies.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion. The following comments were raised from the expert advisors:

- Anthracycline antineoplastic agents are known to cause cardiac failure due to myocardial disorders, in addition to arrhythmia and QT prolongation due to conduction disorders, and cumulative toxicity is concerned in many cases. Therefore, Careful Administration section of the package insert should also include precaution on patients with prior treatment with anthracycline antineoplastics.

In view of the comments from the Expert Discussion, PMDA has concluded that patients with prior treatment with anthracycline antineoplastics should be included in the Careful Administration section of the package insert. PMDA instructed the applicant to do so. The applicant responded appropriately, and PMDA accepted it.

1.2 Efficacy and clinical significance of anamorelin

PMDA has drawn the following conclusions on the efficacy and clinical significance of anamorelin (See Section 7.R.1 of the Review Report).

PMDA considers that anamorelin has a certain clinical significance for patients with cancer cachexia because it has demonstrated to increase LBM and to improve appetite-related QOL in patients with cancer cachexia in Studies 04 and 05.

The PMDA's discussions based on the comments raised by the First Committee on New Drugs on the efficacy and clinical significance of anamorelin are described below.

(1) Appropriateness of efficacy indicators

Cancer cachexia is a condition with various symptoms and is defined as "a complex metabolic abnormality characterized by persistent body weight loss (particularly muscle mass) that cannot be fully recovered by conventional nutritional support in patients with cancer and may decrease the tolerance to cancer chemotherapies and the quality of life (QOL) significantly, affecting the prognosis of the patients" (*Support Care Cancer.* 2016;24:3473-80, *BMC Cancer*. 2009;9:255, etc.). In the clinical practice guidelines for cancer cachexia in and outside Japan, cancer cachexia is characterized by decreased muscle tissues, and medications for the treatment of cancer cachexia are expected to relieve anorexia and to maintain/improve body weight, especially LBM which consists of skeletal muscles and organ tissues, through anti-inflammatory activity and promotion of protein synthesis or inhibition of protein catabolism (EPCRC. Clinical practice guidelines on cancer cachexia in advanced cancer patients with a focus on refractory cachexia: European Clinical Guidelines

2011; Clinical Guidelines for Infusion Therapy in Advanced Cancer Patients, 2013 [in Japanese]. Guidelines Committee of the Japanese Society for Palliative Medicine[5)]).

In Studies 04 and 05, "lean body mass" determined by dual energy X-ray absorptiometry (DEXA) was specified as the primary endpoint according to the clinical practice guidelines. Various symptoms associated with cancer cachexia affect QOL of patients, and especially, body weight loss and anorexia are regarded as important factors (*J Cachexia Sarcopenia Muscle*. 2013:4:95-109). Therefore, an endpoint related to "appetite" was included in the secondary endpoints.

PMDA considered it acceptable that "LBM" and an endpoint related to "appetite" were specified as the primary endpoint and a co-secondary endpoint, respectively, in Studies 04 and 05 to comprehensively evaluate the efficacy of anamorelin based on these results, in light of the definition of cancer cachexia in the clinical practice guidelines in and outside Japan and the expected effects of treatment medications, as well as the following facts; that anamorelin has a ghrelin-like effect; that ghrelin has been reported to regulate the biological energy metabolism including increased appetite and promotion of fat producing; and that at the time of planning Studies 04 and 05, no well-validated methods had been established for the investigation of anorexia in patients with cancer cachexia.

As for the appropriateness of the efficacy indicators, the efficacy indicators used in clinical studies of anorexia (increases in LBM and improvement in appetite-related QOL) have been used in relatively many clinical studies among clinical evaluation indicators in various clinical studies shown in recent review reports. In addition, though not for all of the improvement in the status of cancer cachexia, these indicators are considered to allow a certain level of evaluation.

- Pharmacological management of cachexia in adult cancer patients: a systematic review of clinical trials. (*BMC Cancer.* 2018;18:1174-98)

  A literature review between 2004 and 2018 identified 19 literature reports (a total of 20 randomized controlled clinical trials). The following efficacy indicators are described in these literature reports.
  - QOL (clearly specified as 'QOL,' regardless of score types): 12 studies
  - LBM: 8 studies
  - Body weight: 7 studies
  - Handgrip strength: 8 studies
  - Appetite: 6 studies
  - Physical activity: 3 studies
  - 10% nonfluid weight gain from baseline: 2 studies
  - Others (Anorexia [FAACT], Anorexia cachexia Score, BMI, Body composition, FACIT-F, Fatigue, Functional assessment, Muscle mass, Survival, Symptom assessment, and ASAS score): 1 study for each.

[5)] Conflicts of interest by all committee members involved in the preparation of the guidelines have been disclosed and approved by the Japanese Society for Palliative Medicine.

The authors point out the efficacy of anamorelin in the reports while indicating that cancer cachexia involves complex pathological conditions, the treatment evaluation is not straightforward, and body weight-related indicators have limitations.

- Evaluation of the true endpoint of clinical trials for cancer cachexia. (*Asia Pac J Oncol Nurs.* 2019;6:227-33)

  A literature review between 2003 and 2018 identified a total of 65 randomized controlled clinical trials. The following efficacy indicators are described in these literature reports (for indicators with frequency of 20%, in no particular order).

  - Body weight/BMI: 75%
  - LBM: 48%
  - Food intake: 35%
  - Performance status: 29%
  - Hand-grip strength: 23%
  - Symptom-Anorexia: 37%
  - Symptom-Fatigue: 26%
  - QOL-Global: 66%
  - Overall survival: 32%
  - Biomarker-Inflammatory: 38%
  - Biomarker-Nutritional: 38%
  - Biomarker-Metabolic: 20%

  The authors point out that the ultimate goal of cancer cachexia treatment is not clearly established and that although comprehensive improvement in skeletal muscle mass, physical function, QOL, and overall survival is the ideal goal, these indices do not always correlate with each other. In addition, data have shown that body weight loss occurs in the early course of cancer cachexia followed by muscular weakness and decline in walking ability, leading to multiple disabilities in daily living.

(2) Clinical significance of the efficacy of anamorelin demonstrated in studies

In Study 04 conducted in patients with non-small cell lung cancer and cachexia, the "mean change from baseline in LBM to Week 12" (mean ± SD), the primary endpoint of the study, was 1.38 ± 0.18 kg in the anamorelin 100 mg group and −0.17 ± 0.17 kg in the placebo group, and the least-squares mean [95% CI] of the difference between the groups (the anamorelin 100 mg group − the placebo group) was 1.56 [1.11, 2.00] kg, showing a statistically significant difference between anamorelin 100 mg and placebo. The mean change from baseline in body weight to Week 12 (mean ± SD) was 1.06 ± 0.20 kg in the anamorelin 100 mg group and −0.50 ± 0.19 kg in the placebo group, and the least-squares mean [95% CI] of the difference between the groups (the anamorelin 100 mg group − the placebo group) was 1.56 [1.13, 1.99] kg. The mean change from baseline in scores of the appetite-related QOL-ACD questionnaire to Week 12 showed a tendency toward improvement in appetite in the anamorelin 100 mg group as compared with the placebo group.

In Study 05 conducted in cachexic patients with gastric cancer, pancreatic cancer, or colorectal cancer, the

percentage of "subjects who maintained or gained LBM" of the primary endpoint was 63.3% [48.3%, 76.6%], and the lower limit of 95% confidence interval exceeded the prespecified threshold for efficacy (30.7%). The mean change from baseline in LBM to Week 12 was 1.89 ± 0.36 kg, showing a tendency toward improvement, and the mean change from baseline in body weight to Week 12 (1.36 ± 0.41 kg [mean ± SD]) and the scores of the appetite-related QOL-ACD also showed a tendency toward improvement.

In Studies 04 and 05, the baseline LBM in the anamorelin group was 38.9 kg and 37.1 kg, respectively, and the baseline body weight was 52.2 kg and 50.7 kg, respectively. The mean change from baseline in LBM and body weight to Week 12 was equivalent to 3.6% and 2.0% at baseline in Study 04 and 5.1% and 2.7% in Study 05, respectively. In the foreign phase III studies (HT-ANAM-301 and HT-ANAM-302), the baseline LBM in the anamorelin group was 45.9 kg and 43.9 kg, respectively, and the baseline body weight was 67.6 kg and 63.9 kg, respectively. The mean changes from baseline in LBM to Week 12 (0.99 kg and 2.20 kg in Studies HT-ANAM-301 and HT-ANAM-302, respectively) and those in body weight (0.65 kg, and 0.95 kg in Studies HT-ANAM-301 and HT-ANAM-302, respectively) was equivalent to 2.2% and 3.2% at baseline in Study HT-ANAM-301 and 1.5%, and 1.5% in Study HT-ANAM-302, respectively.

In Studies 04 and 05, QOL was evaluated as a secondary endpoint with the use of the QOL Questionnaire for Cancer Patients Treated with Anticancer Drugs (QOL-ACD)[6)] for cancer pharmacotherapy, and no changes from baseline in total scores were identified with treatment with anamorelin in either study. Since the total QOL-ACD scores are affected by various factors, improvement in the total QOL-ACD scores could not be detected only with treatment with anamorelin, primarily involving ghrelin-like effects. Meanwhile, the mean change from baseline in the score for the appetite-related QOL-ACD questionnaire[7)] to Week 12 showed a tendency toward improvement in the anamorelin 100 mg group as compared with the placebo group in Studies 04 and 05, although caution is needed because the assessment has not been fully validated.

In the EU, the EMA issued negative opinion for anamorelin based on the benefit-risk balance from the results of the foreign phase III studies, and anamorelin has not been approved [see Section 7.R.1 of the Review Report]. However, cancer cachexia is a complex disease with abnormal metabolism characterized by persistent body weight loss that is not completely reversed with conventional nutritional support. In addition, the LBM at Week 12 decreased from baseline in the placebo group in Study 04. In Japan, since no drug is available for the indication of cancer cachexia, new therapies are strongly needed. Furthermore, although the increase in LBM following the administration of anamorelin did not show significant improvement in the Japanese clinical studies, anamorelin tended to inhibit the progression of decreased LBM in patients with cancer cachexia with the tendency toward improvement in appetite. In light of the above, clinically meaningful results have been obtained in the current therapeutic environment in Japan, assuming that appropriate safety measures are taken.

At the Expert Discussion, all expert advisors supported the PMDA's conclusion drawn on the basis of the status

[6)] A self-evaluation questionnaire with a total of 22 questions on 4 main domains (functional, physical, mental, and psychosocial) on a scale of 1 to 5 to access patients' status over the past several days

[7)] Question 8 "Did you have an appetite?" was regarded as a question related to appetite.

of development outside Japan. The following comments were raised from the expert advisors:

- The efficacy indicators (LBM and appetite-related QOL) used in the clinical studies of anamorelin are considered to be appropriate as they suggest improvement in the pathological conditions of cancer cachexia. Patients with cancer cachexia present with persistent body weight loss and cannot fully recover with conventional nutritional support. Since body weight loss is associated with a significant decline in QOL and affects their prognoses, maintaining body weight alone is meaningful. In Japanese clinical studies, administration of anamorelin 100 mg increased LBM (1.38 kg, with a difference of 1.58 kg in comparison with the placebo group), and as a consequence, the patients' appetite improved. Therefore, the changes in LBM observed in the clinical studies of anamorelin are considered to be clinically meaningful in Japanese patients with cancer cachexia.
- Considering that anamorelin has been demonstrated to increase LBM and to improve appetite-related QOL in patients with cancer cachexia, anamorelin is considered to have a certain clinical significance in patients with cancer cachexia.

1.3 Proper use of anamorelin

At the First Committee on New Drugs, the following comments were raised for the proper use of anamorelin:

- When anamorelin is used, sufficient precautions and information on the efficacy and safety demonstrated in the clinical studies should be provided to ensure the proper use of anamorelin.
- When physicians decide whether treatment with anamorelin is continued, physicians need to confirm the QOL status of individual patients with cancer cachexia through careful questioning. Patients should be duly notified and instructed that they should fully understand the clinical effects of anamorelin and they should provide information relevant to response assessment of anamorelin to their physicians.

PMDA asked the applicant to investigate measures to promote the proper use of anamorelin in the post-marketing setting in collaboration with relevant academic societies.

The applicant's response:

The Committee for the Proper Use of Anamorelin in cooperation with external medical experts was established within the company to provide information on the proper use of anamorelin to physicians and healthcare professionals involved in the treatment and palliative care of patients with cancer. Taking account of comments raised by the external medical experts, the diagnosis of cancer cachexia, clinical positioning of anamorelin, patients intended for treatment with anamorelin, and precautions concerning use would be compiled into a document as "For Proper Use of Adlumiz Tablets 50 mg" which would be issued after the approval of anamorelin. In addition, a checklist will be developed for selecting patients for anamorelin treatment and evaluating efficacy and safety in patients receiving anamorelin. The checklist will be used in the post-marketing surveillance in all patients treated with anamorelin to promote the proper use of anamorelin.

Furthermore, data on the efficacy of anamorelin and missing information will be included in a patient information leaflet. The patient information leaflet will also include information to advise that anamorelin should be started after patients and their families fully understand its efficacy, and patients should provide

information relevant to response assessment (e.g., appetite) to their treating physicians during the treatment of anamorelin.

PMDA's view:

For treatment with anamorelin, physicians with adequate knowledge and experience in the diagnosis and treatment of cancer cachexia should carefully determine the appropriateness of anamorelin by taking into consideration of expected benefits and potential risks in individual patients after fully understanding the clinical study data including the characteristics of patients enrolled in the clinical studies of anamorelin. The physicians should provide sufficient explanation about the benefits and risks with anamorelin to patients and their families and should confirm their understanding before deciding to start and continue the treatment. To ensure these, precautions should be newly included in the Warning section of the package insert. As mentioned in the Precautions Concerning Indications and Precautions Concerning Dosage and Administration sections of the package insert, if patients become unable to tolerate oral intake of food or have difficulty digesting and absorbing food due to disease progression, anamorelin should be discontinued. Also, physicians should check body weights and appetite by interviewing patients. When anamorelin becomes ineffective, anamorelin should be discontinued after 3 weeks of treatment, in principle, and physicians should carefully determine, on a regular basis, the need to continue treatment.

Additionally, it is considered appropriate to provide information on the proper use of anamorelin through documents such as the "For Proper Use of Adlumiz Tablets 50 mg" and to explain the importance of periodical communication of the efficacy of anamorelin and appetite to physicians in the patient information leaflet. It is also considered appropriate that the status of use (patient background), the safety, and the efficacy of anamorelin are obtained early in the activities including the post-marketing surveillance in all patients treated with anamorelin so that a system can be established where appropriate measures can be taken promptly.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion. The following comments were raised from the expert advisors:

- The applicant should promote the thorough understanding and awareness of the proper use of anamorelin through collaboration with the relevant academic societies, the use of checklist, and the use of e-learning.

Given the discussion at the Expert Discussion and in light of patients enrolled in the clinical studies, PMDA asked the applicant to address the promotion of the thorough understanding and awareness of the proper use of anamorelin through collaboration with the relevant academic societies. The applicant responded as follows, and PMDA accepted the applicant's response.

- The applicant planned to ask the relevant academic societies[8)] to cooperate in the promotion of the proper use of anamorelin and to post the "For Proper Use of Adlumiz Tablets 50 mg" on their Web sites. In addition, the applicant would continuously and routinely make efforts to promote the thorough

[8)] The Japanese Society of Medical Oncology, the Japan Society of Clinical Oncology, the Japanese Association of Supportive Care in Cancer, Japanese Society for Palliative Medicine, Japanese Society for Clinical Nutrition and Metabolism, Japanese Society for Surgical Metabolism and Nutrition, Japan Lung Cancer Society, the Japanese Respiratory Society, Japanese Society of Gastroenterology, and Japanese Society of Gastroenterological Surgery.

understanding and awareness of the proper use of anamorelin via activities at their annual meetings. The applicant planned to educate physicians and healthcare professionals on the proper use of anamorelin. Furthermore, the applicant would make efforts to provide information by making materials prepared by the relevant academic societies available and accessible by using e-learning.

1.4 Patients eligible for treatment with anamorelin

In addition to the discussions described in the above sections 1.1 to 1.3, the use of anamorelin in patients with cancer types or stages of cancer cachexia which had not been evaluated in the clinical studies was discussed at the First Committee on New Drugs. Taking into account of these discussions, PMDA has concluded that the indications should be determined in accordance with the Japanese clinical studies (Studies 04 and 05) and that the contents of the Precautions Concerning Indications section should be described more specifically.

Although patients with a performance status of ≤2 and an estimated life expectancy of ≥4 months were enrolled in the Japanese clinical studies (Studies 04 and 05) from the point of view of the drug response assessment, there were patients in whom their performance status became ≥3 during treatment with anamorelin in both studies. Therefore, PMDA considers it inappropriate that the use of anamorelin is uniformly restricted based on the performance status or life expectancy.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion.

2. Overall evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following conditions, provided that appropriate precautionary statements will be included in the package insert, that information on the proper use of the product will be provided appropriately after its market launch, and that the compliance with the proper use of the product will be ensured under the supervision of physicians with sufficient expertise and experience in the diagnosis and treatment of cancer cachexia. As the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indications

Cancer cachexia in patients with the following malignancies:
Non-small cell lung cancer, gastric cancer, pancreatic cancer, and colorectal cancer.

Dosage and administration

The usual adult dosage is 100 mg of anamorelin hydrochloride administered orally once daily in a fasted state.

Approval conditions

1. The applicant is required to develop and appropriately implement a risk management plan.

2. The applicant is also required to conduct a drug use-results survey involving all patients treated with the product until data from a certain number of patients have been accumulated in the post-marketing setting in order to collect the safety and efficacy data on the product without delay and to take necessary measures to facilitate the proper use of the product.

Warning

Anamorelin should be used only for patients who are considered appropriate for treatment with anamorelin by physicians with adequate knowledge and experience in the diagnosis and treatment of cancer cachexia. Before starting the treatment with anamorelin, physicians should provide sufficient explanation about the benefits and risks of anamorelin to patients and their families and should confirm their understanding before starting the treatment.

Contraindications

3. Patients with a history of hypersensitivity to anamorelin or any of the excipients
4. Patients with congestive cardiac failure [Anamorelin suppresses the cardiac functions and may worsen the symptoms.]
5. Patients with myocardial infarction or angina pectoris [Anamorelin suppresses the cardiac functions and may worsen the symptoms.]
6. Patients with advanced conduction system disorders (e.g., complete atrioventricular block) [Anamorelin with sodium channel inhibition may have inhibitory effects on the conduction system and may worsen the condition.)
7. Patients being treated with the following drugs: clarithromycin, indinavir, itraconazole, nelfinavir, saquinavir, telaprevir, voriconazole, ritonavir-containing product, and cobicistat-containing product
8. Patients with moderate or severe hepatic impairment (Child-Pugh class B or C) [The liver is a major contributor to the elimination of anamorelin from the body. Therefore, when anamorelin is used in such a patient, the blood anamorelin concentration may increase, which may result in the inhibition of the conduction system.]
9. Patients who have difficulty with oral intake of food due to organic gastrointestinal abnormalities, such as gastrointestinal obstruction.

Precautions Concerning Indications

1. Anamorelin should be used in cachexic patients with unresectable, advanced/relapsed non-small cell lung cancer, gastric cancer, pancreatic cancer, or colorectal cancer.
2. Anamorelin should be used in patients with cancer cachexia with inadequate response to therapies such as nutrition.
3. Anamorelin should be used in patients with a loss of ≥5% of body weight over the preceding 6 months and anorexia, and at least 2 of the following 3 conditions (a) to (c):
   a) Fatigue or malaise
   b) Generalized muscle weakness

c) At least 1 of the following laboratory values: CRP >0.5 mg/dL, hemoglobin <12 g/dL, or albumin <3.2 g/dL.

4. Anamorelin should not be used in patients who have difficulty with oral intake of food or poor digestion and absorption of food.
5. Before selecting patients to be treated with anamorelin, physicians should read carefully and understand thoroughly the content described in the Clinical Studies section and fully understand the characteristics of patients enrolled in the clinical studies, and the efficacy and safety of anamorelin.

Reference: (a) Fatigue or malaise and (b) generalized muscle weakness should be evaluated with a reference to the Japanese version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) translated by the Japan Clinical Oncology Group (JOCG), and the severity of Grade ≥1 should be used as the guideline for symptoms. Muscular weakness should be evaluated with a reference to indicators such as handgrip strength, walking speed, and standing up from a chair.

Precautions Concerning Dosage and Administration

1. Patients should be instructed to take anamorelin in a fasted state and not to eat for at least 1 hour after taking anamorelin to avoid the food effect.
2. If no increase in body weight or improvement in appetite is observed at around Week 3 of the treatment with anamorelin, anamorelin should be discontinued.
3. Because anamorelin has not been used for >12 weeks, physicians should periodically review the need to continue the treatment by checking patient body weight and confirming appetite through interviews, etc.

Appendix

List of abbreviations

ADR	Adverse drug reaction (an adverse event for which a causal relationship with the study drug cannot be ruled out)
AGP	α1-acid glycoprotein
Anamorelin	Anamorelin hydrochloride
ASAS	Anderson Symptom Assessment Scale
AUC	Area under concentration-time curve
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum concentration
CYP	Cytochrome P450
DEXA	Dual energy X-ray absorptiometry
EMA	European Medicines Agency
EPCRC	European palliative care research collaborative
FAACT	Functional Assessment of Anorexia/Cachexia Treatment
FACIT-F	Functional Assessment of Chronic Illness Therapy Fatigue
First Committee on New Drugs	First Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council
GCP	Good clinical practice
LBM	Lean body mass
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
PBPK	physiologically based pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
the product	Adlumiz Tablets 50 mg
PT	Preferred Term
QOL	Quality of life
QOL-ACD	The QOL questionnaire for cancer patients treated with anticancer drugs
QTc	Corrected QT interval
Review Report	Review Report for Adlumiz Tablets 50 mg (August 20, 2019)
SMQ	Standard MedDRA Queries
Study 04	A clinical study for cancer cachexia in patients with non-small cell lung cancer (Study ONO-7643-04)
Study 05	A clinical study for cancer cachexia in patients with gastric cancer, pancreatic cancer, or colorectal cancer (Study ONO-7643-05)