Report on the Deliberation Results

March 2, 2022
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Samtasu for I.V. Infusion 8 mg
	Samtasu for I.V. Infusion 16 mg
Non-proprietary Name	Tolvaptan Sodium Phosphate (JAN*)
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	March 22, 2021

Results of Deliberation

In its meeting held on February 25, 2022, 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 Condition

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

**Japanese Accepted Name (modified INN)*

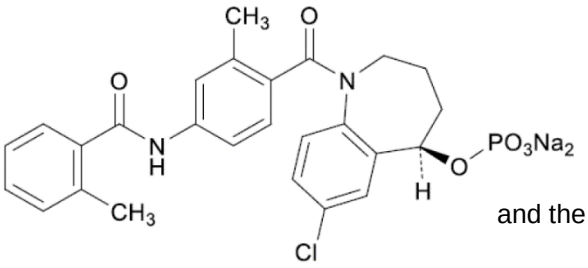
Review Report

February 3, 2022
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	Samtasu for I.V. Infusion 8 mg Samtasu for I.V. Infusion 16 mg
Non-proprietary Name	Tolvaptan Sodium Phosphate
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	March 22, 2021
Dosage Form/Strength	Lyophilized powder for injection: Each vial contains 8.56 or 17.12 mg of tolvaptan sodium phosphate
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



and the enantiomer

Molecular formula: $C_{26}H_{24}ClN_2Na_2O_6P$
Molecular weight: 572.88
Chemical name: Disodium (5*RS*)-7-chloro-1-[2-methyl-4-(2-methylbenzamido)benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepin-5-yl phosphate

Items Warranting Special Mention	None
Reviewing Office	Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of fluid retention in heart failure when treatment with other diuretics including loop diuretics is not sufficiently effective, 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 approval condition. Risks for events including the following require further investigation: hypernatraemia, rapid increase in serum sodium concentration/osmotic demyelination syndrome, dehydration, hyperkalaemia, thirst, thrombosis/thromboembolism, dizziness, syncope/loss of consciousness, excessive blood pressure decreased/ventricular fibrillation/ventricular tachycardia, renal failure/renal impairment.

Indication

Treatment of fluid retention in heart failure when treatment with other diuretics including loop diuretics is not sufficiently effective

Dosage and Administration

The usual adult dosage is 16 mg of tolvaptan sodium phosphate once daily administered as an intravenous infusion over 1 hour.

Approval Condition

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

Attachment

Review Report (1)

December 15, 2021

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	Samtasu for I.V. Infusion 8 mg Samtasu for I.V. Infusion 16 mg
Non-proprietary Name	Tolvaptan Sodium Phosphate
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	March 22, 2021
Dosage Form/Strength	Lyophilized powder for injection: Each vial contains 8.56 or 17.12 mg of tolvaptan sodium phosphate

Proposed Indication

Treatment of fluid retention in heart failure when treatment with other diuretics including loop diuretics is not sufficiently effective

Proposed Dosage and Administration

The usual adult dosage is 16 mg of tolvaptan sodium phosphate once daily administered as an intravenous infusion over 1 hour.

Table of Contents

List of Abbreviations

See Appendix.

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

Samtasu for intravenous (I.V.) infusion (hereinafter referred to as Samtasu) is a lyophilized powder for injection containing the active ingredient of tolvaptan sodium phosphate (hereinafter referred to as OPC-61815), a prodrug of tolvaptan, an approved vasopressin V_2-receptor antagonist, developed by Otsuka Pharmaceutical Co., Ltd. Samtasu selectively and competitively inhibits binding of vasopressin to the V_2-receptor, inhibiting reabsorption of water in the renal collecting duct, thereby exerting an aquaretic effect.

In Japan, Samsca Tablets, an oral drug with the active ingredient tolvaptan, was approved for the "treatment of fluid retention in heart failure when treatment with other diuretics including loop diuretics is not sufficiently effective" in October 2010. Additionally, Samsca Tablets have been approved for the "treatment of fluid retention in hepatic cirrhosis when treatment with other diuretics including loop diuretics is not sufficiently effective" in September 2013, "slowing of the progression of autosomal dominant polycystic kidney disease in patients with an increased kidney volume and a rapid rate of kidney volume increase" in March 2014, and "improvement of hyponatraemia in patients with syndrome of inappropriate secretion of antidiuretic hormone (SIADH)" in June 2020. As of October 2021, oral tolvaptan has been approved in 47 countries and regions including European countries and the US.

Samtasu has been developed as a V_2-receptor antagonist that can be administered intravenously. Recently, the applicant filed an application for marketing approval based on Japanese clinical study results and other data. As of October 2021, Samtasu has not been filed for approval nor has any application been approved in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white crystalline powder or granule. Its appearance, solubility, hygroscopicity, dissociation constant, partition coefficient, optical rotation, thermal analysis, and crystallinity have been determined.

The chemical structure of the drug substance has been elucidated by elemental analysis, ultraviolet-visible spectroscopy (UV-VIS), infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) (proton-NMR and ^{13}C-NMR), mass spectrometry (MS), and [redacted]. The drug substance is a racemate having an asymmetric carbon.

2.1.2 Manufacturing process

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

[redacted], [redacted], and [redacted] steps have been defined as critical steps. [redacted] and crude tolvaptan sodium phosphate are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (sodium salts and phosphate salts [qualitative test], tolvaptan sodium phosphate [UV-VIS, IR]), purity (appearance of solution, related substances [high performance liquid chromatography (HPLC)]), bacterial endotoxins, microbial limits, and assays (HPLC). In addition, water content and purity (Impurity A [UV-visible spectrophotometry]) were specified during the review process.

2.1.4 Stability of drug substance

Table 1 summarizes the main stability studies for the drug substance. The long-term and accelerated testing results for the primary batches showed that the drug substance is stable. However, in the long-term and accelerated testing for the process validation (PV) batches, an out of trend (OOT) result, which is an increase in the content of Impurity B over time, was identified. The photostability testing showed that the drug substance is photostable.

Table 1. Main stability studies for drug substance

Study type	Number of batches	Temperature	Humidity	Storage package	Storage period
Long-term	Pilot-scale 3 primary batches[a] 3 PV batches[b]	30°C	65% RH	Low-density polyethylene bag + aluminum bag + fiber drum	24[a] or 6[b] months
Accelerated		40°C	75% RH		6 months

a, batches used in the stability studies for the application for marketing approval; b, batches manufactured for PV

On the basis of the above, a retest period of [redacted] months was proposed for the drug substance when packed in a low-density polyethylene bag, placed in an aluminum bag, further placed in a fiber drum, and stored at room temperature.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized powder for injection supplied in a vial containing 8.56 or 17.12 mg of the drug substance. Excipients contained in the drug product are sucrose, dibasic sodium phosphate hydrate, sodium dihydrogen phosphate dihydrate, sodium hydroxide, and phosphoric acid. To ensure that the labeled amount (8 or 16 mg) of the drug substance can be administered as an intravenous infusion, each vial contains an overfill to compensate for the loss during preparation and injection.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of [redacted], [redacted], [redacted], [redacted], [redacted], and packaging/labeling. [redacted], [redacted], and [redacted] steps have been defined as critical steps, and process control items and values have been specified for these steps.

2.2.3 Control of drug product

The proposed specification for the drug product consists of strength, description, identification (HPLC-ultraviolet spectroscopy [HPLC-UV]), pH, related substances (HPLC), water content, bacterial endotoxins, uniformity of dosage units (mass variation test), foreign insoluble matter, insoluble particulate matter, sterility, and assay (HPLC).

2.2.4 Stability of drug product

Table 2 summarizes the main stability studies for the drug product. The results indicate that the drug product is stable. Photostability testing demonstrated that the drug product is photostable.

Table 2. Main stability studies for drug product

Study type	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25°C	60% RH	Glass vial + chlorinated butyl rubber stopper + aluminum cap	18 months
Accelerated		40°C	75% RH		6 months

On the basis of the above, a shelf life of 30 months was proposed for the drug product when loaded into a glass vial with a chlorinated butyl rubber stopper and an aluminum cap and stored at room temperature according to the ICH Q1E Guidelines. The long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

PMDA concluded that the quality of the drug substances and the drug product is adequately controlled based on the submitted data and discussions in the following section.

2.R.1 The OOT observed in PV batches of the drug substance in the stability study

The applicant's explanation:

After the application was filed, an increase in Impurity B over time was reported as an OOT result in the stability study for the drug substance batches manufactured for PV (the long-term study for 6 months, accelerated study for 6 months). It was also shown that formation of Impurity B can be suppressed by controlling [redacted] in the drug substance. Therefore, the applicant proposed defining the lower limit of [redacted], in addition to the upper limit, for the specification of the drug substance, and at the same time, selecting a retest period of [redacted] months.

PMDA concluded, based on the submitted data and other information, that a retest period of [redacted] months for the drug substance will assure the quality of the drug substance provided that the [redacted] in the drug substance is controlled within the range proposed by the applicant.

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

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity for vasopressin receptors (CTD 4.2.1.1-01, 4.2.1.1-02, 4.2.1.1-03, 4.2.1.1-04)

The inhibitory effect of OPC-61815[1)] on binding of ^{3}H-labeled vasopressin to human vasopressin receptors was assessed using human endocervical carcinoma cell lines (HeLa cells) stably expressing human vasopressin V_2 (V_2)-receptor, V_{1a}-receptor, and V_{1b}-receptor. The inhibition constant (K_i) values (mean ± standard error) were 6.13 ± 1.34 and 54.2 ± 16.8 nmol/L for human V_2-receptor and V_{1a}-receptor, respectively, while OPC-61815 did not inhibit V_{1b}-receptor binding by ≥50% even at 10 μmol/L.

The inhibitory effect of OPC-61815[2)] on binding of ^{3}H-labeled vasopressin to rat vasopressin receptors (V_2- and V_{1a}-receptors) was assessed using cell membrane specimens prepared from the kidney and liver of rats. The K_i values (mean ± standard error) were 5.62 ± 1.75 and 3601 ± 385 nmol/L for rat V_2-receptor and V_{1a}-receptor, respectively.

3.1.1.2 Effects of OPC-61815 on cAMP production (CTD 4.2.1.1-05)

The inhibitory effect of OPC-61815 on cyclic adenosine monophosphate (cAMP) production by vasopressin was assessed by adding OPC-61815 (1 μmol/L) to HeLa cells stably expressing human V_2-receptor in the presence of vasopressin (1 nmol/L). cAMP production was significantly lower in samples spiked with OPC-61815 than in non-spiked samples. In the absence of vasopressin, there was no effect of addition of OPC-61815 on cAMP production levels.

3.1.2 *In vivo* studies

3.1.2.1 Aquaretic effects in rats (CTD 4.2.1.1-06, 4.2.1.1-08)

A single intravenous dose of OPC-61815 (0.1275, 0.3825, 1.275, 3.825, or 12.75 mg/kg) or vehicle (0% OPC-61815 formulation[3)]) was administered to male rats (N = 8/group), and urine volume, urine osmolality, and urinary electrolyte excretion were measured every 2 hours up to 8 hours post-dose. Up to 2 hours post-dose, OPC-61815 dose-dependently increased both urine volume and urinary excretion of Na, K, and Cl, and decreased urine osmolality. For all indicators, the greatest increase or decrease was observed within 2 hours of dosing.

Repeated intravenous doses of OPC-61815 (1.275 or 12.75 mg/kg) or vehicle (0% OPC-61815 formulation[3)]) were administered to male rats (N = 8/group) once daily for 7 days, and urine volume, urine osmolality, and urinary electrolyte excretion up to 2 and 24 hours post-dose were measured on Days 1, 4, and 7. On all days, up to 2 and 24 hours post-dose, OPC-61815 dose-dependently increased urine volume, and decreased urine osmolality. On all days, OPC-61815 dose-dependently increased urinary excretion of Na, K, and Cl up to 2 hours post-dose; however, no effects were observed in the excretion up to 24 hours post-dose.

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1) V_2-receptor, 1 to 100 nmol/L; V_{1a}-receptor, 100 nmol/L to 10 μmol/L; V_{1b}-receptor, 10 μmol/L
2) V_2-receptor, 1 to 300 nmol/L; V_{1a}-receptor, 1 to 10 μmol/L
3) A pH8.5 solution containing 5.5 g/100 mL sucrose, 1.8 g/100 mL dibasic sodium phosphate hydrate, and 0.03 g/100 mL sodium dihydrogen phosphate dihydrate

3.1.2.2 Aquaretic effects in dogs (CTD 4.2.1.1-07)

A single intravenous dose of OPC-61815 (0.1275, 0.3825, 1.275, or 3.825 mg/kg), furosemide (1 mg/kg), or vehicle (0% OPC-61815 formulation[3)]) was administered to male dogs (N = 8/group). Urine volume, urine osmolality, free water clearance,[4)] and urinary electrolyte excretion up to 3 hours post-dose, as well as plasma electrolyte concentrations, plasma osmolality, and plasma hormone concentrations at 3 hours post-dose were measured. The results showed that OPC-61815 dose-dependently increased urine volume, and decreased urine osmolality. OPC-61815 dose-dependently increased free water clearance, becoming positive. In the furosemide group, urine volume increased, and urine osmolality decreased, while free water clearance remained negative. The urinary excretion of Na and Cl was significantly higher at OPC-61815 ≥0.3825 mg/kg and in the furosemide group compared with the vehicle. Urinary K excretion was significantly higher at OPC-61815 ≥0.1275 mg/kg and in the furosemide group compared with the vehicle. OPC-61815 increased plasma Na concentrations, plasma osmolality, and plasma vasopressin concentrations roughly dose-dependently, whereas no changes were noted in the furosemide group. Plasma K concentrations, which did not show changes at any dose level of OPC-61815, were significantly lower in the furosemide group compared with the vehicle. There was no change in plasma renin activity at any dose level of OPC-61815; in contrast, plasma renin activity was significantly higher in the furosemide group compared with the vehicle.

3.1.2.3 Effects on a model of increased vascular permeability induced by histamine (CTD 4.2.1.1-09)

A single intravenous dose of OPC-61815 (0.3825, 1.275, or 3.825 mg/kg), furosemide (3 mg/kg), or vehicle (0% OPC-61815 formulation[3)]) was administered to male rats (N = 8/group), which was followed by intravenous 1% Evans blue solution 0.5 mL and intradermal histamine 10 µg at 2 hours post-dose. The dye leakage area at the injection site 1 hour after administration of histamine decreased in a dose-dependent manner of OPC-61815, with the value at 1.275 mg/kg of OPC-61815 being similar to that of the furosemide group.

3.1.2.4 Effects on a carrageenan-induced paw edema model(CTD 4.2.1.1-10)

A single intravenous dose of OPC-61815 (1.275, 3.825, or 12.75 mg/kg), furosemide 10 mg/kg, or vehicle (0% OPC-61815 formulation[3)]) was administered to male rats (N = 8/group), followed by subcutaneous plantar administration of 1% carrageenan 100 µL at 1 hour post-dose. Measurement of increase in foot volume up to 5 hours after administration of carrageenan showed a dose-dependent suppression of carrageenan-induced increase in paw volume by OPC-61815, with the degree of suppression at 3.825 mg/kg of OPC-61815 being similar to that in the furosemide group.

3.1.3 Other pharmacological effects

3.1.3.1 Effects on various receptors and ion channels (CTD 4.2.1.1-12)

A radioligand binding assay was performed to investigate the inhibitory effect of OPC-61815 (10 µmol/L) on 31 types of receptors and 4 types of ion channels. OPC-61815 did not inhibit any ligand binding by ≥50%.

[4)] The free water clearance was calculated using the following equation. Free water clearance = urine volume × (pre-dosing plasma osmolality – urine osmolality) / pre-dosing plasma osmolality

3.2 Safety pharmacology

Table 3 shows the results of safety pharmacology studies.

Table 3. Summary of results of safety pharmacology studies

Organ system	Test system	Evaluation parameter/ method	Dosage regimen	Route of administration	Findings	CTD
Central nervous system	SD rats (1 male group 6 animals)	Modified Irwin test	0,[a] 12.75, 63.75, 255 mg/kg Single dose	IV	At ≥12.75 mg/kg: increased urine volume At 255 mg/kg: decreased spontaneous activity, decreased touch response, decreased body tone, decreased respiratory rate, abnormal body posture	4.2.1.3-01
Cardiovascular system/ respiratory system	CHO-K1 cells stably expressing hERG channel	hERG current	0,[b] 1, 10, 100 μmol/L	*In vitro*	No effects	4.2.1.3-03
	Beagle dogs (4 males)	Blood pressure, heart rate, electrocardiogram, respiratory rate, blood gas	0,[a] 12.75, 38.25, 127.5 mg/kg Single dose	IV	At ≥12.75 mg/kg: increased urine volume, increased plasma Na and Cl concentrations, decreased T-wave amplitude At ≥38.25 mg/kg: increased heart rate At 127.5 mg/kg: decreased mean blood pressure, shortened PR interval, vomiting, defecation, increased respiratory rate	4.2.1.3-02
	Anesthetized beagle dogs (4 males)	Blood pressure, heart rate, plasma histamine concentration	(1) 0, [a] (2) 127.5 mg/kg of OPC-61815, (3) DPH (3 mg/kg) + CM (10 mg/kg) + 127.5 mg/kg of OPC-61815		At 127.5 mg/kg: decreased mean blood pressure, increased heart rate, increased plasma histamine concentration No effects of pretreatment with DPH and CM[c]	4.2.1.3-04

a, 0% OPC-61815 formulation[3)]
b, 0.1% (v/v) dimethyl sulfoxide (DMSO)
c, Pretreatment with diphenhydramine (DPH) and cimetidine (CM) did not inhibit blood pressure decrease; therefore, the applicant considers that blood pressure decrease by OPC-61815 is unrelated to increased endogenous histamine levels.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effects of OPC-61815 on fluid retention in heart failure

The applicant's explanation about OPC-61815's effect in correcting fluid retention in heart failure:

OPC-61815, a prodrug of tolvaptan, is synthesized by phosphorylation of the hydroxyl group of tolvaptan to improve water solubility to allow intravenous administration. When administered, the phosphate ester is hydrolyzed by phosphatase and tolvaptan forms.

In vitro, OPC-61815 shows an antagonistic effect against V_2-receptor. The K_i value of OPC-61815 for human V_2-receptor is approximately 14-fold that of tolvaptan. In humans, tolvaptan forms immediately after intravenous administration of OPC-61815; therefore, primarily, tolvaptan is considered to be involved in the

antagonistic effect against V_2-receptor following administration of OPC-61815. Studies in rats and dogs also demonstrated that tolvaptan formed immediately after intravenous administration of OPC-61815 [see Section "4.1 Absorption"]. *In vivo* studies showed aquaretic effects of intravenous OPC-61815 characterized by increases in urine volume and free water clearance and a decrease in urine osmolality, similar to those of oral tolvaptan (see Review Report of Samsca Tablets 15 mg, dated July 14, 2010). The study using rat models of peripheral edema showed anti-edematous effects associated with aquaretic effect. Aquaretic effects were observed in rats and dogs at the studied dose level similar to or lower than the tolvaptan exposure[5)] (C_{max}, 282 ng/mL; $AUC_{0-\infty}$, 2830 ng·h/mL) at the clinical dose of OPC-61815 in humans. The results suggest that the efficacy of OPC-61815 in humans can be estimated based on the *in vivo* test results.

The above findings suggest that OPC-61815 can be expected to correct fluid retention in heart failure via an antagonistic effect against V_2-receptor by tolvaptan, which forms immediately after intravenous administration of OPC-61815, thereby exerting an aquaretic effect.

PMDA's view:
The *in vivo* studies in rats and dogs demonstrated the aquaretic effects of intravenous OPC-61815 and associated anti-edematous effects. Given that the phosphate ester of tolvaptan was eliminated and tolvaptan formed immediately after intravenous administration of OPC-61815 in rats and dogs [see Section "4.1 Absorption"], if similar pharmacokinetics (PK) is observed in humans, intravenous OPC-61815 can be expected to correct fluid retention in heart failure to a similar degree as oral tolvaptan. Although its K_i values are higher than those of tolvaptan, the phosphate ester of tolvaptan also has an antagonistic effect against V_2-receptor. In addition, given the changes in the blood concentrations of the phosphate ester of tolvaptan and tolvaptan over time after intravenous administration of OPC-61815 to humans, safety issues associated with the aquaretic effect in the early phase following administration of OPC-61815 should be discussed further, together with whether a cautionary statement should be provided, in Section "7.R.3 Safety."

3.R.2 Safety pharmacology

The applicant's explanation about the findings reported in the safety pharmacology studies of OPC-61815:
The effects of OPC-61815 on the central nervous system were evaluated. The following findings were noted in rats at 255 mg/kg of OPC-61815 but were not observed in the safety pharmacology study of tolvaptan: decreased spontaneous activity, decreased touch response, decreased body tone, decreased respiratory rate, and abnormal body posture. However, these findings were considered to have resulted from an excessive pharmacological effect (aquaretic effect) caused by high exposure, approximately 10-fold that at the maximum dose level of tolvaptan in the safety pharmacology study of tolvaptan. In addition, the exposure to the phosphate ester of tolvaptan and tolvaptan at 255 mg/kg (C_{max}, 709.1 and 38.64 μg/mL, respectively; AUC_{0-24h}, 326.1 and 284.7 μg·h/mL, respectively) is approximately 96- to 385-fold (phosphate ester of tolvaptan) and 119- to 137-fold (tolvaptan) compared with the exposure[5)] to the phosphate ester of tolvaptan and tolvaptan at the clinical dose (C_{max}, 1840 and 282 ng/mL, respectively; AUC_{0-24h}, 3400 and 2400 ng·h/mL, respectively). Therefore, it

[5)] The exposure to phosphate ester of tolvaptan and tolvaptan after a single intravenous dose of OPC-61815 16 mg in the multiple intravenous dose study (Study 00001) in Japanese patients with congestive heart failure

is unlikely that these findings will translate into clinical problems. The effects of OPC-61815 on the respiratory system and cardiovascular system were evaluated. Decreased T wave amplitude was observed in dogs at ≥12.75 mg/kg of OPC-61815, and this was considered to be a change caused by the pharmacological effect of the phosphate ester of tolvaptan and tolvaptan (increased urine volume, increased plasma Na and Cl concentrations). The exposure to the phosphate ester of tolvaptan and tolvaptan at 12.75 mg/kg (C_{max}, 39.95 and 1.218 μg/mL, respectively; $AUC_{0\text{-}24h}$, 18.99 and 3.788 μg·h/mL, respectively) is approximately 6- to 22-fold (phosphate ester of tolvaptan) and 1.6- to 4-fold (tolvaptan) compared with the exposure[5)] to the phosphate ester of tolvaptan and tolvaptan at the clinical dose. Additionally, increased heart rate at ≥38.25 mg/kg, increased respiratory rate, decreased mean blood pressure, and shortened PR interval at 127.5 mg/kg were reported. These findings occurred at exposure sufficiently higher than the exposure of each component at the clinical dose; therefore, it is unlikely that these findings will translate into clinical problems.

PMDA's view:
The applicant's explanation about findings involved in the central nervous system that occurred in the safety pharmacology studies of OPC-61815 but did not occur in those of tolvaptan is appropriate and it is unlikely that these findings will translate into clinical problems taking into consideration the difference between the exposure at which findings were observed and the exposure at the clinical dose. Findings reported in the evaluation of the cardiovascular system, such as decreased T wave amplitude and decreased mean blood pressure, had also been reported in the safety pharmacology studies of tolvaptan, and therefore they can be expected from the pharmacological effects of the phosphate ester of tolvaptan and tolvaptan. The safety in humans should continue to be discussed in Section "7.R.3 Safety."

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

The plasma concentrations of the phosphate ester of tolvaptan and tolvaptan in rats and dogs were measured by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). In both rats and dogs, the lower limit of quantitation for plasma concentration was 10 ng/mL (phosphate ester of tolvaptan) and 5 ng/mL (tolvaptan).

Unless otherwise noted, PK parameters are expressed as mean values or mean ± standard deviation.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-01, 4.2.2.2-03)

Table 4 shows PK parameters of the phosphate ester of tolvaptan and tolvaptan following intravenous administration of a single dose of OPC-61815 to male and female rats.

Table 4. PK parameters of the phosphate ester of tolvaptan and tolvaptan following a single intravenous dose of OPC-61815 to male and female rats

Dose (mg/kg)	Sex	N/time point	C_{max} (μg/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_z (mL/kg)
Phosphate ester of tolvaptan								
1.275	Male	4	4.543[b]	—	0.5274	0.20	2231.7	658.7
3.825	Male	4	9.199[b]	—	1.4429	0.32	2447.2	1123.4
12.75	Male	4	47.633[b]	—	6.4345	0.23	1829.2	617.5
38.25	Male	4	240.566[b]	—	30.2112	0.37	1168.8	615.9
12.75	Female	4	30.628[b]	—	3.9265	0.89	2997.6	3847.6
Tolvaptan								
1.275	Male	4	0.113	0.083	0.0847	0.40	—	—
3.825	Male	4	0.283	0.083	0.2508	0.57	—	—
12.75	Male	4	1.046	0.083	0.9064	0.54	—	—
38.25	Male	4	3.725	0.083	3.7711	0.67	—	—
12.75	Female	4	2.559	0.5	5.2472	1.28	—	—

"—," not calculated
a, median; b, plasma concentration estimated via extrapolation to time = 0

Table 5 shows PK parameters of the phosphate ester of tolvaptan and tolvaptan following intravenous administration of a single dose of OPC-61815 to male and female dogs.

Table 5. PK parameters of the phosphate ester of tolvaptan and tolvaptan following a single intravenous dose of OPC-61815 to male and female dogs

Dose (mg/kg)	Sex	N	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_z (mL/kg)
Phosphate ester of tolvaptan								
0.3825	Male	4	2.674 ± 0.785[a]	—	0.3329 ± 0.1166	0.17 ± 0.05	1203.5 ± 555.9	271.1 ± 68.0
1.275	Male	4	12.290 ± 3.833[a]	—	1.4883 ± 0.4902	0.23 ± 0.10	884.2 ± 384.9	286.2 ± 141.9
3.825	Male	4	29.135 ± 3.868[a]	—	4.0356 ± 0.6932	0.40 ± 0.11	894.6 ± 152.7	504.9 ± 108.0
12.75	Male	4	79.550 ± 38.522[a]	—	14.1391 ± 5.2336	1.04 ± 0.80	927.9 ± 350.5	1365.9 ± 952.0
3.825	Female	4	48.931 ± 7.850[a]	—	6.3479 ± 1.5710	0.33 ± 0.06	585.9 ± 163.0	276.4 ± 82.8
Tolvaptan								
0.3825	Male	4	0.070 ± 0.008	0.25 ± 0.00	0.1048 ± 0.0123	1.01 ± 0.24	—	—
1.275	Male	4	0.214 ± 0.047	0.25 ± 0.00	0.3882 ± 0.0825	1.58 ± 0.43	—	—
3.825	Male	4	0.477 ± 0.037	0.40 ± 0.41	1.1645 ± 0.2679	2.35 ± 0.68	—	—
12.75	Male	4	1.292 ± 0.302	0.58 ± 0.49	3.6613 ± 0.3978	2.21 ± 0.79	—	—
3.825	Female	4	0.415 ± 0.071	0.31 ± 0.13	0.9240 ± 0.1708	1.72 ± 0.35	—	—

"—," not calculated
a, plasma concentration estimated via extrapolation to time = 0

4.1.2 Repeated-dose studies (CTD 4.2.3.2-04, 4.2.3.2-05)

Table 6 shows PK parameters of the phosphate ester of tolvaptan and tolvaptan following intravenous administration of repeated doses of OPC-61815 once daily for 4 weeks to male and female rats.

Table 6. PK parameters of the phosphate ester of tolvaptan and tolvaptan following repeated intravenous doses of OPC-61815 to male and female rats

Dose (mg/kg)	Sex	Time point	Phosphate ester of tolvaptan			Tolvaptan		
			C_{max}[a] (μg/mL)	t_{max} (h)	AUC_{0-24h} (μg·h/mL)	C_{max} (μg/mL)	t_{max} (h)	AUC_{0-24h} (μg·h/mL)
12.75	Male	Day 1	12.36	—	—	0.8009[a]	—	—
		Week 4	16.34	—	4.782	0.9929	0.083	1.244
	Female	Day 1	12.49	—	—	0.7976[a]	—	—
		Week 4	13.47	—	3.687	2.419	0.5	6.455
63.75	Male	Day 1	125.7	—	—	5.555[a]	—	—
		Week 4	104.9	—	35.86	6.287	1	13.65
	Female	Day 1	127.8	—	—	6.265[a]	—	—
		Week 4	129.3	—	36.48	14.17	1	41.12
255	Male	Day 1	667.0	—	—	20.42[a]	—	—
		Week 4	638.6	—	319.2	24.28	1	90.74
	Female	Day 1	644.6	—	—	26.54[a]	—	—
		Week 4	671.7	—	251.3	40.17	1	162.8

N = 3/time point; "—," not calculated
a, 0.083 hours post-dose

Table 7 shows PK parameters of the phosphate ester of tolvaptan and tolvaptan following intravenous administration of repeated doses of OPC-61815 once daily for 4 weeks to male and female dogs.

Table 7. PK parameters of the phosphate ester of tolvaptan and tolvaptan following repeated intravenous doses of OPC-61815 to male and female dogs

Dose (mg/kg)	Sex	Time point (Day)	Phosphate ester of tolvaptan			Tolvaptan		
			C_{max}[a] (μg/mL)	t_{max} (h)	AUC_{0-24h} (μg·h/mL)	C_{max} (μg/mL)	t_{max} (h)	AUC_{0-24h} (μg·h/mL)
12.75	Male	1	39.04	—	—	1.127[a]	—	—
		29	54.09	—	29.04	1.761	1.0	6.136
	Female	1	47.53	—	—	0.8965[a]	—	—
		29	39.79	—	18.38	1.407	0.75	5.481
38.25	Male	1	130.4	—	—	4.436[a]	—	—
		29	116.6	—	68.49	5.029	0.63	19.65
	Female	1	140.4	—	—	3.513[a]	—	—
		29	134.1	—	73.98	6.288	0.50	22.92
127.5	Male	1	568.1	—	—	14.02[a]	—	—
		29	387.2	—	306.4	23.52	0.63	144.1
	Female	1	407.9	—	—	9.115[a]	—	—
		29	432.2	—	299.9	21.32	0.75	109.4

N = 3/time point; "—," not calculated
a, 0.083 hours post-dose

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.2-02, 4.2.2.3-01, 4.2.2.3-02)

A single dose of 12.75 mg/kg of ^{14}C-labeled OPC-61815 was intravenously administered to male and female white rats, and tissue radioactivity levels were measured at 0.083, 1, 4, 8, 24, 72, and 168 hours post-dose (N = 3/sex/time point). In male rats, high radioactivity levels were detected in most of the tissues at 0.083 to 8 hours post-dose. The highest radioactivity levels in the liver (102.2 μg eq/g), small intestine (34.43 μg eq/g), kidney (30.46 μg eq/g), and adrenal gland (21.34 μg eq/g) were higher than that in plasma (20.51 μg eq/mL). At 168 hours post-dose, radioactivity levels were below the lower limit of quantitation in all tissues studied except for plasma, blood, the liver, and kidney. In female rats, high radioactivity levels were detected in most of the tissues at 0.083 to 8 hours post-dose. The highest radioactivity levels in the liver (96.68 μg eq/g), small

intestine (40.93 μg eq/g), adrenal gland (25.85 μg eq/g), the Harderian gland (22.29 μg eq/g), and kidney (20.16 μg eq/g) were higher than that in plasma (15.13 μg eq/mL). At 168 hours post-dose, radioactivity levels were below the lower limit of quantitation in all tissues except for the skin.

A single dose of 12.75 mg/kg of ^{14}C-labeled OPC-61815 was intravenously administered to male pigmented rats, and tissue radioactivity levels were measured at 0.083, 1, 4, 8, 24, 72, 168, and 504 hours post-dose (N = 3/time point). Of the melanin-containing issues, the tissue-to-plasma radioactivity ratio in the eyeball and skin at time points ranged from 0.090 to 0.683, which are generally similar to that in white rats (0.090-0.635). The radioactivity levels in the pigmented skin were similar to those in the non-pigmented skin.

4.2.2 Protein binding (CTD 4.2.2.2-04, 4.2.2.3-04)

^{14}C-labeled OPC-61815 (0.25-25 μg/mL) was added to sera from mice, rats, rabbits, and dogs. The protein binding was 88.1% to 89.8% (mice), 94.8% to 95.1% (rats), 93.8% to 94.4% (rabbits), and 92.1% to 93.6% (dogs).

A single dose of 12.75 mg/kg of ^{14}C-labeled OPC-61815 was intravenously administered to male rats (N = 3/time point). The plasma protein binding at 0.083, 1, and 4 hours post-dose ranged from 96.6% to 98.4%.

A single dose of 3.825 mg/kg of ^{14}C-labeled OPC-61815 was intravenously administered to male dogs (N = 3). The plasma protein binding at 0.083, 0.5, 1, 4, and 8 hours post-dose ranged from 90.56% to 97.94%.

4.2.3 Distribution in blood cells (CTD 4.2.2.2-02, 4.2.2.2-04, 4.2.2.3-01)

A single dose of 12.75 mg/kg of ^{14}C-labeled OPC-61815 was intravenously administered to male and female rats (N = 3/sex/time point). The percentage of radioactivity in blood cells relative to the total radioactivity in blood[6)] at 0.083, 1, 4, and 8 hours post-dose was 1.241% to 14.69% in male rats and 1.395% to 26.04% in female rats. In both male and female rats, radioactivity was not distributed in blood cells at 24, 72, and 168 hours post-dose.

A single dose of 3.825 mg/kg of ^{14}C-labeled OPC-61815 was intravenously administered to male dogs (N = 3). The percentage of radioactivity in blood cells relative to the total radioactivity in blood[6)] at 0.083, 0.5, 1, 4, and 8 hours post-dose was 0.49% to 18.03%.

4.2.4 Placental transfer (CTD 4.2.2.3-03)

A single dose of 12.75 mg/kg of ^{14}C-labeled OPC-61815 was intravenously administered to pregnant rats on gestation day 18, and tissue radioactivity levels were measured at 1, 8, and 24 hours post-dose (N = 1/time point). Radioactivity was distributed to fetuses; however, at all time points, radioactivity levels in all fetal tissues were lower than the radioactivity levels in blood in dams.

[6)] Calculated using the formula: [1 – radioactivity concentration in plasma / radioactivity concentration in blood × (100 – hematocrit) / 100] × 100

4.3 Metabolism

4.3.1 *In vivo* metabolism

4.3.1.1 Metabolites in plasma (CTD 4.2.2.4-04, 4.2.2.4-05)

A single dose of 12.75 mg/kg of ^{14}C-labeled OPC-61815 was intravenously administered to male and female rats (N = 3/sex/time point). The following compounds were detected in plasma at 0.083, 1, and 4 hours post-dose: the phosphate ester of tolvaptan, tolvaptan, 8 types of tolvaptan metabolites (DM-4103 [ketocarboxylic acid compound produced by ring cleavage], DM-4104 [diol compound produced by ring cleavage], DM-4105 [hydroxy ketone compound produced by ring cleavage], DM-4107 [hydroxy carboxylic acid compound produced by ring cleavage], DM-4110 [4,5-trans-diol compound], DM-4111 [4,5-cis-diol compound], DM-4119 [3,5-cis-diol compound], DM-4121 [3-hydroxy-5-ketone compound]), and 5 types of metabolites with unknown structure. One of the metabolites of unknown structure was co-eluted with DM-4111.

Repeated-doses of 255 mg/kg of OPC-61815 were intravenously administered to male and female rats (N = 3/sex/time point) once daily for 14 days, and repeated-doses of 127.5 mg/kg of OPC-61815 were intravenously administered to male and female dogs (N = 3/sex) once daily for 15 days. The following compounds were detected in plasma at 0.083, 0.5, 1, 3, and 6 hours post-dose: in rats, the phosphate ester of tolvaptan, tolvaptan, 9 types of tolvaptan metabolites (DM-4103, DM-4104, DM-4105, DM-4107, DM-4110, DM-4111, DM-4119, DM-4121, and MOP-21826 [5-ketone compound]), and 7 types of metabolites of unknown structure; in dogs, the phosphate ester of tolvaptan, tolvaptan, 8 types of tolvaptan metabolites (DM-4103, DM-4104, DM-4105, DM-4107, DM-4110, DM-4111, DM-4119, and DM-4121), and 10 types of metabolites of unknown structure.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion (CTD 4.2.2.2-02, 4.2.2.2-04, 4.2.2.5-01)

A single dose of 12.75 mg/kg of ^{14}C-labeled OPC-61815 was intravenously administered to male and female rats (N = 3/sex). Cumulative excretion of radioactivity in urine and feces (percentage of the total radioactivity administered; the same applies hereinafter in this section) up to 168 hours post-dose was 4.590% (urine) and 91.08% (feces) in male rats and 4.738% (urine) and 93.26% (feces) in female rats.

A single dose of 3.825 mg/kg of ^{14}C-labeled OPC-61815 was intravenously administered to male dogs (N = 3). Cumulative excretion of radioactivity in urine and feces up to 168 hours post-dose was 5.32% and 89.50%, respectively.

A single dose of 12.75 mg/kg of ^{14}C-labeled OPC-61815 was intravenously administered to male and female bile-duct canulated rats (N = 3/sex). Cumulative excretion of radioactivity in urine and bile up to 48 hours post-dose was 4.8% (urine) and 92.2% (bile) in male rats and 5.0% (urine) and 91.5% (bile) in female rats.

4.4.2 Excretion in milk (CTD 4.2.2.5-02)

A single dose of 12.75 mg/kg of ^{14}C-labeled OPC-61815 was intravenously administered to female rats (N = 3) at 15 to 16 days postpartum. At 0.5 to 48 hours post-dose, the radioactivity levels were higher in milk than in plasma, and the milk to blood $AUC_{0-\infty}$ ratio of radioactivity was 5.7.

4.R Outline of the review conducted by PMDA

PMDA concluded that the non-clinical pharmacokinetics of OPC-61815 has been evaluated in an appropriate manner based on the submitted data and discussions in the following section.

4.R.1 Tissue distribution

In the tissue distribution studies [see Section "4.2.1 Tissue distribution"], high radioactivity levels were found in the liver, small intestine, kidney, and adrenal gland. PMDA asked the applicant to explain whether distribution of the phosphate ester of tolvaptan or metabolites in these tissues could cause safety-related problems in humans.

The applicant's explanation:

The repeated-dose toxicity studies in rats and dogs [see Section "5.2 Repeated-dose toxicity"] indicated no toxicities in the small intestine or the kidney. In rats, hepatocyte hypertrophy accompanied by an increase in liver weight, and hypertrophy of the adrenal fasciculata and zona reticularis accompanied by an increase in adrenal gland weight were noted. In dogs, increased liver weight, hypertrophy of the adrenal fasciculata and zona reticularis, and fat decrease in the adrenal fasciculata and zona reticularis were noted. Given that there were no morphological anomalies in hepatocytes, and that tolvaptan was shown to induce hepatic drug-metabolizing enzymes (see Review Report of Samsca Tablets 15 mg, dated July 14, 2010), the liver findings reported in rats and dogs were considered to be caused by an adaptive response to the induction of hepatic drug-metabolizing enzymes. On the other hand, findings of the adrenal gland are considered to be a stress-induced secondary response caused by an excessive pharmacological effect. In conclusion, findings of the liver and adrenal gland are not toxicologically significant. High radioactivity levels in the liver, small intestine, kidney, and adrenal gland were also reported at the time of the application for initial approval of tolvaptan. In the repeated-dose toxicity studies of tolvaptan in rats, liver and adrenal gland findings similar to those of OPC-61815 were reported, and these findings were considered to be responses to the induction of hepatic drug-metabolizing enzymes and stress, respectively. Due to absence of associated histopathological changes, both findings were determined to be toxicologically insignificant (Attached document submitted at the application for initial approval of "Samsca Tablets 15 mg").

Furthermore, in all repeated-dose toxicity studies, exposures at the no-observed-adverse-effect level (NOAEL) of the phosphate ester of tolvaptan were higher than exposures[5)] at the clinical dose level [see Section "5.2 Repeated-dose toxicity"]. Given that sufficiently high safety margin has been confirmed, it is unlikely that distribution of OPC-61815 or its metabolites in the liver, small intestine, kidney, and adrenal gland would cause safety-related problems in humans.

On the basis of the applicant's explanation, PMDA concluded that the results of non-clinical study suggest no safety concerns associated with the distribution of OPC-61815 or its metabolites in tissues with high radioactivity levels reported in the tissue distribution studies.

5. Toxicity and Outline of the Review Conducted by PMDA

The results of the following toxicity studies of OPC-61815 were submitted: single-dose toxicity, repeated-dose toxicity, genotoxicity, reproductive and developmental toxicity, local tolerance, and other studies (phototoxicity and hemolysis).

5.1 Single-dose toxicity

Single-dose toxicity studies in rats and dogs were conducted (Table 8).

Table 8. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	CTD
Male and female rats (SD)	IV	0,[a] 127.5, 255, 510	At 510: death (female, 1 of 3 animals), hunchback position, eyelid closure, prone position, tremor, spasm, enlargement of the adrenal gland, thymic atrophy, hypertrophy of the adrenal fasciculata/ zona reticularis, necrosis of thymic cells, ischemic changes in neurons, spongy degeneration of the cerebral cortex At ≥127.5: decreased body weight, low food consumption, decreased spontaneous activity At 510: cool sensation on the body surface	510	4.2.3.1-01
Male and female dogs (beagle)	IV	127.5, 255	≥127.5: e.g., low food consumption, decreased spontaneous activity, eyelid closure, salivation, vomiting, irregular respiration (male) At 255: e.g., licking chops, loss of touch response	>255	4.2.3.1-02

a, A pH8.5 solution containing 5.5 g/100 mL sucrose, 1.8 g/100 mL dibasic sodium phosphate hydrate, and 0.03 g/100 mL sodium dihydrogen phosphate dihydrate

5.2 Repeated-dose toxicity

Two- and 4-week repeated-dose toxicity studies were conducted in rats and dogs (Table 9). The findings were generally similar to those reported in the repeated-dose toxicity studies of tolvaptan. Among changes attributable to OPC-61815 treatment, mainly changes associated with the aquaretic effect of tolvaptan (e.g., increase in urine volume and water consumption, and low urine osmolality) were observed. The applicant considered that these changes were caused by the pharmacological effect and were toxicologically insignificant. The exposure ($AUC_{0\text{-}24h}$) to the phosphate ester of tolvaptan at the NOAEL of 4-week repeated-dose toxicity studies in rats and dogs (rats, 63.75 mg/kg/day [male] and 12.75 mg/kg/day [female]; dogs, 38.25 mg/kg/day) was 3.687 to 35.86 μg·h/mL (rats) and 68.49 to 73.98 μg·h/mL (dogs), which are 1.1- to 10.5-fold and 20.1- to 21.8-fold, respectively, compared with the exposure[5)] at the clinical dose level ($AUC_{0\text{-}24h}$, 3400 ng·h/mL).

Table 9. Repeated-dose toxicity studies

Test system	Route of adminis-tration	Treatment period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	CTD
Male and female rats (SD)	IV	2 weeks (once daily) + 2-week recovery period	0,[a] 0,[b] 12.75, 63.75, 255	At ≥12.75: increased water consumption,[c] low urine osmolality/pH,[c] increased negative test results of urine protein/ketone,[c] low Na[c] At ≥63.75: decreased spontaneous activity, low Cl,[c] low hemoglobin/hematocrit, high liver weight, hepatocyte hypertrophy At 255: decreased food consumption (male), decrease in body weight gain (male), increased food consumption (female), increased body weight (female), increased urine volume,[c] salivation, lacrimation (female), low red blood cell count, high platelet count, high reticulocyte count, prolonged APTT, high total bilirubin (male), low total cholesterol (female), low phospholipid (female), erythropoiesis in the bone marrow/spleen, high adrenal gland weight, hypertrophy of the adrenal fasciculata/zona reticularis, injection site blood clot (male), increased mitotic figures in hepatocytes (female), diffuse hypertrophy of thyroid follicular cells (female), decreased thymus weight (male), low testis weight Reversibility, reversible (except for organized blood clot at the injection site)	63.75 (male) 12.75 (female)	4.2.3.2-01
Male and female rats (SD)	IV	4 weeks (once daily)	0,[a] 0,[b] 12.75, 63.75, 255	At ≥12.75: increased urine volume/water consumption,[c] low urine osmolality,[c] low Na,[c] low Cl[c] At ≥63.75: decreased spontaneous activity At 225: salivation, lacrimation (female), high white blood cell count/lymphocyte count (female),[d] high platelet count,[d] high reticulocyte count,[d] prolonged APTT (female), high triglycerides, low glucose, increased negative urine ketone test results,[c] high adrenal gland weight, hypertrophy of the adrenal fasciculata/zona reticularis, high liver weight, hepatocyte hypertrophy, diffuse hypertrophy of thyroid follicular cells (female), low prostate/seminal gland weight,[d] hypertrophy of bladder smooth muscle cells[c]	63.75 (male) 12.75 (female)	4.2.3.2-04
Male and female dogs (beagle)	IV	2 weeks (once daily) + 2-week recovery period	0,[a] 0,[b] 12.75, 38.25, 127.5	At ≥12.75: increased urine volume/water consumption,[c] low urine osmolality[c] At 127.5: salivation, vomiting, defecation, urinary incontinence, decreased spontaneous activity, irregular respiration, decreased body weight, increased heart rate (female), high liver weight (male),[d] fat decrease in the adrenal fasciculata/zona reticularis,[e] thymic atrophy (male)[e] Reversibility, reversible	38.25	4.2.3.2-02
Male and female dogs (beagle)	IV	4 weeks (once daily)	0,[a] 0,[b] 12.75, 38.25, 127.5	At ≥12.75: increased urine volume/water consumption,[c] low urine osmolality,[c] hypertrophy of bladder smooth muscle cells[c] At 127.5: salivation, vomiting, defecation, urinary incontinence, decreased spontaneous activity, licking chops, ananastasia, tremor, clonic convulsion, discoloration of palate, conjunctival injection, increased heart rate, high liver weight, (female),[d] fat decrease in the adrenal fasciculata/zona reticularis,[e] hypertrophy of the adrenal fasciculata/zona reticularis (female),[e] thymic atrophy (female)[e]	38.25	4.2.3.2-05

a, Physiological saline

b, A pH8.5 solution containing 5.5 g/100 mL sucrose, 1.8 g/100 mL dibasic sodium phosphate hydrate, and 0.03 g/100 mL sodium dihydrogen phosphate dihydrate

c, The finding, which was associated with the aquaretic effect of OPC-61815, was deemed to be toxicologically insignificant by the applicant.

d, Due to absence of associated histopathological changes, the finding was deemed to be toxicologically insignificant by the applicant.

e, The finding, which was attributable to stress caused by treatment, was deemed to be toxicologically insignificant by the applicant.

5.3 Genotoxicity

Genotoxicity studies consisted of an *in vitro* bacterial reverse mutation assay, an *in vitro* forward mutation test using cultured mammalian cells, and an *in vivo* micronucleus assay in rats. The results indicated that OPC-61815 was negative for genotoxicity (Table 10).

Table 10. Genotoxicity studies

Type of study		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg/day)	Test result	CTD
In vitro	Bacterial reverse mutation assay (Ames test)	*Salmonella Typhimurium*: TA98, TA100, TA102, TA1535, TA1537	S9 −/+	0,[a] 200, 500, 1000, 2000, 5000	Negative	4.2.3.3.1-01
	Forward mutation test using cultured mammalian cells	Mouse lymphoma cells	S9 −, 3 hours	0,[b] 200, 500, 1000, 2000, 3000	Negative	4.2.3.3.1-02
			S9 −, 24 hours	0,[b] 20, 50, 100, 200, 500, 1000, 2000, 3000		
			S9 +, 3 hours	0,[b] 200, 500, 1000, 2000, 3000		
In vivo	Rat micronucleus assay	Male and female rats (SD) Bone marrow		0,[c] 63.75, 127.5, 255, 510 (male)	Negative	4.2.3.3.2-01

a, 3.125% (v/v) DMSO

b, 1% (v/v) DMSO

c, A pH8.5 solution containing 5.5 g/100 mL sucrose, 1.8 g/100 mL dibasic sodium phosphate hydrate, and 0.03 g/100 mL sodium dihydrogen phosphate dihydrate

5.4 Carcinogenicity

Since OPC-61815 is not intended to be used for more than 6 months in the clinical setting, no carcinogenicity studies were conducted in accordance with the ICH S1 Guidelines. The applicant considered that OPC-61815 is unlikely to be carcinogenic, based on the following factors.

- It has not been demonstrated that OPC-61815 is genotoxic [see Section "5.3 Genotoxicity"].
- It has not been demonstrated that tolvaptan is carcinogenic (see Review Report of Samsca Tablets 15 mg, dated July 14, 2010).

5.5 Reproductive and developmental toxicity

The following reproductive and developmental toxicity studies were conducted: a study on fertility and early embryonic development to implantation in male and female rats, embryo-fetal development studies in rats and rabbits, and a study of the effects on pre- and postnatal development including maternal function in rats (Table 11). In the embryo-fetal development studies in rats and rabbits, increased embryonic and fetal deaths and delayed ossification were observed. Spontaneous abortion was also noted in rabbits. In addition to these findings, developmental toxicities were confirmed in the embryo-fetal development study of tolvaptan in rabbits (see Review Report of Samsca Tablets 15 mg, dated July 14, 2010). Therefore, the applicant concluded that OPC-61815 should be contraindicated in patients who are or may be pregnant, and information to this effect should be provided in the package insert in an appropriate manner. The exposure ($AUC_{0\text{-}24h}$) to the phosphate ester of tolvaptan in dams at the NOAEL for embryos/fetuses from the embryo-fetal development studies in rats and rabbits (63.75 mg/kg/day for both rats and rabbits) was 30.56 μg·h/mL and 183.9 μg·h/mL, respectively, which are 9.0-fold (rats) and 54.1-fold (rabbits) compared with the exposure[5)] at the clinical dose level ($AUC_{0\text{-}24h}$, 3400 ng·h/mL).

Table 11. Reproductive and developmental toxicity studies

Type of study	Test system	Route of adminis-tration	Treatment period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	CTD
Fertility and early embryonic development to implantation	Male and female rats (SD)	IV	(Male) 14 days before mating until 1 day before necropsy (once daily) (Female) 14 days before mating until gestation day 7 (once daily)	0,[a] 0,[b] 12.75, 63.75, 255	Parent animals: Died, at 255 (female, 2 of 20 animals), prone position, decreased body temperature, and other findings At ≥63.75: e.g., aquaretic effect-related findings Fertility and early embryonic development: At ≥63.75: low seminal gland weight At 255: low epididymal/prostate weight, decreased estrus expression (female)	Parent animals: (general toxicity): 12.75 (male fertility): 255 (female fertility): 63.75 (early embryonic development): 255	4.2.3.5.1-01
Embryo-fetal development	Female rats (SD)	IV	Gestation days 7-17 (once daily)	0,[a] 0,[b] 12.75, 63.75, 255	Dams: Died, at 255 (1 of 20 animals), eyelid closure, no food consumption, and other findings At ≥63.75: decreased body weight, decreased food consumption At 255: e.g., vaginal bleeding, loose stool Fetuses: At 255: total embryonic resorption, high percentage of post-implantation loss, low number of surviving fetuses, decreased fetal body weight, delayed ossification, increase in bipartite ossification of the thoracic vertebra	Dams: (general toxicity): 12.75 (fertility): 255 Embryos and fetuses: 63.75	4.2.3.5.2-03
	Female rabbits (NZW)	IV	Gestation days 6-18 (once daily)	0,[a] 0,[b] 12.75, 63.75, 255	Dams: Died, at 255 (2 of 19 animals), emaciation and other findings At ≥12.75: decreased body weight, decreased food consumption At 255: abortion, discoloration/swelling of the injection site Fetuses: At 255: total embryonic resorption, high percentage of post-implantation loss, decreased fetal body weight, delayed ossification	Dams: (general toxicity): <12.75 (fertility): 63.75 Embryos and fetuses: 63.75	4.2.3.5.2-04
Effects on pre- and postnatal development including maternal function	Female rats (SD)	IV	Gestation day 7 to postpartum day 20 (once daily)	0,[a] 0,[b] 12.75, 63.75, 127.5	Dams: Died, at 127.5 (1 of 20 animals), difficult delivery At ≥63.75: decreased body weight, decreased food consumption, all pups died during the lactation period At 63.75: undelivered At 127.5: vaginal bleeding, all pups died at the time of delivery, prolonged gestation, low birthrate Live pups: At ≥63.75: low body weight, low survival rate	Dams: 12.75 Live pups: 12.75	4.2.3.5.3-01

a, Physiological saline

b, A pH8.5 solution containing 5.5 g/100 mL sucrose, 1.8 g/100 mL dibasic sodium phosphate hydrate, and 0.03 g/100 mL sodium dihydrogen phosphate dihydrate

5.6 Local tolerance

A vascular irritation study was conducted using rabbits (Table 12). OPC-61815 did not cause vascular irritation up to a concentration of 0.6375%, which corresponds to 20.7-fold of the clinical dose. The applicant concluded that it is unlikely that vascular irritation would become a problem in clinical use.

Table 12. Local irritation study

Type of study	Test system	Testing method	Main findings	CTD
Vascular irritation	Male rabbits (NZW)	0.05 mL of physiological saline, OPC-61815 0%,[a] 0.6375%, or 2.55% was intravenously administered through the auricular vein and allowed to be retained for 3 minutes, once daily for 3 days to evaluate vascular irritation	At 2.55% of OPC-61815, hyperemia, induration, blood clot, perivascular edema/inflammatory cell infiltration/fibrosis It was concluded that OPC-61815 does not cause irritation up to 0.6375%	4.2.3.6-01

a, A pH8.5 solution containing 5.5 g/100 mL sucrose, 1.8 g/100 mL dibasic sodium phosphate hydrate, and 0.03 g/100 mL sodium dihydrogen phosphate dihydrate

5.7 Other studies

5.7.1 Phototoxicity

An *in vitro* phototoxicity study was conducted, and the applicant concluded that OPC-61815 is not phototoxic (Table 13).

Table 13. Phototoxicity study

Type of study	Test system	Testing method	Result	CTD
Phototoxicity	Mouse fibroblasts BALB/3T3	The samples were exposed to 0-1000 μg/mL of OPC-61815 for 60 minutes with or without UV-A irradiation, and cell viability was calculated	Not phototoxic	4.2.3.6-02

5.7.2 Hemolysis testing (CTD 4.2.3.7.7-01)

Hemolysis testing was conducted using human blood, and the applicant concluded that OPC-61815 is not hemolytic.

5.R Outline of the review conducted by PMDA

PMDA concluded that the non-clinical toxicity evaluation indicated no problems with the clinical use of OPC-61815 based on the submitted data and discussions in the following sections.

5.R.1 Effects on the nervous system

In the single-dose toxicity study of OPC-61815 in rats, effects on brain neurons were reported. The applicant's explanation:

In the single-dose toxicity study of OPC-61815 in rats, 1 animal died in the 510 mg/kg group, and the analysis indicated ischemic changes in neurons (in the cerebral cortex, caudate nucleus, hippocampus, and thalamus) and spongy degeneration of the cerebral cortex. Because these brain tissues are particularly vulnerable to damage from ischemia (*Exp Toxicol Pathol*. 2004;56:45-52), it is likely that these findings occurred

secondarily to circulatory disturbance accompanying rapid dehydration due to excessive pharmacological effects. In addition, similar findings were reported in a single-dose toxicity study in rats treated with the optical isomers of tolvaptan (see Review Report of Samsca Tablets 15 mg, dated July 14, 2010); therefore, it is reasonable to attribute the findings to the excessive pharmacological effects of OPC-61815.

Effects on neurons were not reported in the repeated-dose toxicity studies in rats. The exposure to the phosphate ester of tolvaptan and tolvaptan at 255 mg/kg/day, the maximum dose level (C_{max}, 638.6-671.7 μg/mL and 24.28-40.17 μg/mL, respectively) is approximately 347- to 365-fold (phosphate ester of tolvaptan) and 86- to 142-fold (tolvaptan) compared with the exposure[5)] to the phosphate ester of tolvaptan and tolvaptan at the clinical dose (C_{max}, 1840 and 282 ng/mL, respectively). Therefore, it is unlikely that effects on neurons will become a problem in the clinical use of OPC-61815. However, the applicant plans to provide a cautionary statement in the package insert in an appropriate manner regarding the rapid dehydration resulting from the excessive pharmacological effects, in a manner equivalent to those implemented for tolvaptan.

PMDA's view:
The applicant's discussion of the mechanism of the effects on brain neurons reported in the single-dose toxicity study in rats is reasonable. Rapid dehydration is likely to be involved in the development of the neuronal findings, and in fact, it is one of the pharmacological effects that can result from administration of the phosphate ester of tolvaptan or tolvaptan; therefore, caution should be exercised in clinical use. The safety in humans and cautionary statements will be discussed in Section "7.R.3 Safety."

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

Unless otherwise noted, PK parameters are expressed as mean value or mean ± standard deviation.

6.1 Summary of biopharmaceutic studies and associated analytical methods

Plasma concentrations of the phosphate ester of tolvaptan and tolvaptan were measured by LC-MS/MS, and the lower limit of quantitation was 1 to 46.2 ng/mL and 2 ng/mL, respectively.

6.2 Clinical pharmacology

6.2.1 *In vitro* studies using human biological samples

6.2.1.1 Protein binding (CTD 4.2.2.3-04)

^{14}C-labeled OPC-61815 (0.25-25 μg/mL) was added to human serum. The protein binding was 97.9% to 98.3%.

6.2.1.2 *In vitro* metabolism

6.2.1.2.1 OPC-61815 metabolism (CTD 4.2.2.4-01, 4.2.2.4-02, 4.2.2.4-03)

^{14}C-labeled OPC-61815 (10 μmol/L) was added to serum, liver S9, small intestine S9, lung S9, and kidney S9 from humans, and incubated at 37°C for 60 minutes. While elimination of the phosphate ester of tolvaptan was

not observed in human serum, approximately 23.9% to 72.7% of the phosphate ester of tolvaptan was metabolized to tolvaptan in liver S9, small intestine S9, lung S9, and kidney S9.

^{14}C-labeled OPC-61815 (50 μmol/L) was added to human liver S9, and incubated at 37°C for 90 minutes. Tolvaptan was detected as the main metabolite, accounting for 4.13% of the total radioactivity.

^{14}C-labeled OPC-61815 (50 μmol/L) was added to cryopreserved human hepatocytes, and incubated at 37°C for 4 hours. Tolvaptan (20.73% of the total radioactivity) was the only metabolite detected.

6.2.1.2.2 Identification of metabolizing enzymes involved in OPC-61815 metabolism (CTD 4.2.2.4-01)

In the presence/absence of phosphatase inhibitor, ^{14}C-labeled OPC-61815 (9.7 μmol/L) was added to kidney S9, and incubated at 37°C for 60 minutes. In the presence of phosphatase inhibitor, elimination of the phosphate ester of tolvaptan was not observed, while in the absence of phosphatase inhibitor, 35.8% of the phosphate ester of tolvaptan was metabolized to tolvaptan.

^{14}C-labeled OPC-61815 (10 μmol/L) was added to human acid phosphatase (ACP) or alkaline phosphatase (ALP), and incubated at 37°C for 60 minutes. In ACP, 45.5% of the phosphate ester of tolvaptan was metabolized to tolvaptan, while in ALP, 96.5% of the phosphate ester of tolvaptan was metabolized to tolvaptan.

6.2.1.3 Enzyme inhibition (CTD 5.3.2.2-01)

Using human liver microsomes and substrates for human cytochrome P450 (CYP) isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4), the inhibitory effects of OPC-61815 (1-100 μmol/L) on the metabolism of the substrates of CYP isoforms were evaluated. The K_i values of OPC-61815 on CYP2C19 and CYP2E1 were 217 and 57.9 μmol/L, respectively. OPC-61815 showed hardly any inhibitory effects on the rest of the CYP isoforms (IC_{50}, >100 μmol/L).

6.2.1.4 Enzyme induction (CTD 5.3.2.2-03, 5.3.2.2-04)

OPC-61815 (1-100 μmol/L) was added to primary-cultured human hepatocytes, and incubated at 37°C for 72 hours. There was no increase in messenger ribonucleic acid (mRNA) expression of CYP1A2, while mRNA expression levels of CYP2C9 and CYP3A4 were increased by 33% to 144% and 288% to 805%, respectively, compared with the control.

OPC-61815 (1-100 μmol/L) was added to cryopreserved human hepatocyte, and incubated at 37°C for 48 hours. The mRNA expression of CYP2B6 was increased by 157% to 405% compared with the control.

6.2.1.5 Transporters (CTD 5.3.2.2-07 through 5.3.2.2-13)

OPC-61815 (1 or 10 μmol/L) was added to Lewis lung carcinoma pork kidney cell line (LLC-PK) 1 expressing P-glycoprotein (P-gp) and the control cells. The efflux ratio (apparent permeability coefficient [P_{app}] basolateral-to-apical / P_{app} apical-to-basolateral; P_{app} B→A/P_{app} A→B) was 1.27 and 1.05, respectively, at 1 or

10 μmol/L in P-gp expressing cells, while the efflux ratio was not calculable and 0.994, respectively, in the control cells. When 1 or 10 μmol/L of OPC-61815 was added in the presence of verapamil (P-gp inhibitor), the efflux ratio was 0.857 and 1.00, respectively, at 1 or 10 μmol/L in P-gp expressing cells, while the efflux ratio was not calculable and 1.09, respectively, in control cells.

OPC-61815 (10-100 μmol/L) was added to Madin-Darby canine kidney (MDCK) II cells expressing breast cancer resistance protein (BCRP) and the control cells. The efflux ratio was 0.836 to 1.33 in BCRP-expressing cells, and 0.874 to 1.10 in control cells. When OPC-61815 (10-100 μmol/L) was added in the presence of Ko143 (BCRP inhibitor), the efflux ratio was 0.728 to 0.738 in BCRP-expressing cells, and 0.976 to 1.12 in the control cells.

^{14}C-labeled OPC-61815 (1 μmol/L) was added to human embryonic kidney 293 (HEK) cells expressing organic anion transporting polypeptide (OATP) 1B1 or OATP1B3, or the control cells. Cellular uptake of OPC-61815 in OATP1B1-expressing cells and OATP1B3-expressing cells was 1.7- to 4.3-fold and 3.9- to 11.4-fold, respectively, compared with the control cells. When ^{14}C-labeled OPC-61815 (1 μmol/L) was added in the presence of rifampicin (OATP1B1/OATP1B3 inhibitor), the percentage of radioactivity that was not internalized into cells compared with that in the absence of rifampicin was 15.1% for OATP1B1-expressing cells and 3.7% for OATP1B3-expressing cells.

Using LLC-PK1 cells expressing P-gp or MDCK II cells expressing BCRP, the inhibitory effect of OPC-61815 on the transport of the substrate for each transporter was evaluated at concentrations of 0.3 to 100 μmol/L for P-gp, and 1 to 100 μmol/L for BCRP. OPC-61815 showed almost no inhibitory effect on any transporter (IC_{50}, >100 μmol/L).

Using HEK293 cells expressing OATP1B1 or OATP1B3, the inhibitory effect of OPC-61815 on the transport of the substrate for each transporter was evaluated at concentrations of 0.3 to 100 μmol/L. OPC-61815 inhibited OATP1B1 (IC_{50}, 9.36 μmol/L) and OATP1B3 (IC_{50}, 10.7 μmol/L).

Using HEK293 cells expressing organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 1, or OCT2, MDCK II cells expressing multidrug and toxin extrusion (MATE) 1 or MATE2-K, and membrane vesicles from insect cells expressing bile salt export pump (BSEP), the inhibitory effect of OPC-61815 on the transport of the substrate for each transporter was evaluated at concentrations of 0.3 to 100 μmol/L. OPC-61815 inhibited OAT1 (IC_{50}, 61.1 μmol/L), but showed almost no inhibitory effect on the rest of the transporters (IC_{50}, >100 μmol/L).

6.2.2 Studies in healthy adults

6.2.2.1 Single intravenous dose study in healthy Japanese adults (Study 263-[redacted]-001, CTD 5.3.3.1-01 [study period, [redacted] 20[redacted] to [redacted] 20[redacted]])

A single dose of 0.3, 1, 3, 7.5, 15, or 30 mg of OPC-61815 was administered intravenously (by 5-minute infusion) to healthy Japanese adult men. Table 14 shows PK parameters of the phosphate ester of tolvaptan and tolvaptan.

Table 14. PK parameters of the phosphate ester of tolvaptan and tolvaptan following a single intravenous dose of OPC-61815

Dose (mg)	N	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)
Phosphate ester of tolvaptan						
0.3	6	53.02 ± 29.28	0.020[b]	—	—	—
1	6	182.2 ± 21.72	0.000	175.0[c]	0.7170[c]	5.280[c]
3	6	559.5 ± 85.52	0.000	427.2 ± 61.14	0.6335 ± 0.1065	6.610 ± 1.051
7.5	6	1832 ± 294.0	0[d]	1242 ± 182.2	1.172 ± 0.2819	5.675 ± 0.8755
15	6	3348 ± 637.7	0.000	3008 ± 416.6	1.730 ± 0.3279	4.648 ± 0.5539
30	6	7670 ± 755.3	0[d]	4882 ± 817.9	1.683 ± 0.4837	5.820 ± 1.032
Tolvaptan						
0.3	6	3.843 ± 0.6681	0.750	24.80 ± 8.680	4.158 ± 2.127[b]	—
1	6	11.98 ± 3.212	1.000	51.55 ± 15.90	2.207 ± 0.6038	—
3	6	34.58 ± 5.420	1.000	172.2 ± 29.24	3.743 ± 1.713	—
7.5	6	116.7 ± 30.23	0.500	557.3 ± 139.4	3.320 ± 0.6282	—
15	6	268.8 ± 52.66	1.000	1638 ± 592.2	5.685 ± 0.9334	—
30	6	442.5 ± 64.87	0.500	2010 ± 523.4	3.960 ± 1.273	—

"—," not calculated

a, median; b, N = 5; c, N = 1; d, In all subjects, t_{max} was 0 (at the end of administration).

6.2.2.2 Multiple intravenous dose study in healthy Japanese adults (Study 263-[redacted]-001, CTD 5.3.3.1-02 [study period, [redacted]20[redacted] to [redacted] 20[redacted]])

Multiple doses of 1.25, 5, or 20 mg of OPC-61815 were administered intravenously (by 1-minute infusion) to healthy Japanese adult men once daily for 7 days. Table 15 shows PK parameters of the phosphate ester of tolvaptan and tolvaptan.

Table 15. PK parameters of the phosphate ester of tolvaptan and tolvaptan following multiple intravenous doses of OPC-61815

Dose (mg)	N	Time point (Day)	C_{max} (ng/mL)	t_{max}[a]	AUC[b] (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)
Phosphate ester of tolvaptan							
1.25	9	1	371.8 ± 78.15[c]	3.0[c]	167.3 ± 32.55[c]	0.5308 ± 0.1074	5.540 ± 0.8344[c]
		7	320.0 ± 89.42	3.0	169.0 ± 33.05	0.5748 ± 0.1549[c]	7.042 ± 1.406
5	8	1	1165 ± 394.4	3.0	784.0 ± 150.2[d]	1.193 ± 0.3741	5.321 ± 0.8341[d]
		7	1375 ± 368.4	3.0	924.8 ± 136.9	1.329 ± 0.4530	5.091 ± 0.7657
20	9	1	4351 ± 1496	3.0	3178 ± 400.1[c]	2.510 ± 1.927	5.574 ± 0.7725[c]
		7	4137 ± 955.7	3.0	3416 ± 344.7	2.419 ± 1.145	5.467 ± 0.5627
Tolvaptan							
1.25	9	1	16.37 ± 3.463	1.00	62.08 ± 14.64[c]	2.803 ± 0.8142	—
		7	15.42 ± 1.910	1.00	68.44 ± 13.74	3.012 ± 0.4045	—
5	8	1	70.25 ± 15.61	1.00	312.1 ± 73.41[d]	2.811 ± 0.4467	—
		7	69.78 ± 19.15	1.00	346.0 ± 92.71	2.894 ± 0.4030	—
20	9	1	252.2 ± 23.15	1.00	1351 ± 330.3[c]	5.159 ± 1.344	—
		7	261.0 ± 64.12	1.00	1384 ± 453.4	5.228 ± 0.6134	—

"—," not calculated

a, median; the unit is minutes for the phosphate ester of tolvaptan and hours for tolvaptan; b, data on Day 1 are AUC_{0-t} and data on Day 7 are AUC_{0-24h}; c, N = 8; d, N = 7

6.2.2.3 Study on the effects of rate of administration in healthy Japanese adults (Study 263-[redacted]-005, CTD 5.3.3.1-03 [study period, [redacted] to [redacted] 20[redacted]])

In this study, a single dose of placebo, 7.5, or 15 mg of OPC-61815 was administered to healthy Japanese adult men by 2-hour infusion in Period 1, by 5-minute infusion in Period 2 (72 hours after the start of Period 1), and by 1-minute infusion in Period 3 (144 hours after the start of Period 1). Table 16 shows the design of treatment groups, and Table 17 shows PK parameters of the phosphate ester of tolvaptan and tolvaptan.

Table 16. Treatment groups of Study 263-[redacted]-005

Group	N	Period 1	Period 2	Period 3
A	3	OPC-61815 7.5 mg	OPC-61815 7.5 mg	Placebo
B	3	OPC-61815 7.5 mg	Placebo	OPC-61815 7.5 mg
C	3	Placebo	OPC-61815 7.5 mg	OPC-61815 7.5 mg
D	3	OPC-61815 15 mg	OPC-61815 15 mg	Placebo
E	3	OPC-61815 15 mg	Placebo	OPC-61815 15 mg
F	3	Placebo	OPC-61815 15 mg	OPC-61815 15 mg

Table 17. PK parameters of the phosphate ester of tolvaptan and tolvaptan following a single intravenous dose of OPC-61815

Dose (mg)	Duration of administration	N	C_{max} (ng/mL)	t_{max}[a]	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)
Phosphate ester of tolvaptan							
7.5	2 hours	6	511.0 ± 74.25	105.0	1232 ± 186.3[b]	1.034 ± 0.2184	5.718 ± 0.7965[b]
	5 minutes	6	1860 ± 733.8	5.0	—	—	—
	1 minute	6	2130 ± 335.8[c]	5.0[c]	—	—	—
15	2 hours	6	1206 ± 265.3	120.0	2932 ± 780.5	1.306 ± 0.6365	5.017 ± 1.427
	5 minutes	6	4392 ± 1028	5.0	—	—	—
	1 minute	6	4405 ± 804.0	5.0	—	—	—
Tolvaptan							
7.5	2 hours	6	92.47 ± 20.81	2.30	580.8 ± 184.3[b]	4.585 ± 0.8663	—
	5 minutes	6	91.43 ± 26.39	1.00	—	—	—
	1 minute	6	99.60 ± 19.03[c]	0.50[c]	—	—	—
15	2 hours	6	157.7 ± 23.98	2.30	912.7 ± 244.9	3.922 ± 0.7246	—
	5 minutes	6	161.0 ± 26.12	0.50	—	—	—
	1 minute	6	168.8 ± 41.25	0.75	—	—	—

"—," not calculated
a, median; the unit is minutes for the phosphate ester of tolvaptan and hours for tolvaptan; b, N = 5; c, N = 4

6.2.2.4 Mass balance study (Study 263-102-00006, CTD 5.3.3.1-04 [study period, November to December 2019])

A single dose of 15.2 mg of ^{14}C-labeled OPC-61815 was administered intravenously (by 1-hour infusion) to 8 healthy Japanese adult men. Up to 168 hours post-dose, 54.30% and 40.80% of the administered radioactivity was excreted in urine and feces, respectively. DM-4107, a tolvaptan metabolite, was mainly excreted in urine up to 48 hours post-dose and in feces up to 120 hours post-dose, which account for 14.14% and 7.82% of the administered radioactivity, respectively. In urine and feces, the phosphate ester of tolvaptan was not detected, while tolvaptan was found in very small amounts. In plasma, DM-4103 and the phosphate ester of tolvaptan were mainly detected, accounting for 31.8% and 12.3% of the total radioactivity in plasma, which was calculated by relative comparison of exposure (AUC_{0-last}).

6.2.3 A study in patients

6.2.3.1 Multiple-intravenous dose study in Japanese patients with congestive heart failure (Study 263-102-00001, CTD 5.3.3.2-01 [study period, November 2017 to April 2018])

Multiple doses of 2, 4, 8, or 16 mg of OPC-61815 were administered intravenously (by 1-hour infusion) once daily for 5 days, or multiple doses of 15 mg of tolvaptan once daily for 5 days orally to Japanese patients with congestive heart failure. Table 18 shows PK parameters of the phosphate ester of tolvaptan and tolvaptan following a single-dose of OPC-61815 or tolvaptan, while Table 19 shows the post multiple-dose to first-dose ratio of trough plasma concentration (C_{trough}) of the phosphate ester of tolvaptan and tolvaptan in subjects receiving multiple doses of OPC-61815 or tolvaptan.

Table 18. PK parameters of the phosphate ester of tolvaptan and tolvaptan following a single dose of OPC-61815 or tolvaptan

Drug administered	N	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	$AUC_{0\text{-}\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)
Phosphate ester of tolvaptan							
OPC-61815 2 mg	11	296 ± 186	1.03	454 ± 182	455 ± 182	1.8 ± 0.7	4.59 ± 1.54
OPC-61815 4 mg	12	524 ± 130	1.04	980 ± 384	986 ± 393	2.8 ± 1.1	4.29 ± 1.64
OPC-61815 8 mg	12	831 ± 215	1.03	1440 ± 429	1440 ± 437	2.5 ± 0.9	5.50 ± 1.45
OPC-61815 16 mg	11	1840 ± 457[b]	1.03[b]	3400 ± 735	3430 ± 742	3.8 ± 0.6	4.50 ± 0.953
Tolvaptan							
OPC-61815 2 mg	11	41.4 ± 11.4	1.48	356 ± 157	453 ± 250[b]	8.1 ± 2.7[b]	—
OPC-61815 4 mg	12	98.6 ± 43.7	1.73	983 ± 563	1210 ± 778	8.6 ± 2.2	—
OPC-61815 8 mg	12	149 ± 61.7	1.76	1340 ± 522	1630 ± 700	8.5 ± 3.1	—
OPC-61815 16 mg	11	282 ± 96.0	1.52	2400 ± 1030	2830 ± 1400	7.4 ± 2.5	—
Tolvaptan 15 mg	12	325 ± 194	4.07	2850 ± 1580	4010 ± 1760[c]	7.4 ± 2.0[c]	5.01 ± 3.47[c]

"—," not calculated
a, Median; b, N = 10; c, N = 8

Table 19. The post multiple-dose to first-dose ratio of C_{trough} (phosphate ester of tolvaptan and tolvaptan) in subjects receiving multiple doses of OPC-61815 or tolvaptan

Drug administered	Phosphate ester of tolvaptan	Tolvaptan
OPC-61815 2 mg	—	1.35 ± 0.558[a]
OPC-61815 4 mg	—	1.24 ± 0.387[b]
OPC-61815 8 mg	—	1.23 ± 0.238[c]
OPC-61815 16 mg	1.14 ± 0.216[b]	1.41 ± 0.659[c]
Tolvaptan 15 mg	—	1.28 ± 0.612[a]

"—," not calculated
a, N = 9; b, N = 10; c, N = 11

Tables 20 and 21 show the change from baseline in body weight to the final dose and the daily urine volume, respectively, in subjects receiving multiple doses of OPC-61815 or tolvaptan.

Table 20. Change from baseline in body weight to the final dose in subjects receiving multiple doses of OPC-61815 or tolvaptan

Drug administered	N	Body weight at baseline (kg)	Body weight at final dose (kg)	Change from baseline (kg)
OPC-61815 2 mg	13	56.4 ± 12.9	55.8 ± 12.9	−0.6 ± 0.6
OPC-61815 4 mg	12	51.7 ± 9.4	50.5 ± 9.1	−1.1 ± 0.8
OPC-61815 8 mg	12	65.6 ± 11.3	64.1 ± 11.4	−1.5 ± 1.1
OPC-61815 16 mg	11	59.6 ± 13.9	57.5 ± 12.7	−2.1 ± 1.8
Tolvaptan 15 mg	12	59.6 ± 15.9	57.9 ± 15.2	−1.7 ± 1.2

Table 21. Daily urine volume in subjects receiving multiple doses of OPC-61815 or tolvaptan

Drug administered	N	Time point[a]	Daily urine volume (mL)	Change from baseline (mL)
OPC-61815 2 mg	13	Baseline	1552.7 ± 329.2	—
	13	Day 1	1932.1 ± 468.0	409.4 ± 479.4
	13	Day 2	1846.2 ± 483.7	323.5 ± 405.2
	13	Day 3	1858.5 ± 489.8	335.8 ± 477.0
	13	Day 4	1782.3 ± 519.6	259.6 ± 477.4
	13	Day 5	2015.2 ± 535.1	492.5 ± 553.0
OPC-61815 4 mg	12	Baseline	1391.3 ± 301.5	—
	12	Day 1	1863.3 ± 717.4	472.1 ± 560.1
	12	Day 2	1758.3 ± 671.4	367.1 ± 492.9
	9	Day 3	1916.7 ± 611.2	452.2 ± 488.6
	10	Day 4	2007.0 ± 570.0	554.0 ± 458.9
	10	Day 5	1963.0 ± 497.9	510.0 ± 505.5
OPC-61815 8 mg	12	Baseline	1536.9 ± 403.5	—
	12	Day 1	2775.8 ± 882.6	1238.8 ± 681.9
	12	Day 2	2333.0 ± 851.8	796.1 ± 588.2
	12	Day 3	2116.3 ± 729.8	579.3 ± 495.2
	12	Day 4	2266.8 ± 775.9	729.8 ± 672.8
	12	Day 5	2106.5 ± 607.2	569.6 ± 449.3
OPC-61815 16 mg	11	Baseline	1725.5 ± 531.6	—
	11	Day 1	2793.9 ± 976.1	1068.5 ± 892.4
	11	Day 2	2359.0 ± 1080.6	633.5 ± 1000.4
	10	Day 3	1983.0 ± 694.0	270.0 ± 739.3
	11	Day 4	2021.2 ± 568.4	295.7 ± 556.4
	11	Day 5	1923.0 ± 529.1	122.5 ± 509.2
Tolvaptan 15 mg	12	Baseline	1259.2 ± 421.6	—
	10	Day 1	1955.8 ± 736.3	674.6 ± 437.9
	10	Day 2	1893.8 ± 590.8	612.6 ± 473.5
	9	Day 3	1849.6 ± 420.0	501.6 ± 496.1
	9	Day 4	1866.6 ± 534.2	518.6 ± 392.9
	9	Day 5	1796.6 ± 663.2	448.6 ± 440.0

a, Day 1 is defined as the day of the first dose of study drug.

6.2.4 Studies on intrinsic factors

6.2.4.1 Population pharmacokinetic analysis (Analysis 263-102-0002J, CTD 5.3.3.5-01)

A population pharmacokinetic (PPK) analysis was conducted using plasma concentration data of the phosphate ester of tolvaptan measured at 918 time points in 197 subjects and those of tolvaptan at 1785 time points in 349 subjects. These data were obtained from 350 participants from studies conducted in Japanese patients with congestive heart failure: Study 263-102-00001 (Study 00001, 59 subjects), a phase II study; and Study 263-102-00003 (Study 00003, 291 subjects), a phase III study. The PK of the phosphate ester of tolvaptan was described by a 3-compartment model with first-order elimination, while the PK of tolvaptan was described by a 2-compartment model with first-order absorption and first-order elimination (Figure 1).

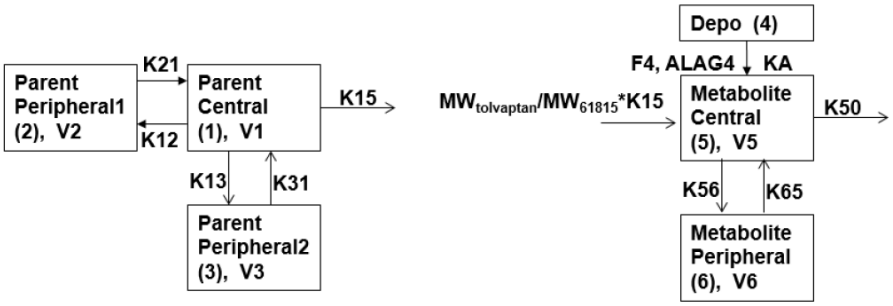

Figure 1. Final models for the phosphate ester of tolvaptan (left) and tolvaptan (right)

ALAG4: absorption lag time of tolvaptan after oral administration of tolvaptan; F4: relative bioavailability of tolvaptan after oral administration of tolvaptan; K12, K21, K13, K31, K56, and K65: rate constants between compartments; K15: elimination rate constant for the phosphate ester of tolvaptan; K50: elimination rate constant of tolvaptan; KA: absorption rate constant of tolvaptan after oral administration of tolvaptan; MW_{61815}: molecular weight of the phosphate ester of tolvaptan; $MW_{tolvaptan}$: molecular weight of tolvaptan; V1, V2, V3, V4, V5, and V6: volume of distribution for each compartment

The main demographic characteristics and distribution of subjects analyzed were as follows: sex, 249 males and 101 females; treatment, 197 subjects treated with OPC-61815 and 153 subjects treated with tolvaptan; New York Heart Association (NYHA) functional classification, 39 subjects in Class I, 234 subjects in Class II, 75 subjects in Class III, and 2 subjects in Class IV; kidney function classification (estimated glomerular filtration rate; eGFR), 5 subjects with normal renal function (≥90 mL/min), 59 subjects with mild renal impairment (≥60 mL/min and ≤89 mL/min), 210 subjects with moderate renal impairment (≥30 mL/min and ≤59 mL/min), 75 subjects with severe renal impairment (≥15 mL/min and ≤29 mL/min), and 1 subject with end stage renal failure (<15 mL/min); liver function classification (according to National Cancer Institute Organ Dysfunction Working Group [NCI ODWG] classification), 281 subjects in Class A, 14 subjects in Class B1, 40 subjects in Class B2, and 15 subjects in Class C; median age of 77 years [40, 85] (minimum, maximum; the same applies hereinafter); median body weight of 59.9 kg [31.7, 102]; median ALP of 240 U/L [8.00, 831]; median prostatic acid phosphatase (PAP) of 0.900 ng/mL [0.200, 6.50]; and median tartrate resistant acid phosphatase-5b (TRACP-5b) of 433 mU/dL [64.0, 3420]. A covariate search was performed to identify factors affecting the PK of the phosphate ester of tolvaptan. Body weight, age, ALP, PAP, TRACP-5b, sex, age group (<65 years vs ≥65 years), NYHA functional classification, liver function classification, and kidney function classification were analyzed. Body weight was selected as a covariate with a significant effect on total body clearance (CL) in the final model for the phosphate ester of tolvaptan. In addition, CL was selected as a factor affecting the PK of tolvaptan, while body weight was selected as a factor that has a significant effect on the clearance between the central compartment and peripheral compartment, volume of distribution of the central compartment, and volume of distribution of the peripheral compartment.

The population mean of PK parameters was estimated by the final models. For the phosphate ester of tolvaptan, population mean CL was 4.53 L/h (coefficient of variation [CV] of 26%) and population mean volume of distribution of the central compartment was 3.78 L (CV not estimated). For tolvaptan, the population mean CL was 4.81 L/h (CV of 61.3%) and population mean volume of distribution of the central compartment was 20.3 L (CV of 35.2%).

Using the final model for the phosphate ester of tolvaptan and that for tolvaptan, the PK parameters following a single intravenous dose of 16 mg of OPC-61815 administered by 1-hour infusion to randomized subjects with varying body weight (1000 subjects for each treatment) were simulated. Table 22 shows the results of the simulation.

Table 22. PK parameters of the phosphate ester of tolvaptan and tolvaptan following a single intravenous dose of OPC-61815

	Body weight	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)
Phosphate ester of tolvaptan	30 kg	2220 ± 207	4520 ± 1220
	60 kg	2020 ± 234	3520 ± 1010
	90 kg	1910 ± 233	3080 ± 869
Tolvaptan	30 kg	492 ± 173	4200 ± 2010
	60 kg	313 ± 107	2790 ± 1240
	90 kg	229 ± 77.0	2120 ± 901

Using the information on 197 patients who had received OPC-61815 in Studies 00001 and 00003, the PK parameters by kidney function classification and by liver function classification following a single intravenous dose of 16 mg of OPC-61815 administered by 1-hour infusion were simulated by the final model for the phosphate ester of tolvaptan and that for tolvaptan. Table 23 shows the results of the simulation.

Table 23. PK parameters of the phosphate ester of tolvaptan and tolvaptan following a single intravenous dose of OPC-61815

		N	C_{max} (ng/mL)	$AUC_{0\text{-}\infty}$ (ng·h/mL)
By kidney function classification (eGFR) (mL/min)				
Phosphate ester of tolvaptan	≥90	4	1900 ± 103	3050 ± 410
	60-89	36	1860 ± 261	3080 ± 1090
	30-59	116	1960 ± 209	3400 ± 922
	15-29	40	1980 ± 220	3530 ± 1070
	<15	1	2130	4060
Tolvaptan	≥90	4	372 ± 206	4490 ± 4390
	60-89	36	299 ± 102	2670 ± 1240
	30-59	116	299 ± 88.7	3090 ± 1610
	15-29	40	358 ± 160	4410 ± 3340
	<15	1	418	4710
By liver function classification (NCI ODWG classification)				
Phosphate ester of tolvaptan	Class A	154	1930 ± 224	3310 ± 993
	Class B1	10	1930 ± 254	3320 ± 1020
	Class B2	21	2030 ± 179	3660 ± 815
	Class C	12	2000 ± 229	3610 ± 1110
Tolvaptan	Class A	154	321 ± 119	3350 ± 2320
	Class B1	10	311 ± 124	3340 ± 1480
	Class B2	21	274 ± 74.3	2880 ± 1530
	Class C	12	286 ± 67.7	3690 ± 1510

6.2.5 Drug interaction studies

6.2.5.1 Drug interactions with rifampicin (CTD 5.3.3.4-01 [study period, November to December 2019])

The study was conducted in 14 healthy Japanese adult men. In the OPC-61815 monotherapy period, subjects received a single intravenous dose of 4 mg of OPC-61815 (by 1-hour infusion). In the coadministration period,

subjects received a single intravenous dose of 4 mg of OPC-61815 (by 1-hour infusion) in combination with a single oral dose of 600 mg of rifampicin (washout period of 2 days). The coadministration-to-monotherapy geometric mean ratio with the 90% confidence interval (CI) was 1.2636 [1.2254, 1.3029] and 1.9226 [1.8368, 2.0123], respectively, for C_{max} and $AUC_{0-\infty}$ of the phosphate ester of tolvaptan, and 0.8602 [0.8151, 0.9077] and 1.0141 [0.9579, 1.0735] respectively, for C_{max} and $AUC_{0-\infty}$ of tolvaptan.

6.2.6 Evaluation of QT/QTc interval (Study 263-102-00005, CTD 5.3.4.1-01 [study period, April to July 2018])

An 8-treatment, 4-period crossover study was conducted in 48 healthy Japanese adult men to evaluate the effect on QT intervals. Subjects received a single intravenous dose of placebo, 16, or 32 mg of OPC-61815 (by 1-hour infusion), or a single oral dose of 400 mg of moxifloxacin.

Following a single intravenous dose of 16 or 32 mg of OPC-61815, the PK parameters for the phosphate ester of tolvaptan were as follows: the median t_{max} was 1.02 hours for both dose levels, C_{max} was 1760 ± 240 and 3560 ± 460 ng/mL, respectively, and $AUC_{0-\infty}$ was 2510 ± 421 and 5200 ± 804 ng·h/mL, respectively; while the PK parameters for tolvaptan were as follows: the median t_{max} was 1.52 hours for both dose levels, C_{max} was 209 ± 45.5 and 424 ± 108 ng/mL, respectively, and $AUC_{0-\infty}$ was 1230 ± 384 and 2540 ± 790 ng·h/mL, respectively.

The difference in the least squares mean for the change from baseline in Fridericia-corrected QT interval (QTcF) compared with the placebo (ΔΔQTcF) [90% CI] at 16 or 32 mg of OPC-61815 was 2.7 ms [0.4, 4.9] and 2.0 ms [−0.2, 4.2], respectively, at maximum. The upper limit of the 90% CI was <10 ms at all time points. When moxifloxacin was administered, the ΔΔQTcF [98% CI] was 11.5 ms [8.3, 14.7] at maximum, with the lower limit of 98% CI being >0 ms at all time points.

6.R Outline of the review conducted by PMDA

6.R.1 Rationale for the dosage regimen in the phase III study

The applicant's explanation about the rationale for selecting the dosage regimen of OPC-61815 in the phase III study (Study 00003):

(1) Duration of administration

In Study 263-[redacted]-001, in which OPC-61815 was administered by 1-minute infusion, feeling abnormal (9 of 27 subjects), pruritus (5 of 27 subjects), pruritus generalised (3 of 27 subjects), and erythema (3 of 27 subjects) occurred at a high frequency during or immediately after the completion of administration, none of which were reported in Study 263-[redacted]-001, in which OPC-61815 was administered by 5-minute infusion, or in the clinical pharmacology studies[7)] of oral tolvaptan in healthy adults. In Study 263-[redacted]-005, which was conducted to evaluate the effect of infusion rate, adverse events such as feeling abnormal, pruritus, erythema, hyperhidrosis, and feeling hot occurred following a 1-minute or 5-minute infusion, while none of these adverse events occurred following a 2-hour infusion. The results suggested that a longer duration of OPC-61815 infusion

[7)] Studies 156-[redacted]-001, 156-[redacted]-002, 156-[redacted]-003, and 156-[redacted]-001 (see Review Report of Samsca Tablets 15 mg, dated July 14, 2010)

would reduce the risk of developing the adverse events mentioned above. On the other hand, in Study 263-[redacted]-005, the mean daily urine volume and the maximum value of mean urine excretion rate did not differ markedly in relation to the duration of infusion (Table 24), suggesting that the duration of infusion does not have a significant impact on the strength of the aquaretic effect of OPC-61815.

Table 24. Mean daily urine volume and the maximum value of mean urine excretion rate following a single intravenous dose of OPC-61815

Dose (mg)	Duration of administration	N	Mean daily urine volume (mL)	Maximum value of mean urine excretion rate[a] (mL/h)
7.5	2 hours	6	3353.0 ± 861.8	444.7 ± 138.6
	5 minutes	6	3647.5 ± 828.9	606.0 ± 141.0
	1 minute	5	3276.8 ± 614.1	563.2 ± 104.3
15	2 hours	6	4765.2 ± 1583.9	569.7 ± 207.9
	5 minutes	6	4818.3 ± 1358.6	643.0 ± 191.4
	1 minute	6	5584.8 ± 953.0	677.7 ± 199.8

a, maximum values when the mean urine excretion rate is calculated every 30 minutes up to 4 hours post-dose, every 2 hours up to 8 hours post-dose, between 8 to 12 hours post-dose, and between 12 to 24 hours post-dose

In Study 263-[redacted]-005, the time at which the mean urine excretion rate reached maximum was slightly delayed compared with the t_{max} of tolvaptan at each duration of administration. To find a regimen that enables the aquaretic effect of OPC-61815 to be achieved as early as possible while reducing infusion-rate related risks such as feeling abnormal, the duration that would be likely to decrease the t_{max} compared to oral tolvaptan 15 mg (2 hours) was evaluated. On the basis of the PK model constructed using data of plasma concentrations of the phosphate ester of tolvaptan and tolvaptan obtained from clinical studies in healthy adults (Studies 263-[redacted]-001, 263-[redacted]-001, and 263-[redacted]-005), the t_{max} of tolvaptan following intravenous administration of 8 mg of OPC-61815 by 1-minute, 5-minute, 1-hour, and 2-hour infusion was estimated to be 1 hour, 1 hour, 1.5 hours, and 2.25 hours, respectively. Accordingly, 1-hour infusion was selected as the duration of administration of OPC-61815.

The above results indicated that the dosage regimen for OPC-61815 in the phase III study should be intravenous infusion once daily over 1 hour.

(2) Dose level

In Study 00001 conducted in patients with congestive heart failure, the exposure to tolvaptan (C_{max} and $AUC_{0\text{-}24h}$) following intravenous administration of 16 mg of OPC-61815 was similar to the exposure to 15 mg of oral tolvaptan [see Section "6.2.3.1 Multiple-intravenous dose study in Japanese patients with congestive heart failure"]. The K_i value of OPC-61815 for the V_2-receptor is approximately 14-fold that of tolvaptan [see Section "3.R.1 Pharmacological effects of OPC-61815 on fluid retention in heart failure"], and the contribution of OPC-61815 to the total activity is approximately 10% based on the $AUC_{0\text{-}24h}$ (molar basis). For these and other reasons, it was considered that the pharmacological effect of OPC-61815 does not need to be taken into account when selecting the dose level. Therefore, it is appropriate to select a dose level of 16 mg of OPC-

61815 for Study 00003, a level at which tolvaptan exposure equivalent to that of oral tolvaptan 15 mg can be achieved in patients with congestive heart failure.

PMDA's view:
The dosage regimen of OPC-61815 for the phase III study was once daily, and an intravenous infusion over 1 hour was selected. The applicant balanced the concern for an increasing incidence of adverse events associated with a shorter intravenous infusion of OPC-61815 compared to slower administration with the need to achieve the aquaretic effect of tolvaptan early. This approach is rational to some extent. Furthermore, it is appropriate for the applicant to select a dose of 16 mg of OPC-61815 to achieve efficacy and safety similar to those achieved with 15 mg of oral tolvaptan based on exposure to tolvaptan. The applicant considered that it is tolvaptan, rather than the phosphate ester of tolvaptan, that is mainly involved in the activity, even though the phosphate ester of tolvaptan also shows an antagonistic effect against the V_2-receptor but does not contribute significantly to the pharmacological effects when taking into account the strength of the antagonistic effect against the V_2-receptor and exposure relative to that of tolvaptan. The appropriateness of the dosage regimen of OPC-61815 will be discussed further in Section "7.R.4 Dosage and administration" based on the efficacy and safety results in the phase III study.

6.R.2 Induction of CYP3A4 and CYP2C9 by OPC-61815

The applicant's explanation about the induction of CYP3A4 and CYP2C9 by OPC-61815 in *in vitro* studies:
Tolvaptan has been reported to be a substrate for CYP3A4 (see Review Report of Samsca Tablets 15 mg, dated July 14, 2010). In Study 263-[redacted]-001, the exposure (C_{max} and AUC) at steady state predicted from the PK data for the first dose of OPC-61815 (Day 1) did not differ markedly from the actual exposure for the final dose (Day 7) [see Section "6.2.2.2 Multiple intravenous dose study in healthy Japanese adults"], therefore, CYP3A4 induction by OPC-61815 would not become a significant problem in the clinical use of OPC-61815. In addition, OPC-61815 is hydrolyzed in the body to form tolvaptan, followed by rapid elimination; thus, it is unlikely to accumulate in the body. Furthermore, the results of the clinical drug interaction study of tolvaptan and warfarin suggested that there was no CYP2C9 induction by tolvaptan or its metabolites that could become a problem in clinical use (see Review Report of Samsca Tablets 15 mg, dated July 14, 2010). The physiologically-based pharmacokinetics (PBPK) modeling analysis indicated that the effect of OPC-61815 on the PK of the substrate for CYP2C9 is fairly slight. These data indicated that CYP2C9 induction by OPC-61815 is unlikely to become a significant problem in clinical use.

PMDA concluded that induction of CYP3A4 and CYP2C9 by OPC-61815, as indicated by the findings of the *in vitro* studies, will not translate into significant clinical problems based on the applicant's explanation.

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

The applicant submitted efficacy and safety data, in the form of results data from the 6 main clinical studies summarized in Table 25 [see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA" for PK].

Table 25. Summary of main clinical studies

Data	Location	Study ID	Phase	Study population	Number of subjects receiving study drug	Summary of dosage regimen	Main endpoints
Evaluation	Japan	263-[redacted]-001	I	Healthy adults	54	A single intravenous dose of 0.3, 1, 3, 7.5, 15, or 30 mg of OPC-61815 or placebo	PK/PD Safety
	Japan	263-[redacted]-001	I	Healthy adults	36	Multiple intravenous doses of 1.25, 5, or 20 mg of OPC-61815 or placebo (7 days)	PK/PD Safety
	Japan	263-[redacted]-005	I	Healthy adults	18	A single intravenous dose of placebo, 7.5, or 15 mg of OPC-61815 over 2 hours (Period 1), 5 minutes (Period 2), or 1 minute (Period 3)	Safety PK/PD
	Japan	263-102-00001	II	Patients with congestive heart failure	60	OPC-61815 group: 2, 4, 8, or 16 mg of OPC-61815 once daily intravenously + placebo once daily orally (5 days) Oral tolvaptan group: placebo once daily intravenously + 15 mg of oral tolvaptan once daily orally (5 days)	Efficacy PK/PD Safety
	Japan	263-102-00003	III	Patients with congestive heart failure	294	OPC-61815 group: 16 mg of OPC-61815 once daily intravenously + placebo once daily orally (5 days) Oral tolvaptan group: placebo once daily intravenously + 15 mg of oral tolvaptan once daily orally (5 days)	Efficacy Safety PK/PD
	Japan	263-102-00004	III	Patients with congestive heart failure who have difficulty with or are incapable of oral intake	45	8 mg of OPC-61815 once daily intravenously for 1 day or 2 days, followed by 8 or 16 mg of OPC-61815 once daily intravenously (for up to 5 days)	Safety Efficacy PD

7.1 Phase I studies

7.1.1 Single intravenous dose study in healthy Japanese adults (Study 263-[redacted]-001, CTD 5.3.3.1-01 [study period, [redacted] 20[redacted] to [redacted] 20[redacted])

A double-blind, randomized, dose-escalation study was conducted in 54 healthy Japanese adult men (36 subjects in the OPC-61815 group and 18 subjects in the placebo group) to investigate the PK, pharmacodynamics (PD), safety, and tolerability of a single intravenous dose of OPC-61815. Subjects received a single dose of 0.3, 1, 3, 7.5, 15, or 30 mg of OPC-61815, or placebo intravenously (by 5-minute infusion).

The incidence of adverse events occurring by the follow-up visit (Days 15-21) was 27.8% (5 of 18 subjects) in the placebo group, 16.7% (1 of 6 subjects) in the OPC-61815 0.3 mg group (hereinafter referred to as 0.3 mg group), 16.7% (1 of 6 subjects) in the 1 mg group, 33.3% (2 of 6 subjects) in the 3 mg group, 50.0% (3 of 6 subjects) in the 7.5 mg group, 33.3% (2 of 6 subjects) in the 15 mg group, and 66.7% (4 of 6 subjects) in the 30 mg group. Adverse events occurring in ≥2 subjects in all the OPC-61815 groups combined were ventricular extrasystoles, abdominal pain, and blood cholesterol increased in 2 subjects each. Among these events, a causal relationship to the study drug could not be ruled out for the events in 5 subjects in the placebo group (abdominal pain/diarrhoea/faeces hard, feeling hot/hyperhidrosis, body temperature increased/limb discomfort, nausea, and peripheral coldness in 1 subject each), 1 subject in the OPC-61815 1 mg group (abdominal pain), 1 subject in the 3 mg group (headache), 3 subjects in the 7.5 mg group (ventricular extrasystoles/blood cholesterol increased/blood triglycerides increased/differential white blood cell count abnormal, malaise/pyrexia, and heart rate increased in 1 subject each), 1 subject in the 15 mg group (diarrhoea), and 4 subjects in the 30 mg group

(abdominal discomfort/hypoaesthesia, ventricular extrasystoles, alanine aminotransferase [ALT] increased, and blood cholesterol increased in 1 subject each).

No adverse events led to death, and none of the adverse events were classified as serious, or led to study drug treatment discontinuation.

7.1.2 Multiple intravenous dose study in healthy Japanese adults (Study 263-[redacted]-001, CTD 5.3.3.1-02 [study period, [redacted] 20[redacted] to [redacted] 20[redacted]])

A double-blind, randomized, dose-escalation study was conducted in 36 healthy Japanese adult men (27 subjects in the OPC-61815 group and 9 subjects in the placebo group) to investigate the PK, PD, and safety of multiple intravenous doses of OPC-61815. Subjects received 1.25, 5, or 20 mg of OPC-61815, or placebo intravenously (by 1-minute infusion) once daily for 7 days.

The incidence of adverse events occurring by the follow-up visit (Days 23-29) was 44.4% (4 of 9 subjects) in the placebo group, 77.8% (7 of 9 subjects) in the OPC-61815 1.25 mg group, 88.9% (8 of 9 subjects) in the 5 mg group, and 100% (9 of 9 subjects) in the 20 mg group. Adverse events occurring in ≥3 subjects in all the OPC-61815 groups combined were feeling abnormal (9 subjects; 1 subject in the 1.25 mg group, 7 subject in the 5 mg group, 1 subject in the 20 mg group), pruritus (5 subjects in the 20 mg group), blood uric acid increased (5 subjects; 3 subjects in the 5 mg group, 2 subjects in the 20 mg group), diarrhoea (4 subjects; 2 subjects in the 1.25 mg group, 1 subject in the 5 mg group, and 1 subject in the 20 mg group), pruritus generalised (3 subjects in the 20 mg group), erythema (3 subjects in the 20 mg group), and bradycardia (3 subjects; 1 subject in the 1.25 mg group, 2 subjects in the 20 mg group). Among these events, a causal relationship to the study drug could not be ruled out for the events in 2 subjects in the placebo group (blood creatine phosphokinase/haemorrhage subcutaneous, stomatitis in 1 subject each), 3 subjects in the 1.25 mg group (abdominal discomfort, diarrhoea, ALT increased), 8 subjects in the 5 mg group (feeling abnormal in 4 subjects; feeling abnormal/blood uric acid increased in 2 subjects; abdominal pain/diarrhoea/feeling abnormal/blood uric acid increased, nausea in 1 subject each), and 9 subjects in the 20 mg group (pruritus generalised in 2 subjects; ocular hyperaemia/blood uric acid increased/hypoaesthesia/dysuria, erythema/nausea/pruritus, palpitations/blood uric acid increased/pruritus/pruritus genital, erythema/pruritus, erythema/pruritus generalised, feeling abnormal/hypoaesthesia, pruritus in 1 subject each).

No adverse events led to death, and none of the adverse events were classified as serious. Adverse events led to study drug treatment discontinuation in 1 of 9 subjects (feeling abnormal) in the 5 mg group.

7.1.3 Study on the effects of rate of administration in healthy Japanese adults (Study 263-[redacted]-005, CTD 5.3.3.1-03 [study period, [redacted] to [redacted] 20[redacted]])

A 6-treatment, 3-period, double-blind, randomized study was conducted in 18 healthy Japanese adult men to investigate the effect of infusion rate on safety, PK, and PD in the single intravenous administration of OPC-61815. Subjects received a single dose of placebo, 7.5, or 15 mg of OPC-61815 in each period: by 2-hour

infusion in Period 1, by 5-minute infusion in Period 2, (72 hours after the start of Period 1), and by 1-minute infusion in Period 3 (144 hours after the start of Period 1).

The incidence of adverse events[8)] in the placebo group, 7.5 mg group, and 15 mg group were as follows: in Period 1, 83.3% (5 of 6 subjects), 66.7% (4 of 6 subjects), and 33.3% (2 of 6 subjects), respectively; in Period 2, 50.0% (3 of 6 subjects), 83.3% (5 of 6 subjects), and 83.3% (5 of 6 subjects), respectively; and in Period 3, 66.7% (4 of 6 subjects), 100% (5 of 5 subjects), and 83.3% (5 of 6 subjects), respectively. Adverse events occurring in ≥2 subjects in any group in each period were as follows: in Period 1, activated partial thromboplastin time prolonged (1 of 6 subjects in the placebo group, 2 of 6 subjects in the 7.5 mg group, and 0 of 6 subjects in the 15 mg group; the same applies hereinafter for the sequence of groups); in Period 2, erythema (2 of 6 subjects, 3 of 6 subjects, and 4 of 6 subjects), pruritus (0 of 6 subjects, 3 of 6 subjects, and 4 of 6 subjects), feeling abnormal (0 of 6 subjects, 1 of 6 subjects, and 4 of 6 subjects), hyperhidrosis (0 of 6 subjects, 2 of 6 subjects, and 2 of 6 subjects), feeling hot (1 of 6 subjects, 2 of 6 subjects, and 0 of 6 subjects); in Period 3, erythema (3 of 6 subjects, 5 of 5 subjects, and 5 of 6 subjects), feeling abnormal (0 of 6 subjects, 3 of 5 subjects, and 5 of 6 subjects), pruritus (0 of 6 subjects, 4 of 5 subjects, and 4 of 6 subjects), feeling hot (1 of 6 subjects, 2 of 5 subjects, and 0 of 6 subjects), hyperhidrosis (1 of 6 subjects, 0 of 5 subjects, and 2 of 6 subjects). Among these events, a causal relationship to the study drug could not be ruled out for the following: in Period 1, in 4 of 6 subjects (66.7%) in the placebo group (ventricular extrasystoles, pruritus, activated partial thromboplastin time prolonged, blood pressure decreased), 2 of 6 subjects (33.3%) in the 7.5 mg group (activated partial thromboplastin time prolonged in 2 subjects), and 1 of 6 subjects (16.7%) in the 15 mg group (headache/diarrhoea); in Period 2, 2 of 6 subjects (33.3%) in the placebo group (erythema/feeling hot, erythema in 1 subject each), 4 of 6 subjects (66.7%) in the 7.5 mg group (erythema/pruritus/feeling abnormal/feeling hot, erythema/pruritus/feeling hot/hyperhidrosis, erythema/pruritus, hyperhidrosis in 1 subject each), and 5 of 6 subjects (83.3%) in the 15 mg group (erythema/pruritus/feeling abnormal in 2 subjects; erythema/hyperhidrosis/itchy sensation/feeling abnormal, dyspnoea/hyperhidrosis/itchy sensation/feeling abnormal, erythema in 1 subject each); in Period 3, 4 of 6 subjects (66.7%) in the placebo group (erythema in 2 subjects; erythema/hyperhidrosis, feeling hot in 1 subject each), 5 of 5 subjects (100%) in the 7.5 mg group (epigastric discomfort/erythema/pruritus/feeling abnormal/feeling hot, erythema/pruritus/feeling abnormal, erythema/pruritus/feeling hot, nausea/erythema/feeling abnormal, erythema/pruritus in 1 subject each), and 5 of 6 subjects (83.3%) in the 15 mg group (erythema/hyperhidrosis/pruritus/feeling abnormal, erythema/pruritus/feeling abnormal in 2 subjects each; diarrhoea/erythema/feeling abnormal in 1 subject).

No adverse events led to death, and none of the adverse events were classified as serious, or led to study drug treatment discontinuation.

8) Adverse events data were to be collected from study drug administration up to 3 days post-dose in Periods 1 and 2, and in Period 3, from study drug administration in Period 3 up to the follow-up visit (7-13 days post-dose).

7.1.4 Multiple intravenous dose study in patients with congestive heart failure (Study 263-102-00001, CTD 5.3.3.2-01 [study period, November 2017 to April 2018])

A double-blind, randomized, parallel-group study was conducted at 41 study centers (target sample size, 55 subjects [11 subjects per group]) in patients with congestive heart failure who had excessive fluid retention despite treatment with conventional diuretics other than V_2-receptor antagonists. In this study, intravenous doses of 2, 4, 8, or 16 mg of OPC-61815, or oral doses of 15 mg of tolvaptan were administered in order to find the dose of OPC-61815 that achieves tolvaptan exposure equivalent to that with oral tolvaptan 15 mg.

This study consisted of (1) the screening period, (2) run-in period (3 days), (3) treatment period (6 days), and (4) follow-up period. Subjects were randomly assigned to the treatment groups at the start of treatment period (Day 1).

Eligible patients are those (aged 20-85 years inclusive) with congestive heart failure who meet the following main inclusion criteria:

- Patients are on treatment with any of the following oral diuretics (including those who are scheduled to receive treatment from the run-in period): loop diuretics equivalent to ≥40 mg/day of furosemide, concomitant use of a loop diuretic and a thiazide diuretic at any dose, or concomitant use of a loop diuretic and an aldosterone antagonist or potassium-sparing diuretic at any dose;
- Patients are presenting with lower limb edema, pulmonary congestion, and/or jugular venous distension due to excessive fluid retention;
- Patients are capable of taking oral tablets;

Only subjects who meet the following criteria in the run-in period and are determined by the investigator or subinvestigator to be suitable for enrollment in the treatment period were to start the treatment period.

- Subjects have been given diuretics with no change in dose or regimen during the run-in period;
- Subjects have ≤1.0 kg change in body weight over 2 days prior to the start of treatment period;
- Subjects are presenting with lower limb edema, pulmonary congestion, and/or jugular venous distension on the last day of the run-in period.

Patients were excluded from the study if they had acute heart failure, patients with mainly noncardiogenic congestive symptoms, patients who are unable to sense thirst or who have difficulty with fluid intake, and patients with serum sodium >147 mEq/L or serum potassium >5.5 mEq/L.

Intravenous doses of 2, 4, 8, or 16 mg of OPC-61815 (by 1-hour infusion), or oral doses of 15 mg of tolvaptan were to be administered once daily for 5 days after breakfast. Use of V_2-receptor antagonists, heart failure medications (injections) (i.e., human atrial natriuretic peptide [hANP], phosphodiesterase [PDE] III inhibitors, catecholamine, and colforsin), diuretic injections, and drugs or any substance that may inhibit or induce CYP3A4 was prohibited. Modification of dosage regimens of diuretics (oral) other than V_2-receptor antagonists, and drugs that may affect fluid retention or underlying disease was allowed if the dose and regimen were kept unchanged from the start of the run-in period to the end-of-treatment examination (Day 6).

Of the randomized 61 subjects, 60 subjects received study drug treatment (13 subjects in the OPC-61815 2 mg group, 12 subjects in the 4 mg group, 12 subjects in the 8 mg group, 11 subjects in the 16 mg group, and 12 subjects in the oral tolvaptan 15 mg group) and were included in the safety analysis set. Among these, 5 subjects were withdrawn from the study (2 subjects in the 4 mg group and 3 subjects in the oral tolvaptan 15 mg group) due to "adverse events" (2 subjects in the 4 mg group and 1 subject in the oral tolvaptan 15 mg group) and "elevation in aspartate aminotransferase (AST) or ALT" (2 subjects in the oral tolvaptan 15 mg group).

The incidence of adverse events occurring from the start of treatment period (Day 1) to the follow-up visit (Days 12-15) in the OPC-61815 2 mg, 4 mg, 8 mg, 16 mg groups, and oral tolvaptan 15 mg group were 53.8% (7 of 13 subjects), 58.3% (7 of 12 subjects), 33.3% (4 of 12 subjects), 72.7% (8 of 11 subjects), and 83.3% (10 of 12 subjects), respectively. Among these events, a causal relationship to the study drug could not be ruled out for the following: 2 subjects in the 2 mg group (dry mouth, electrocardiogram QT prolonged in 1 subject each), 2 subjects in the 4 mg group (atrial fibrillation/petechiae/abdominal pain upper/acute kidney injury, hyperkalaemia/renal impairment in 1 subject each), 2 subjects in the 16 mg group (blood creatinine increased/blood urea increased, headache in 1 subject each), and 5 subjects in the oral tolvaptan 15 mg group (blood urea increased/blood uric acid increased, liver disorder, hypernatraemia, renal impairment, hypotension in 1 subject each).

No adverse events led to death. Serious adverse events occurred in 1 of 12 subjects (8.3%, atrial fibrillation/endocarditis) in the 4 mg group, and a causal relationship to the study drug could not be ruled out for atrial fibrillation. Adverse events led to study drug treatment discontinuation in 2 of 12 subjects in the 4 mg group (16.7%, atrial fibrillation, renal impairment in 1 subject each) and 3 of 12 subjects in the oral tolvaptan 15 mg group (25.0%, hepatic congestion, liver disorder, renal impairment in 1 subject each).

7.2 Phase III studies

7.2.1 Non-inferiority study comparing intravenous OPC-61815 to oral tolvaptan (Study 263-102-00003, CTD 5.3.5.1-01 [study period, January 2019 to July 2020])

A double-blind, randomized, parallel-group study was conducted at 72 study centers (target sample size, 288 subjects[9)] [144 subjects/group]) to confirm the non-inferiority of once-daily intravenous OPC-61815 16 mg to once-daily oral tolvaptan 15 mg in terms of the improvement in fluid retention (change in body weight) in patients with congestive heart failure who had excessive fluid retention despite treatment with conventional diuretics other than V_2-receptor antagonists.

This study consisted of (1) the screening period, (2) run-in period (3 days), (3) treatment period (6 days), and (4) follow-up period. Subjects were randomly assigned to the treatment groups at the start of treatment period.

9) Assuming the mean (± standard deviation) change from baseline in body weight (kg) to the final administration is −1.30 ± 1.25 for both the OPC-61815 group and oral tolvaptan group, the number of subjects required for this study was determined to be 288 (144 subjects/group) to demonstrate that the upper limit of the two-sided 95% CI for the difference in body weight change between groups (OPC-61815 – oral tolvaptan) is below the non-inferiority margin of 0.48 at a detection power of 90%.

Eligible patients are those (aged 20-85 years inclusive) with congestive heart failure who meet the following main inclusion criteria:

- Patients are on treatment with any of the following oral diuretics (including those who are scheduled to receive treatment from the run-in period): loop diuretics equivalent to 40 mg/day of furosemide, concomitant use of a loop diuretic and a thiazide diuretic at any dose, or concomitant use of a loop diuretic and an aldosterone antagonist or potassium-sparing diuretic at any dose;
- Patients are presenting with lower limb edema, pulmonary congestion, and/or jugular venous distension due to excessive fluid retention;
- Patients are capable of taking oral tablets;

Only subjects who meet the following criteria in the run-in period and are determined by the investigator or subinvestigator to be suitable for enrollment in the treatment period were to start the treatment period. Subjects were to be hospitalized from the day before the start of run-in period (Day −4) to at least the end of the treatment period (Day 6).

- Subjects have been given diuretics with no change in dose or regimen during the run-in period;
- Subjects have ≤1.0 kg change in body weight over 2 days prior to the start of treatment period;
- Subjects are presenting with lower limb edema, pulmonary congestion, and/or jugular venous distension on the last day of the run-in period.

Patients were excluded from the study if they had acute heart failure, patients with mainly noncardiogenic congestive symptoms, patients who are unable to sense thirst or who have difficulty with fluid intake, and patients with serum sodium <125 mEq/L or >147 mEq/L, or serum potassium >5.5 mEq/L.

Intravenous doses of 16 mg of OPC-61815 (by 1-hour infusion), or oral doses of 15 mg of tolvaptan were to be administered once daily for 5 days after breakfast. Use of V_2-receptor antagonists, heart failure medications (injections) (i.e., hANP, PDE III inhibitors, catecholamine, and colforsin), diuretic injections, and drugs or any substance that may inhibit or induce CYP3A4 was prohibited. Modification of dosage regimens of diuretics (oral) other than V_2-receptor antagonists, sodium glucose cotransporter 2 (SGLT2) inhibitors, and drugs that may affect fluid retention or underlying disease was allowed if the dose and regimen were kept unchanged from the start of the run-in period to the end-of-treatment examination.

All 294 randomized subjects (149 subjects in the OPC-61815 group and 145 subjects in the oral tolvaptan group) received study drug treatment and were included in the safety analysis set. Of the safety analysis set, all 294 subjects had post-treatment body weight data, and were included in the full analysis set (FAS), which was used for the primary efficacy analysis. Among these, 14 of 149 subjects (9.4%) in the OPC-61815 group and 10 of 145 subjects (6.9%) in the oral tolvaptan group were withdrawn from the study mainly due to "adverse events" in 11 subjects (8 subjects in the OPC-61815 group and 3 subjects in the oral tolvaptan group), "protocol deviation" in 6 subjects (4 subjects in the OPC-61815 group and 2 subjects in the oral tolvaptan

group), “investigator’s decision” in 5 subjects (2 subjects in the OPC-61815 group and 3 subjects in the oral tolvaptan group), “withdrawal of consent” in 2 subjects in the oral tolvaptan group.

Table 26 shows the change from baseline (before study drug administration on Day 1) in body weight, the primary endpoint, to final administration (on the day following the final study drug administration). The upper limit of the two-sided 95% CI for the difference in body weight change between groups (OPC-61815 – oral tolvaptan) is lower than the acceptable non-inferiority margin of 0.48, demonstrating the non-inferiority of OPC-61815 to oral tolvaptan. Figure 2 shows the change from baseline on a daily basis.

Table 26. Change from baseline in body weight to final dose administration (FAS)

	OPC-61815 (N = 149)	Oral tolvaptan (N = 145)
Baseline (kg) (Mean ± standard deviation)	149 subjects 61.68 ± 14.28	145 subjects 59.48 ± 13.20
At final dose administration (kg) (Mean ± standard deviation[a])	149 subjects 59.97 ± 13.92	144 subjects 58.14 ± 12.82
Change from baseline (kg) Least squares mean [two-sided 95% CI][a, b]	149 subjects −1.67 [−1.93, −1.41]	144 subjects −1.36 [−1.62, −1.10]
Difference from the oral tolvaptan group (kg) Least squares mean [two-sided 95% CI][a, b]	−0.31 [−0.68, 0.06]	—

a, For a missing value on the day following final study drug administration, the last measured value up until that day was used.
b, an analysis of covariance (ANCOVA) model with treatment as the fixed effect factor and baseline body weight as a covariate

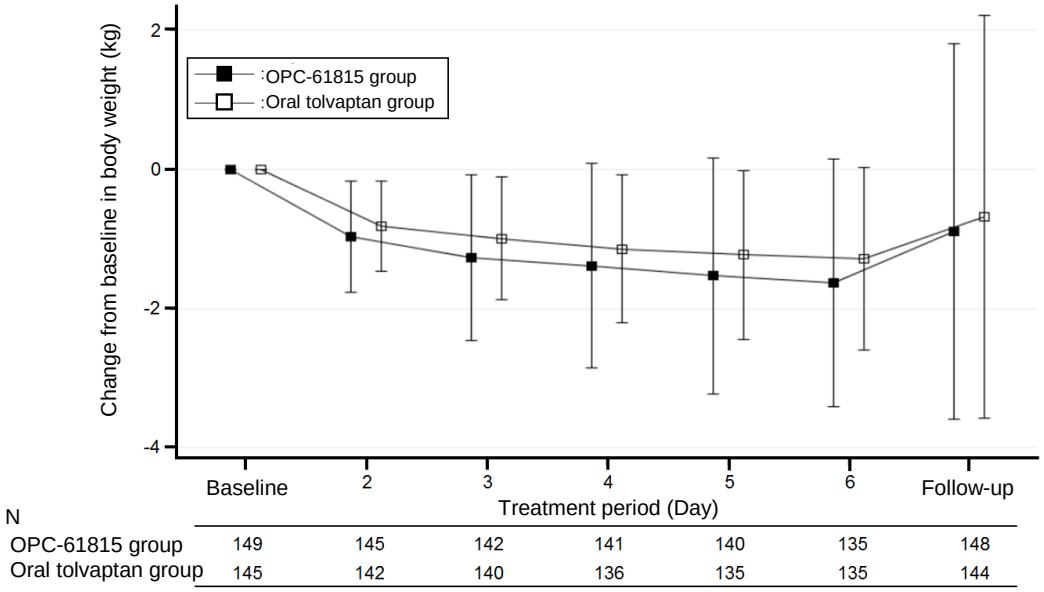

Figure 2. Change from baseline in body weight (FAS, mean ± standard deviation)

Table 27 shows the results for main secondary endpoints.

Table 27. Congestive symptoms and NYHA functional classification at final dose administration (FAS)

		OPC-61815	Oral tolvaptan
Lower limb edema	% improved[a, b]	68.9 (84/122)	75.7 (84/111)
	% disappeared[a, c]	59.8 (73/122)	58.6 (65/111)
Pulmonary congestion	% improved[a, b]	56.1 (69/123)	64.7 (77/119)
	% disappeared[a, c]	43.1 (53/123)	52.9 (63/119)
Change in jugular venous distension (cm)[a, d] (Least squares mean [two-sided 95% CI][a, e])		52 subjects −2.89 [−3.45, −2.33]	59 subjects −3.15 [−3.68, −2.62]
Change in cardiothoracic ratio (%)[a, d] (Least squares mean [two-sided 95%][a, e])		148 subjects −2.06 [−2.62, −1.51]	143 subjects −1.99 [−2.56, −1.42]
NYHA functional classification proportion of subjects improved[a, f]		44.9 (61/136)	42.5 (51/120)

a, For a missing value on the day following final study drug administration, the last measured value up until that day was used.
b, when subjects presenting with symptoms at baseline were assessed for the severity using a 4-level rating system ("absent," "mild," "moderate," and "severe"), the proportion of subjects whose symptoms improved by ≥1 level compared with baseline or whose symptoms disappeared (number of subjects improved / number of subjects analyzed, by percentage)
c, among subjects presenting with symptoms at baseline, the proportion of subjects whose symptoms disappeared (number of subjects improved / number of subjects analyzed, by percentage)
d, in subjects with measured values at baseline, the change from baseline to the day following final study drug administration
e, an ANCOVA model with treatment as the fixed effect factor and the baseline value as a covariate
f, among subjects who were assessed as NYHA Class ≥ II at baseline, the proportion of subjects whose symptoms improved by ≥1 category on the day following final study drug administration (number of subjects improved / number of subjects analyzed, by percentage)

The incidence of adverse events occurring from the start of treatment period (Day 1) to the follow-up visit (7-10 days post-final dose) was 55.7% (83 of 149 subjects) in the OPC-61815 group and 58.6% (85 of 145 subjects) in the oral tolvaptan group. Table 28 shows adverse events occurring in ≥2% of subjects in either group.

Table 28. Adverse events occurring in ≥2% of subjects in either group (safety analysis set)

	OPC-61815 (N = 149)	Oral tolvaptan (N = 145)
Thirst	8.7 (13)	11.0 (16)
Dehydration	10.1 (15)	4.1 (6)
Constipation	6.0 (9)	6.2 (9)
Dry mouth	2.7 (4)	5.5 (8)
Hyperkalaemia	6.0 (9)	2.1 (3)
Hypotension	2.0 (3)	3.4 (5)
Anaemia	2.0 (3)	2.8 (4)
Hypernatraemia	2.7 (4)	2.1 (3)
Pyrexia	2.7 (4)	1.4 (2)
Rash	2.0 (3)	2.1 (3)
Renal impairment	2.7 (4)	1.4 (2)
Atrial fibrillation	1.3 (2)	2.1 (3)
Ventricular tachycardia	2.0 (3)	1.4 (2)
Hyperuricaemia	2.7 (4)	0.7 (1)
Blood potassium increased	2.0 (3)	0.7 (1)
Nausea	2.0 (3)	0 (0)
Eczema	2.0 (3)	0 (0)

Incidence, % (n)

No adverse events led to death. The incidence of serious adverse events was 4.0% in the OPC-61815 group (6 of 149 subjects; hyperkalaemia, cardiac failure, cardiac failure acute, sepsis, gastric antral vascular ectasia, atrial fibrillation in 1 subject each) and 3.4% in the oral tolvaptan group (5 of 145 subjects; coronary artery stenosis, ventricular tachycardia, sinus node dysfunction, urinary tract infection, cerebral infarction in 1 subject each). Among these events, a causal relationship to the study drug could not be ruled out for hyperkalaemia in 1 subject in the OPC-61815 group. The incidence of adverse events leading to study drug treatment discontinuation was 5.4% in the OPC-61815 group (8 of 149 subjects; blood sodium increased in 2 subjects; dehydration/hypernatraemia, dehydration/blood creatinine increased, dehydration, renal impairment, rapid correction of hyponatraemia, congestive hepatopathy in 1 subject each) and 2.1% in the oral tolvaptan group (3 of 145 subjects; dry mouth/blood pressure decreased, hypernatraemia, chronic kidney disease in 1 subject each).

7.2.2 Study to evaluate safety in patients who have difficulty with or are incapable of oral intake (Study 263-102-00004, CTD 5.3.5.2-01 [study period, June 2019 to June 2020])

An open-label, uncontrolled study was conducted at 30 study centers in patients with congestive heart failure who had excessive fluid retention despite treatment with conventional diuretics other than V_2-receptor antagonists and who had difficulty with or were incapable of oral intake to evaluate the safety and efficacy of OPC-61815 (target sample size, 40 subjects).

Eligible patients are those (aged 20-85 years inclusive) with congestive heart failure who meet the following main inclusion criteria:

- Patients who are on treatment with loop diuretic injection equivalent to intravenous furosemide ≥20 mg/day;
- Patients are presenting with lower limb edema, pulmonary congestion, and/or jugular venous distension due to excessive fluid retention;
- Patients who are determined by the investigator or subinvestigator to have difficulty or be incapable of oral intake (including patients who are determined by the investigator or subinvestigator to require nothing by mouth management).

Patients ineligible for the study include patients who have difficulty with spontaneous respiration or who have been on tracheal intubation under sedative therapy, patients with severe disturbed consciousness (i.e., coma or stupor), and patients with serum or plasma sodium concentration <125 mEq/L, serum or plasma sodium concentration >147 mEq/L, or serum or plasma potassium >5.5 mEq/L.

Subjects were to receive intravenous doses of OPC-61815 (by 1-hour infusion) once daily, beginning at a starting dose of 8 mg. Eligibility for dose escalation was to be assessed on Day 2 or Day 3, and if the dose escalation criteria shown in Table 29 were met, the dose was to be increased to 16 mg of OPC-61815 (subjects undergoing dose escalation to 16 mg), if the criteria were not met, treatment was to continue at 8 mg of OPC-61815 (subjects continuing with the 8 mg dose). If dose reduction becomes necessary after dose escalation because of adverse events associated with the aquaretic effect, the dose may be reduced to 8 mg. Once the dose

had been reduced, re-escalation was not allowed. The infusion solution volume was to be adjusted based on the measurement of blood pressure/pulse, body weight, serum sodium concentration, serum potassium concentration, urine volume, water intake, and other parameters at least 3 times on the day treatment starts, at least twice on the day of dose escalation, and at least once daily for the rest of the treatment period. The maximum duration of treatment was 5 days; however, treatment was to be terminated earlier if the investigator or subinvestigator determined that either of the following was met: (1) all congestive symptoms resolved and no further improvement in fluid retention was deemed necessary, or (2) the subject became capable of fluid management by oral intake alone. The results showed that while 38 subjects continued to receive 8 mg, the dose in 7 subjects was escalated to 16 mg. Table 30 shows the results of treatment duration. All 7 subjects underwent dose escalation on Day 2, and none of the subjects underwent dose reduction to 8 mg once the dose had been increased. The concomitant use of drugs such as V_2-receptor antagonists, drugs or any substance that may inhibit or induce CYP3A4 was prohibited.

Table 29. Dose escalation criteria

(1) Day 2 dose escalation criteria	(2) Day 3 dose escalation criteria
When all of the following criteria 1) through 4) are met: 1) When either of the following is met: • Increase in daily urine volume from baseline is ≤500 mL: any congestive symptom[a] is present • Increase in daily urine volume from baseline is >500 mL, or cannot be definitely determined to be ≤500 mL: body weight did not decrease as compared with predose with the study drug, and any congestive symptom[a] is present 2) The serum sodium concentration[b] at predose on Day 2 is ≤147 mEq/L 3) An increase of >10 mEq/L in serum sodium concentration[b] is not observed within 24 hours of the start of study drug administration on Day 1 4) In the opinion of the investigator or subinvestigator, no safety concerns have arisen since the start of study drug administration on Day 1.	These criteria apply when only 2) of the "(1) Day 2 dose escalation criteria" was not met: When all of the following criteria 1) through 4) are met: 1) Body weight did not decrease as compared with predose on Day 2, and any congestive symptom[a] is present 2) The serum sodium concentration[b] at predose on Day 3 is ≤147 mEq/L 3) An increase of >10 mEq/L in serum sodium concentration[b] is not observed within 24 hours of the start of study drug administration on Day 2 4) In the opinion of the investigator or subinvestigator, no safety concerns have arisen since the start of study drug administration on Day 2.

a, lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, cardiothoracic ratio, pulmonary rales, or cardiac third sound

b, If serum sodium concentration measurement is difficult to perform at the study site, plasma sodium concentrations were used for assessment

Table 30. Duration of treatment

	Subjects who continued to receive 8 mg (N = 38)	Subjects who underwent dose escalation to 16 mg (N = 7)	Overall (N = 45)
1 day	34.2 (13)	—	28.9 (13)
2 days	36.8 (14)	57.1 (4)	40.0 (18)
3 days	13.2 (5)	14.3 (1)	13.3 (6)
4 days	0 (0)	14.3 (1)	2.2 (1)
5 days	15.8 (6)	14.3 (1)	15.6 (7)

Percentage, % (n)

All 45 subjects who received study drug treatment were included in the safety analysis set. Of the safety analysis set, all 45 subjects had post-treatment efficacy data, and were included in the efficacy analysis set.

Four of 45 subjects (8.9%) were withdrawn from the study due to "decision by the investigator" (2 subjects), "adverse events" (1 subject), and "other" (1 subject).

Table 31 shows the change from baseline (before study drug administration on Day 1) in body weight to final administration (on the day following the final study drug administration). Table 32 shows the results for congestive symptoms and NYHA functional classification.

Table 31. Change from baseline in body weight to final dose administration (efficacy analysis set)

	Subjects who continued to receive 8 mg (N = 38)	Subjects who underwent dose escalation to 16 mg (N = 7)	Overall (N = 45)
Baseline Mean ± standard deviation	38 subjects 65.02 ± 18.73	6 subjects 58.40 ± 13.74	44 subjects 64.12 ± 18.14
At final dose administration Mean ± standard deviation [a]	38 subjects 61.88 ± 17.65	7 subjects 54.01 ± 14.46	45 subjects 60.66 ± 17.28
Change from baseline Mean [two-sided 95% CI][a]	38 subjects −3.14 [−4.03, −2.24]	6 subjects −2.20 [−3.12, −1.28]	44 subjects −3.01 [−3.79, −2.23]

a, For a missing value on the day following final study drug administration, the last measured value up until that day was used.

Table 32. Congestive symptoms and NYHA functional classification at final dose administration (efficacy analysis set)

		Subjects who continued to receive 8 mg (N = 38)	Subjects who underwent dose escalation to 16 mg (N = 7)	Overall (N = 45)
Lower limb edema	% improved[a, b]	71.0 (22/31)	85.7 (6/7)	73.7 (28/38)
	% disappeared[a, c]	51.6 (16/31)	42.9 (3/7)	50.0 (19/38)
Pulmonary congestion	% improved[a, b]	78.9 (30/38)	100.0 (6/6)	81.8 (36/44)
	% disappeared[a, c]	23.7 (9/38)	16.7 (1/6)	22.7 (10/44)
Change in jugular venous distension (cm)[a, d]		14 subjects −4.39 [−5.92, −2.87]	5 subjects −3.14 [−4.30, −1.98]	19 subjects −4.06 [−5.20, −2.93]
Dyspnea	Paroxysmal nocturnal dyspnea, % disappeared[a, c]	95.8 (23/24)	80.0 (4/5)	93.1 (27/29)
	Orthopnea[a, c] % disappeared	85.7 (24/28)	80.0 (4/5)	84.8 (28/33)
	Dyspnea % improved[a, e]	100.0 (30/30)	83.3 (5/6)	97.2 (35/36)
Change in cardiothoracic ratio (%)[a, d]		38 subjects −1.83 [−3.22, −0.45]	7 subjects −4.74 [−8.00, −1.49]	45 subjects −2.29 [−3.55, −1.02]
NYHA functional classification proportion of subjects improved[a, f]		67.6 (23/34)	85.7 (6/7)	70.7 (29/41)

a, For a missing value on the day following final study drug administration, the last measured value up until that day was used.
b, when subjects presenting with symptoms at baseline were assessed for the severity using a 4-level rating system ("absent," "mild," "moderate," and "severe"), the proportion of subjects whose symptoms improved by ≥1 level compared with baseline or whose symptoms disappeared (number of subjects improved / number of subjects analyzed, by percentage)
c, among subjects presenting with symptoms at baseline, the proportion of subjects whose symptoms disappeared (number of subjects improved / number of subjects analyzed, by percentage)
d, in subjects with measured values at baseline, the change from baseline to final dose administration
e, in subjects presenting with symptoms at baseline, when dyspnea symptoms were assessed as compared with those of the screening period using the 7-level scale from "markedly deteriorated" through "markedly improved," the proportion of subjects whose symptoms were either "mildly improved," "moderately improved," or "markedly improved (number of subjects improved / number of subjects analyzed, by percentage)
f, among subjects who were assessed as NYHA Class ≥ II at baseline, the proportion of subjects whose symptoms improved by ≥1 category at final dose administration (number of subjects improved / number of subjects analyzed, by percentage)

The incidence of adverse events occurring from the start of treatment period (Day 1) to the follow-up visit (7-10 days post-final dose) was 76.3% (29 of 38 subjects) in subjects continuing with the 8 mg dose and 85.7% (6 of 7 subjects) in subjects undergoing dose escalation to 16 mg. Table 33 shows adverse events occurring in ≥2 subjects in the overall group.

Table 33. Adverse events occurring in ≥2 subjects (safety analysis set)

	Subjects continuing with 8 mg dose (N = 38)	Subjects undergoing dose escalation to 16 mg (N = 7)	Overall (N = 45)
Constipation	28.9 (11)	14.3 (1)	26.7 (12)
Hepatic dysfunction	13.2 (5)	0 (0)	11.1 (5)
Hypokalaemia	5.3 (2)	28.6 (2)	8.9 (4)
Urinary tract infection	10.5 (4)	0 (0)	8.9 (4)
Insomnia	10.5 (4)	0 (0)	8.9 (4)
Delirium	5.3 (2)	14.3 (1)	6.7 (3)
Ventricular tachycardia	7.9 (3)	0 (0)	6.7 (3)
Injection site inflammation	5.3 (2)	0 (0)	4.4 (2)
Eczema	5.3 (2)	0 (0)	4.4 (2)
Dry skin	5.3 (2)	0 (0)	4.4 (2)
Back pain	5.3 (2)	0 (0)	4.4 (2)
Dry mouth	5.3 (2)	0 (0)	4.4 (2)
Haematochezia	5.3 (2)	0 (0)	4.4 (2)
Phlebitis	5.3 (2)	0 (0)	4.4 (2)

Incidence, % (n)

No adverse events led to death. The incidence of serious adverse events was 4.4% (2 of 45 subjects; ventricular tachycardia and pleural effusion in 1 subject each; both were subjects continuing with the 8 mg dose). Among these events, a causal relationship to the study drug could not be ruled out for ventricular tachycardia (1 subject). The incidence of adverse events leading to study drug treatment discontinuation was 2.2% (1 of 45 subjects; ventricular tachycardia in 1 subject continuing with the 8 mg dose).

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

The applicant's explanation about the clinical positioning of OPC-61815:

Diuretics are effective in improving fluid retention in patients with heart failure. The *Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure* (2017 revised edition) [in Japanese] recommend loop diuretics, thiazide diuretics, and aldosterone antagonists as Class I indication[10)] for improvement of congestive symptoms. In the guidelines, V_2-receptor antagonists are recommended as Class IIa indications[11)] for improvement of symptoms associated with fluid retention in patients with heart failure who have an inadequate response to loop and other diuretics.

Diuretics that can be administered intravenously are used when oral administration is difficult: such as in patients with acute heart failure who are using noninvasive positive pressure ventilation (NPPV) to mitigate

10) Evidence and/or general agreement that a given treatment/procedure is effective/useful.
11) The weight of evidence/opinion is in favor of usefulness/efficacy.

dyspnea symptoms, or who are experiencing decreased consciousness due to poor oxygenation; in patients with chronic heart failure whose swallowing function has deteriorated due to aging, cerebrovascular disorder, nerve degeneration, or other factors, or who are using gastrostomy or enterostomy. In patients with heart failure with fluid retention, intestinal edema associated with central venous pressure elevation occurs frequently (*Heart Vessels.* 2018;33:740-51). Because intestinal edema may cause disturbance of absorption via the intestinal tract due to inhibition of drug permeability from the gut lumen into epithelial cells and drug transport from the gastrointestinal epithelial cells into the portal blood flow (*Clin Pharmacokinet.* 2014;53:1083-114), the use of intravenous diuretics may be appropriate in patients who are capable of oral intake in cases where absorption disturbance is likely to be present due to intestinal edema. Intravenous diuretics currently available in Japan include loop diuretics and aldosterone antagonists. Loop diuretics are the first-line therapy, and concomitant use of an aldosterone antagonist is recommended when an adequate response is not obtained with loop diuretics, or depletion of electrolytes such as potassium in blood constitute a problem. However, there are cases where an adequate response cannot be obtained with conventional intravenous diuretics, or adverse drug reactions such as electrolyte depletion prevent administration of adequately high doses.

OPC-61815, a prodrug of tolvaptan, is synthesized by phosphorylation to improve water solubility and is developed as an intravenously injectable V_2-receptor antagonist. The clinical studies in patients with heart failure who had excessive fluid retention despite treatment with other diuretics such as loop diuretics demonstrated that OPC-61815 is noninferior to tolvaptan, an approved oral drug, in terms of the effect on body weight reduction, and improves congestive symptoms and NYHA functional classification. In addition, the results of the clinical study in patients with heart failure who had difficulty with or were incapable of oral intake showed that OPC-61815 can be expected to demonstrate efficacy [see Section "7.R.2 Efficacy"]. Furthermore, no significant safety problems were noted associated with OPC-61815 treatment [see Section "7.R.3 Safety"], suggesting that any potential risk may be mitigated or avoided by providing cautionary statements in the package insert.

The above discussions suggest that OPC-61815 can provide a new treatment option for fluid retention in heart failure when treatment with oral tolvaptan and other diuretics including loop diuretics are not sufficiently effective. In particular, OPC-61815 can be useful for the treatment of patients with acute heart failure or chronic heart failure during the acute exacerbation phase who are experiencing dyspnea or who have difficulty with or are incapable of taking oral medications due to treatment of dyspnea (e.g., NPPV, oxygen therapy), patients with heart failure who are capable of taking oral medications but may have absorption disturbance due to intestinal edema, etc., and patients who present with more intense symptoms of heart failure such as dyspnea and in whom an immediate effect is needed.

PMDA's view:

Diuretics are used to mitigate congestive symptoms such as dyspnea on exertion and edema in patients with heart failure. The approved oral tolvaptan has been administered to patients with fluid retention who had an inadequate response to loop and other diuretics, and are considered to be effective for fluid management in patients experiencing intense congestive symptoms due to diuretic resistance (*Guidelines for Diagnosis and*

Treatment of Acute and Chronic Heart Failure [2017 revised edition] [in Japanese]). Samtasu, which contains the active ingredient tolvaptan sodium phosphate, a prodrug of tolvaptan, has been demonstrated to be non-inferior to oral tolvaptan in terms of efficacy in Study 00003 conducted in patients with heart failure who had excessive fluid retention despite treatment with conventional diuretics and were capable of oral intake, and was suggested to be effective also in Study 00004 conducted in patients who had difficulty with or were incapable of oral intake [see Section "7.R.2 Efficacy"]. OPC-61815 has clinically acceptable safety in view of efficacy demonstrated in these clinical studies [see Sections "7.R.3 Safety" and "7.R.5 Indication and patient population"]. Therefore, it is concluded that OPC-61815 is clinically meaningful because it makes a new treatment option available for patients with heart failure who have fluid retention despite treatment with other diuretics such as loop diuretics and have difficulty with or are incapable of taking oral medications, and patients with heart failure who are capable of taking oral medications but in whom intravenous treatment is considered appropriate [see Section "7.R.5 Indication and patient population"].

7.R.2 Efficacy

7.R.2.1 Appropriateness of the design of Study 00003 and efficacy of OPC-61815

The applicant's explanation about the appropriateness of the design of Study 00003 and efficacy of OPC-61815:

Because tolvaptan is primarily involved in the activity of OPC-61815, and OPC-61815 was developed with the objective of achieving efficacy and safety similar to those of oral tolvaptan, the applicant planned to demonstrate the non-inferiority using oral tolvaptan as a comparator, based on the primary endpoint: change from baseline in body weight to final dose administration, which was used as the primary endpoint for the Japanese phase III study of oral tolvaptan (Study 156-06-002). Placebo-controlled studies of oral tolvaptan (Japanese phase II [Study 156-03-001] and phase III [Study 156-006-002] studies) were conducted with a treatment duration of 7 days; however, differences between the groups in the change from baseline in body weight to 5 days post-dose and thereafter were roughly stable. Therefore, for Study 00003, a treatment duration of 5 days was considered sufficient for evaluating the change in body weight. The non-inferiority margin was selected as follows. An ANCOVA analysis was performed for the change in body weight at final dose administration measured on the morning after Day 5 in Studies 156-03-001 and 156-06-002 using baseline body weight as a covariate. The least squares mean [95% CI] of the difference between the oral tolvaptan 15 mg group and placebo group was −0.99 kg [−1.57, −0.42] in Study 156-03-001 and −0.96 kg [−1.37, −0.55] in Study 156-06-002. Therefore, a non-inferiority margin of 0.48 kg was selected, which corresponds to half of the between-treatment group difference of Study 156-06-002, 0.96 kg. Typically, body weight gain associated with edema can be as much as several kilograms, and for a body weight increase of ≥2 kg within 3 days, the dose of the diuretic needs to be increased (*Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure* [2017 revised edition] [in Japanese]). Therefore, a clinically acceptable difference of 0.48 kg was considered reasonable because it is sufficiently less (approximately 1/4) than 2 kg, which requires the dose of the diuretic to be increased.

Study 00003 assessed the non-inferiority of 16 mg of OPC-61815 to 15 mg of oral tolvaptan in terms of the change from baseline in body weight to final dose administration, the primary endpoint [see Section "7.2.1

Non-inferiority study comparing intravenous OPC-61815 to oral tolvaptan"]. The congestive symptoms and NYHA functional classification, the secondary endpoints, at final administration in the OPC-61815 16 mg group showed disappearance of symptoms and improvements similar to those in the oral tolvaptan 15 mg group (Table 27). The above results are considered to demonstrate the efficacy of 16 mg of OPC-61815 for fluid retention in heart failure, with non-inferiority to 15 mg of oral tolvaptan.

No clinical studies have been conducted to evaluate the mid- to long-term prognosis of Japanese patients with heart failure for the present application. However, based on the data on oral tolvaptan, effects on prognosis are considered as follows. In a post-marketing clinical study (Study 156-10-005[12)]), in which oral tolvaptan 15 mg or placebo was administered orally once daily for up to 14 days to patients with congestive heart failure who had an inadequate response to other diuretics such as loop diuretics, the cumulative incidence of events (Kaplan-Meier estimates) of "death due to cardiovascular events or worsening of heart failure" up to Week 26 was 35.6% in the oral tolvaptan group and 43.8% in the placebo group. The results suggest that tolvaptan is unlikely to worsen mid- to long-term prognosis, and so far, there is no concern over the prognosis for patients receiving OPC-61815 either.

PMDA's view:
In view of the active ingredient of Samtasu and expected clinical positioning, the patient population, control drug, and primary endpoint defined for Study 00003, a confirmatory study, were all appropriate, and the non-inferiority margin is also appropriate based on the applicant's explanation. Given that Study 00003 demonstrated the non-inferiority of 16 mg of OPC-61815 to 15 mg of oral tolvaptan in terms of change in body weight, and that the results for secondary endpoints, congestive symptoms and NYHA functional classification did not differ markedly between the groups, the efficacy of 16 mg of OPC-61815 for fluid retention in patients with heart failure who have an inadequate response to other diuretics has been demonstrated, with non-inferiority to oral tolvaptan. At this point, tolvaptan is considered unlikely to have an adverse impact on the mid- to long-term prognosis in patients with heart failure as explained by the applicant.

7.R.2.2 Appropriateness of the design of Study 00004 and efficacy of OPC-61815

The applicant's explanation about the appropriateness of the design of Study 00004 and efficacy of OPC-61815:
OPC-61815 is expected to be used for the treatment of fluid retention in patients with heart failure who have difficulty with or are incapable of taking oral medications, the same patient population as that for the approved intravenous diuretics. In Study 00003, a confirmatory study; however, this patient population needed to be excluded for the comparison with oral tolvaptan. Study 00004 was therefore conducted to confirm the safety and efficacy of OPC-61815 in "patients who have difficulty with or are incapable of oral intake." This study was conducted as an uncontrolled study for reasons that included the following: patients eligible for Study 00004 had difficulty with taking oral tolvaptan and patients who required immediate improvement of

[12)] A double-blind, placebo-controlled, parallel-group study (50 subjects/group) conducted to assess the effect of short-term treatment of oral tolvaptan on mid- to long-term prognosis in patients with congestive heart failure who had an inadequate response to other diuretics such as loop diuretics. Subjects were to receive oral tolvaptan 15 mg or placebo once daily for up to 14 days (mean treatment duration, 4.8 days in the oral tolvaptan group and 4.9 days in the placebo group).

congestive symptoms were also included; in addition, the main purpose of Study 00004 was to evaluate safety. Eligible patients cannot have adequate fluid intake from drinking water; therefore, to reduce the risk of hypernatraemia and dehydration caused by the aquaretic effect immediately after the start of administration, OPC-61815 treatment was to be started at 8 mg, and eligibility for dose escalation was to be decided according to the dose escalation criteria.

The breakdown of the reasons for determining that patients enrolled in Study 00004 had difficulty with or were incapable of oral intake: "patient was on NPPV" (26 subjects), "aspiration risk (associated with the signs of heart failure)" (14 subjects), "dyspnea" (3 subjects), "deteriorated swallowing function (not associated with the signs of heart failure or treatment)" (1 subject), "pneumonia" (1 subject), "potential worsening of respiratory function" (1 subject), and "need for continuous use of an oxygen mask with reservoir bag" (1 subject). The study population was considered to contain patients who were incapable of swallowing solids or drinking water due to severe dyspnea, patients who wanted to avoid taking oral medications and drinking water to prevent aspiration risks, and patients who could not drink water when thirsty or at the desired timing because the patient was placed on NPPV or on oxygen therapy. The patient characteristics of Study 00004 were compared with those of Study 00003 to investigate the differences in the features of the two population (Table 34). There were more subjects presenting with progression of heart failure according to the NYHA functional classification at baseline in Study 00004 than in Study 00003, with the proportion of subjects who had moderate or severe lower limb edema and pulmonary congestion at baseline, jugular venous distension, and cardiothoracic ratio also being greater in Study 00004. The status of dyspnea was also assessed in Study 00004. The respiratory rate at baseline was 21.2 ± 5.0/minute, the proportion of subjects presenting with paroxysmal nocturnal dyspnea at baseline was 64.4% (29 of 45 subjects), and the proportion of subjects presenting with orthopnea was 73.3% (33 of 45 subjects), and the proportion of subjects presenting with subject-assessed dyspnea was 80.0% (33 of 45 subjects).

Table 34. Comparison of patient characteristics in Studies 00003 and 00004 (safety analysis set)

		00003 (N = 294)	00004 (N = 45)
NYHA functional classification[a]	Class I	12.2 (36)	0 (0)
	Class II	66.7 (196)	4.4 (2)
	Class III	20.4 (60)	26.7 (12)
	Class IV	0.7 (2)	64.4 (29)
	Not performed	0 (0)	4.4 (2)
Severity of lower limb edema[a]	Absent	20.7 (61)	15.6 (7)
	Mild	61.6 (181)	44.4 (20)
	Moderate	12.9 (38)	26.7 (12)
	Severe	4.8 (14)	13.3 (6)
Severity of pulmonary congestion[a]	Absent	17.0 (50)	2.2 (1)
	Mild	66.3 (195)	17.8 (8)
	Moderate	16.3 (48)	51.1 (23)
	Severe	0.3 (1)	28.9 (13)
Jugular venous distension[b]		4.2 ± 3.3 (111)	5.3 ± 2.5 (19)
Cardiothoracic ratio[c]		59.1 ± 7.5 (293)	62.7 ± 6.5 (45)

a, % (n)
b, Mean ± standard deviation (cm) (N)
c, % (N)

Tables 31 and 32 show the efficacy results for OPC-61815 in Study 00004. Body weight decreased from baseline following administration of OPC-61815, and there was a trend towards improvement in congestive symptoms and NYHA functional classification. While the uncontrolled study design represents a limitation in the efficacy evaluation, the change from baseline to final dose administration was roughly the same or greater than the results for the OPC-61815 group and tolvaptan group in Study 00003. The results suggest that OPC-61815 is also effective in patients who have difficulty with or are incapable of oral intake.

PMDA's view:

It is appropriate that the applicant verified the efficacy of OPC-61815 based on the results of Study 00003, which was conducted in patients who were capable of taking oral medications to compare OPC-61815 with oral tolvaptan. In addition, the applicant conducted Study 00004, an open-label, uncontrolled study, to confirm the safety and efficacy of OPC-61815 in patients who had difficulty with or were incapable of oral intake. The applicant's policy for development as well as the design for Study 00004 are appropriate. Although comparison of results from different studies precludes strict interpretation, data obtained from Study 00004 indicate that the efficacy is roughly the same or greater than that in the OPC-61815 group and oral tolvaptan group in Study 00003. Therefore, PMDA concluded that OPC-61815 can be expected to demonstrate clinically relevant efficacy also in patients who have difficulty with or are incapable of taking oral medications.

7.R.3 Safety

The data on the incidence of adverse events in the clinical studies submitted for the present application and discussions in the following sections indicated that OPC-61815 has higher risks associated with elevation of blood potassium concentration compared with oral tolvaptan. However, this can be managed through appropriate cautionary statement, and PMDA concluded that OPC-61815 has clinically acceptable safety in view of the efficacy demonstrated in Section "7.R.2 Efficacy."

7.R.3.1 Risks associated with increase in blood sodium concentration

The applicant's explanation about the risks associated with an increase in blood sodium concentration caused by OPC-61815:

Table 35 shows the incidence of hypernatraemia-related adverse events,[13)] events related to rapid increase in serum sodium concentration,[14)] and abnormalities in laboratory test results related to an increase in serum sodium concentration in the pooled analysis data from the studies that used oral tolvaptan as a comparator (pooled data from Studies 00001 and 00003; same applies hereinafter) and in Study 00004. Osmotic demyelination syndrome was not reported in any of the studies. In all studies, subjects were to be withdrawn from the study when serum sodium concentrations measured at the central or local laboratory (1) increased by ≥12 mEq/L from immediate predose value within 24 hours after the start of study drug administration, or (2) ≥155 mEq/L in the treatment period. In Study 00003, 4 subjects in the OPC-61815 group and 1 subject in the

13) Events classified as Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) "hypernatraemia," "blood sodium increased," and "blood sodium abnormal"

14) Events classified as MedDRA PTs "rapid correction of hyponatraemia," "osmotic demyelination syndrome," "blood electrolytes abnormal," "blood electrolytes decreased," "blood osmolarity abnormal," and "blood osmolarity decreased"

oral tolvaptan group met the criteria and were withdrawn from the study. In Studies 00001 and 00004, no subjects were withdrawn from the studies for meeting the criteria.

Table 35. Incidence of events related to an increase in blood sodium concentration in the clinical studies (safety analysis set)

	Pooled data from Studies 00001 and 00003		00004 (N = 45)
	OPC-61815 16 mg (N = 160)	Oral tolvaptan (N = 157)	
Hypernatraemia-related adverse events	3.8 (6)	2.5 (4)	2.2 (1)
Hypernatraemia	2.5 (4)	2.5 (4)	2.2 (1)
Blood sodium increased	1.3 (2)	0 (0)	0 (0)
Events related to rapid increase in serum sodium concentration	0.6 (1)	0 (0)	0 (0)
Rapid correction of hyponatraemia	0.6 (1)	0 (0)	0 (0)
Clinically significant increase in serum sodium concentration[a]	1.9 (3)	1.3 (2)	0 (0)
Increase in serum sodium concentration by ≥12 mEq/L from immediate predose value within 24 hours after the start of study drug administration	0.6 (1)	0.6 (1)	0 (0)
Serum sodium concentration of >147 mEq/L after the start of study drug administration	10.0 (16)	7.6 (12)	4.4 (2)

Incidence, % (n)

a, When graded on a 5-point scale (Grade 0 [≤145 mEq/L], Grade 1 [>145 mEq/L and ≤150 mEq/L], Grade 2 [>150 mEq/L and ≤157 mEq/L), Grade 3 [>157 mEq/L and ≤165 mEq/L], and Grade 4 [>165 mEq/L]), "clinically significant" was defined as worsening by ≥2 grades if the event was rated as ≤Grade 1 at baseline, and as worsening by ≥1 grade if the event was rated as ≥Grade 2 at baseline.

Events related to an increase in blood sodium concentration occurred more frequently in the OPC-61815 16 mg group than in the oral tolvaptan group. PMDA asked the applicant to explain the appropriateness of cautionary statement regarding increases in blood sodium concentration caused by OPC-61815:

The applicant's explanation:

The following details were confirmed regarding the events related to an increase in blood sodium concentration reported in the pooled data from Studies 00001 and 00003:

- During the treatment period (Days 1-6), the initial onset of adverse events or abnormalities in laboratory test results was on Day 1 in 2 of 160 subjects (1.3%), Day 2 in 5 of 160 subjects (3.1%), Day 3 in 9 of 154 subjects (5.8%), Day 4 in 3 of 153 subjects (2.0%) in the OPC-61815 16 mg group; while the onset was on Day 2 in 5 of 157 subjects (3.2%), Day 3 in 6 of 152 subjects (3.9%), and Day 5 in 1 of 146 subjects (0.7%) in the oral tolvaptan group. In the OPC-61815 16 mg group, events were reported as early as the day treatment started, suggesting that the onset of events may be earlier in patients treated with OPC-61815 than in those treated with oral tolvaptan.
- All hypernatraemia-related adverse events and events related to rapid increase in serum sodium concentration were either mild or moderate in severity, and resolved after the completion of study drug treatment or treatment discontinuation.
- In all groups, serum sodium concentrations started to increase at 8 to 12 hours post-initial dose to Day2, and then remained at around the same level throughout the treatment period. There were no clear differences across the groups in terms of the duration or degree of increase.

- In all of the 4 subjects (3 subjects in the OPC-61815 16 mg group and 1 subject in the oral tolvaptan group) who had a serum sodium increase of ≥12 mEq/L within 24 hours after the start of study drug administration (i.e., meeting the discontinuation criteria), serum sodium concentration was rising from baseline through Day 2.
- Among subjects whose serum sodium increased to >147 mEq/L after the start of study drug administration, there were no differences across the groups in terms of the degree of increase from baseline in serum sodium concentration.

In Study 00004, hypernatraemia occurred in 1 subject (147 mEq/L; the subject was among those continuing with the 8 mg dose) on Day 1; however, study drug treatment continued and ended on Day 3 (reported as early completion). Hypernatraemia resolved on Day 5 without treatment. Throughout the study period, no other hypernatraemia-related adverse events or events related to rapid increase in serum sodium concentration occurred. The following abnormalities in laboratory test results occurred. In 2 subjects (both were among those continuing with the 8 mg dose), serum sodium increased to >147 mEq/L after the start of study drug administration. The maximum increase from baseline was by 4 to 7 mEq/L, and the serum sodium concentration exceeded 147 mEq/L for the first time on Day 1 in 1 subject and Day 3 in the other subject. The findings are similar to those in the OPC-61815 16 mg group in the pooled data from Studies 00001 and 00003.

The above results indicated that events related to an increase in blood sodium concentration may occur after administration of OPC-61815 sooner than after administration of oral tolvaptan. However, the risks associated with an increase in blood sodium concentration were manageable through monitoring of blood sodium concentration according to the protocol-specified procedure for Study 00003. Cautionary statements should be included in the package insert (draft), equivalent to those provided for oral tolvaptan (e.g., monitoring, timing of laboratory tests). In patients who have difficulty with or are incapable of oral intake, it is difficult to adjust fluid balance by drinking water, which is likely to increase the risk that hypernatraemia or adverse drug reactions associated with the aquaretic effect of OPC-61815 will occur. Therefore, the following cautionary statements will be included in the package insert (draft) based on the procedure of Study 00004: if the serum sodium concentration has increased by >10 mEq/L within 24 hours after the start of OPC-61815 administration, it is not recommended to increase the dose of OPC-61815 on the following day; after dose-escalation, serum sodium concentrations should be measured 4 to 6 hours and 8 to 12 hours after administration of the escalated dose, equivalent to that implemented after the start of treatment.

PMDA's view:

Oral tolvaptan is contraindicated in "patients who are unable to sense thirst or who have difficulty with fluid intake" and "patients with hypernatremia," and the following cautionary statement is provided in the "Important Precautions" section of the package insert: "because the aquaretic effect is high within 24 hours after the start of administration of tolvaptan, the serum sodium concentration should be measured at least at 4 to 6 hours and 8 to 12 hours after the start of administration. From the day following the start of treatment, serum sodium concentrations should be measured every day for approximately 1 week, and if treatment continues thereafter, measurement should be taken at suitable intervals." On the other hand, in the clinical

studies, the incidence of events related to an increase in blood sodium concentration, and number of subjects who were withdrawn from the study due to "an increase in blood sodium concentration" were higher in subjects treated with OPC-61815 than those treated with oral tolvaptan. Additionally, events related to an increase in blood sodium concentration may occur sooner after administration of OPC-61815 than after administration of oral tolvaptan. However, such risks are manageable through monitoring of blood sodium concentration according to the procedure of Study 00003 except for patients who have difficulty with oral fluid intake. The applicant' plan to provide cautionary statements equivalent to those provided for oral tolvaptan is therefore appropriate. The appropriateness of cautionary statements regarding the risk of increase in blood sodium concentration in patients who have difficulty with oral fluid intake will be discussed further in Section "7.R.5 Indication and patient population."

7.R.3.2 Risks associated with the aquaretic effect

The applicant's explanation about the risks associated with the aquaretic effect of OPC-61815:

Table 36 shows the incidence of aquaretic adverse events[15)] in the pooled data from Studies 00001 and 00003, and in Study 00004. In the pooled data from Studies 00001 and 00003, the incidence of aquaretic adverse events in the OPC-61815 16 mg group does not differ from that in the oral tolvaptan group. The data by event show that thirst and dry mouth tended to occur more in the oral tolvaptan group while dehydration tended to occur more in the OPC-61815 16 mg group. All the adverse events were rated as mild or moderate in severity, and no events were classified as serious adverse events. Dehydration led to study drug treatment discontinuation in 3 subjects in the OPC-61815 16 mg group on Day 1 or Day 2. Among these, a causal relationship to the study drug was denied for 2 subjects, while the event in the remaining 1 subject was considered to have a causal relationship to the study drug, and the outcome of these events were reported as "not resolved." In the oral tolvaptan group, on the other hand, 1 subject developed blood pressure decreased/dry mouth on Days 3 to 4, resulting in study treatment discontinuation. Loss of consciousness did not occur in either group. One subject in the OPC-61815 16 mg group developed syncope accompanied by light-headedness and dizziness when changing to the standing position before urination at approximately 6 hours after the start of administration. A causal relationship to the study drug was denied because the event was not accompanied by anomalies in serum sodium concentration, the syncope event occurred when changing to a standing position, and it is unlikely that the subject was dehydrated based on the fluid balance from the start of study drug administration to the onset of symptoms. The subject continued receiving study drug treatment and the event resolved without treatment on the following day. Aquaretic adverse events that occurred in Study 00004 were mild thirst in 1 subject (Day 2) and mild dry mouth in 2 subjects (Day 1 and Day 2); these subjects were among those who had been continuing with the 8 mg dose. All of them were able to continue treatment.

15) MedDRA standardised MedDRA queries (MedDRA SMQ) "hypovolaemic shock conditions (narrow)"; MedDRA HLT "disturbances in consciousness NEC" and "vascular hypotensive disorders"; MedDRA PT "dry mouth," "dry throat," "lip dry," "mucosal dryness," "polydipsia," "thirst," "tongue dry," "dehydration," "anuria," "oliguria," "urine flow decreased," "urine output decreased," "weight decreased," "dizziness," "dizziness postural," "blood pressure decreased," "blood pressure ambulatory decreased," "blood pressure systolic decreased," "blood pressure diastolic decreased," "blood pressure systolic inspiratory decreased," and "blood pressure orthostatic decreased"

A thrombosis/hypercoagulable state-related adverse event[16] (cerebral infarction) occurred in 1 of 157 subjects (0.6%) in the oral tolvaptan group in the pooled data from Studies 00001 and 00003. No thrombosis/hypercoagulable state-related adverse events were reported in the OPC-61815 16 mg group or in Study 00004.

Table 36. Incidence of aquaretic adverse events in the clinical studies (safety analysis set)

	Pooled data from Studies 00001 and 00003		00004 (N = 45)
	OPC-61815 16 mg (N = 160)	Oral tolvaptan (N = 157)	
Aquaretic adverse events	21.3 (34)	24.8 (39)	6.7 (3)
Thirst	8.1 (13)	10.2 (16)	2.2 (1)
Dehydration	9.4 (15)	3.8 (6)	0 (0)
Dizziness postural	0 (0)	0.6 (1)	0 (0)
Syncope	0.6 (1)	0 (0)	0 (0)
Dizziness	0.6 (1)	1.3 (2)	0 (0)
Dry mouth	2.5 (4)	5.1 (8)	4.4 (2)
Lip dry	0.6 (1)	0 (0)	0 (0)
Blood pressure decreased	0.6 (1)	1.3 (2)	0 (0)
Hypotension	1.9 (3)	3.8 (6)	0 (0)
Orthostatic hypotension	0.6 (1)	0 (0)	0 (0)

Incidence, % (n)

The applicant explained that OPC-61815 may exert its aquaretic effect sooner than oral tolvaptan does. PMDA asked the applicant to explain the appropriateness of cautionary statement regarding the risks associated with the aquaretic effect of OPC-61815.

The applicant's explanation:

In the pooled data from Studies 00001 and 00003, although the incidence and severity of aquaretic adverse events in the OPC-61815 16 mg group did not differ markedly from those in the oral tolvaptan group, the data by event show that dehydration occurred frequently in the OPC-61815 16 mg group (Table 36). The applicant plans to provide a cautionary statement in the "Important Precautions" section in the package insert (draft) to the effect that dose reduction should be considered not only when thirst persists, but also when a dehydration symptom is present. The breakdown data of onset time in the treatment period (Days 1-6) show that aquaresis-related adverse events occurred in 6 of 160 subjects (3.8%) on Day 1, 9 of 160 subjects (5.6%) on Day 2, 11 of 154 subjects (7.1%) on Day 3, 3 of 153 subjects (2.0%) on Day 4, and 1 of 151 subjects (0.7%) on Day 6 in the OPC-61815 16 mg group; 10 of 157 subjects (6.4%) on Day 1, 11 of 157 subjects (7.0%) on Day 2, 4 of 152 subjects (2.6%) on Day 3, 6 of 150 subjects (4.0%) on Day 4, and 1 of 144 subjects (0.7%) on Day 6 in the oral tolvaptan group. There was no marked difference in the time of onset between the groups. One subject (OPC-61815 16 mg) developed dehydration on Day 1, while in the remaining subjects who developed dehydration, the onset time was Day 2 or later in both treatment groups, suggesting that the onset time in the OPC-61815 16 mg was not necessarily early. The above results indicated that, with the exception of patients who have difficulty with oral fluid intake, the risks for dehydration can be managed by providing cautionary statements equivalent to those provided for oral tolvaptan (e.g., monitoring, timing of laboratory tests).

[16] MedDRA SMQ "embolic and thrombotic events (narrow)"

Patients who have difficulty with oral intake cannot adjust the fluid balance effectively through drinking water by themselves, which is likely to increase the risk for hypernatraemia and other adverse drug reactions associated with the aquaretic effect of OPC-61815. In Study 00004, the urine excretion rate started to increase immediately after the start of administration of OPC-61815. The rise in urine excretion rate was particularly high in 0 to 1 hour and 1 to 2 hours after the start of administration, which was followed by decline at 2 hours after administration, but the urine excretion rate remained higher than the predose level. Therefore, the applicant decided to include cautionary statements in the package insert (draft) to the effect that due to concerns regarding dehydration, hypernatraemia, and other adverse drug reactions associated with excessive diuresis at an early stage after the start of treatment or at the time of dose escalation, body weight, blood pressure, pulse rate, and other parameters should be measured frequently; according to the procedure of Study 00004, the urine volume and water intake (including infusion volume) should be monitored at the following approximate time points: every hour up to 2 hours after the start of administration and every 2 hours thereafter up to 8 hours after the start of administration; after dose escalation, at 4 hours and 8 hours after the start of administration. The infusion volume should be adjusted based on the fluid balance.

PMDA's view:

The applicant's plan is to provide a cautionary statement in the package insert (draft) to the effect that dose reduction should be considered not only when thirst persists, but also when a dehydration symptom is present to address the high incidence of dehydration in the OPC-61815 group. This approach is appropriate. In addition, with the exception of dehydration, the incidence of adverse events associated with the aquaretic effect of OPC-61815 was similar to that of oral tolvaptan; therefore, the applicant's plan to provide cautionary statements equivalent to those provided for oral tolvaptan regarding risks associated with the aquaretic effect is reasonable. The appropriateness of cautionary statements regarding the risk of the aquaretic effect in patients who have difficulty with oral fluid intake will be discussed further in Section "7.R.5 Indication and patient population."

7.R.3.3 Risks associated with increase in blood potassium concentration

The applicant's explanation about the risks associated with increase in blood potassium concentration caused by OPC-61815:

Table 37 shows the incidence of hyperkalaemia-related adverse events[17)] and abnormalities in laboratory test results related to an increase in serum potassium concentration in the pooled data from Studies 00001 and 00003, and in Study 00004.

[17)] MedDRA PTs "blood potassium abnormal," "blood potassium increased," "electrolyte imbalance," "hyperkalaemia," "hyperreflexia," "irritability," "muscle contractions involuntary," "muscle contracture," "muscle rigidity," "muscle spasms," and "muscle twitching"

Table 37. Incidence of events related to an increase in blood potassium concentration in the clinical studies (safety analysis set)

	Pooled data from Studies 00001 and 00003		00004 (N = 45)
	OPC-61815 16 mg (N = 160)	Oral tolvaptan (N = 157)	
Hyperkalaemia-related adverse events	8.8 (14)	2.5 (4)	2.2 (1)
Electrolyte imbalance	0.6 (1)	0 (0)	0 (0)
Hyperkalaemia	5.6 (9)	1.9 (3)	2.2 (1)
Muscle spasms	0.6 (1)	0 (0)	0 (0)
Blood potassium increased	1.9 (3)	0.6 (1)	0 (0)
Clinically significant increase in serum potassium concentration[a]	13.1 (21)	9.6 (15)	0 (0)

Incidence, % (n)

a, When graded on a 5-point scale (Grade 0 [≤ upper limit of normal (ULN)], Grade 1 [>ULN and ≤5.5 mEq/L], Grade 2 [>5.5 mEq/L and ≤6 mEq/L], Grade 3 [>6 mEq/L and ≤7 mEq/L], and Grade 4 [>7 mEq/L]), "clinically significant" was defined as worsening by ≥2 grades if the event was rated as ≤Grade 1 at baseline, and as worsening by ≥1 grade if the event was rated as ≥Grade 2 at baseline.

In the pooled data from Studies 00001 and 00003, the incidence of hyperkalaemia-related adverse events was higher in the OPC-61815 16 mg group than in the oral tolvaptan group. Hyperkalaemia in 1 subject (OPC-61815 16 mg) was classified as a serious event and severe in severity and was considered to have a causal relationship to the study drug. This subject, a female patient aged 7[redacted] years, had a high serum potassium level (5.5 mEq/L) at baseline, and was receiving concomitantly an aldosterone antagonist (spironolactone) and an angiotensin converting enzyme (ACE) inhibitor (enalapril maleate). The serum potassium concentration increased to 6.9 mEq/L on the day of onset of hyperkalaemia (Day 3), and remained high to the day (Day 6) following the day of final dose administration (maximum concentration was 7.1 mEq/L, observed on Day 5 and Day 6). The hyperkalaemia resolved by Day 15. The other hyperkalaemia-related adverse events were mild in severity, and subjects continued to receive study drug treatment. Eight subjects who developed hyperkalaemia-related adverse events were among the 36 subjects who developed a clinically significant increase in serum potassium concentration. Of the remaining 28 subjects (15 subjects in the OPC-61815 16 mg group and 13 subjects in the oral tolvaptan group), data from following time points were excluded: time point that showed apparently high values due to hemolysis of red blood cells, and time point at which values substantially differed from the upper limit of the normal range, which is likely to be caused by an error during processes before measurement. In the data from the remaining subjects (11 subjects in the OPC-61815 16 mg group and 9 subjects in the oral tolvaptan group), the maximum increase from baseline was 0.4 to 1.6 mEq/L in the OPC-61815 16 mg group and 0.2 to 1.5 mEq/L in the oral tolvaptan group. The incidence and degree of clinically significant increase in serum potassium concentration did not differ significantly between the groups. The breakdown data of initial onset time during the treatment period (Days 1-6) show that the adverse events or abnormalities in laboratory test results occurred in 7 of 160 subjects (4.4%) on Day 1, 4 of 160 subjects (2.5%) on Day 2, 1 of 154 subjects (0.6%) on Day 3, 3 of 152 subjects (2.0%) on Day 5, and 1 of 151 subjects (0.7%) on Day 6 in the OPC-61815 16 mg group; 2 of 157 subjects (1.3%) on Day 1, 3 of 157 subjects (1.9%) on Day 2, 1 of 152 subjects (0.7%) on Day 3, 1 of 150 subjects (0.7%) on Day 4, 2 of 146 subjects (1.4%) on Day 5, and 1 of 144 subjects (0.7%) on Day 6 in the oral tolvaptan group. The results suggest that the events may occur at an earlier time in the OPC-61815 16 mg group than in the oral tolvaptan group. In 12 subjects (10 subjects in the OPC-61815 16 mg group and 2 subjects in the oral tolvaptan group) who developed hyperkalaemia-related adverse events during the treatment period (Days 1-6), the events resolved after the

completion of treatment or treatment discontinuation. In Study 00004, hyperkalaemia occurred only in 1 subject who had been continuing with the 8 mg dose (Day 7), and was mild in severity. A causal relationship to the study drug was denied, and the event resolved within the same day.

To investigate the patient population that require particular attention to the increase in blood potassium concentration, a subgroup analysis was performed using the pooled data from Studies 00001 and 00003 with vs without concomitant use of drugs known to increase serum potassium concentration (aldosterone antagonists, ACE inhibitors, and angiotensin II receptor blocker [ARB]) by serum potassium concentration at baseline (>5.0 mEq/L or ≤5.0 mEq/L, >4.5 mEq/L or ≤4.5 mEq/L). As shown in Table 38, in the OPC-61815 16 mg group, the incidence of hyperkalaemia was higher in the baseline serum potassium subgroups >5.0 mEq/L and >4.5 mEq/L, the subgroup with concomitant aldosterone antagonists, the subgroup with concomitant ACE inhibitors, and the subgroup without concomitant ARB compared with the respective subgroups.

Table 38. Incidence of hyperkalaemia-related adverse events by patient characteristic (pooled data from Studies 00001 and 00003)

		OPC-61815 16 mg	Oral tolvaptan
Serum potassium concentration at baseline	>5.0 mEq/L	36.4 (4/11)	14.3 (1/7)
	≤5.0 mEq/L	6.7 (10/149)	2.0 (3/150)
Serum potassium concentration at baseline	>4.5 mEq/L	18.0 (9/50)	7.7 (3/39)
	≤4.5 mEq/L	4.5 (5/110)	0.8 (1/118)
Concomitant aldosterone antagonist	Yes	11.7 (11/94)	4.8 (4/84)
	No	4.5 (3/66)	0 (0/73)
Concomitant ACE inhibitor	Yes	16.0 (8/50)	2.6 (1/39)
	No	5.5 (6/110)	2.5 (3/118)
Concomitant ARB	Yes	3.6 (2/56)	3.1 (2/64)
	No	11.5 (12/104)	2.2 (2/93)

Incidence, % (n/N)

The above results indicated that a stronger cautionary statement should be provided regarding hyperkalaemia in the package insert (draft) of OPC-61815 compared to those provided for oral tolvaptan. Therefore, in addition to specifying hyperkalaemia as a clinically significant adverse reaction, time-course of serum potassium concentrations should also be monitored more closely for OPC-61815 than those performed for oral tolvaptan. In Study 00003, in subjects who developed serious hyperkalaemia for which a causal relationship to the study drug could not be ruled out, serum potassium concentration started to increase gradually after the start of administration and continued to increase to Day 3, and thereafter, no marked increase in serum potassium concentration was observed. Therefore, serum potassium concentration should be measured every day for approximately 6 days after the start of treatment, and thereafter, on an as-needed basis if the patient continues to receive treatment. It was decided to provide cautionary statement in the “Precautions for Co-administration” section equivalent to that provided for oral tolvaptan regarding concomitant use of drugs known to increase serum potassium concentration (potassium-sparing diuretics/aldosterone antagonists, ACE inhibitors). Cautionary statement for patients with high baseline serum potassium concentrations will be provided as follows: precaution for patients with hyperkalaemia will be included in the “Precautions Concerning Patients with Specific Backgrounds” section in the package insert (draft), equivalent to that provided for oral tolvaptan; and additional cautionary statements will also be provided in the “Important

Precautions" section of the package insert of OPC-61815 for patients whose baseline serum potassium concentrations exceed the normal range or near the high end of the normal range.

PMDA's view:

In the pooled data from Studies 00001 and 00003, hyperkalaemia-related adverse events occurred more frequently in the OPC-61815 16 mg group than in the oral tolvaptan group; in addition, serious hyperkalaemia occurred only in the OPC-61815 16 mg group, suggesting that patients treated with OPC-61815 are more likely to develop hyperkalaemia-related adverse events compared to those treated with oral tolvaptan. Therefore, PMDA concluded that the applicant's plan to specify hyperkalaemia as a clinically significant adverse reaction to alert healthcare professionals is appropriate. Furthermore, given the onset time of the events related to increase in blood potassium concentration, and data including characteristics of subjects who developed hyperkalaemia-related adverse events, the applicant's plan to provide cautionary statements on specific time intervals for serum potassium measurement and a particular precaution for patients with increased serum potassium concentration in the package insert for OPC-61815 in addition to those provided for oral tolvaptan is appropriate. However, the time interval for measurement should be at least 4 to 6 hours and 8 to 12 hours after start of administration and from the day following the start of treatment, on an every-day basis for approximately 5 days according to the procedure followed in Study 00003. The appropriateness of cautionary statements regarding the risk of increase in blood potassium concentration in patients who have difficulty with oral fluid intake will be discussed further in Section "7.R.5 Indication and patient population." The appropriateness of the PMDA's decision will be finalized taking into account the comments from the Expert Discussion.

7.R.3.4 Other adverse events of special interest

The applicant's explanation about the incidence of adverse events in the clinical studies of OPC-61815 related to the risks known for oral tolvaptan other than those investigated in Sections 7.R.3.1 through 7.R.3.3:

In the pooled data from Studies 00001 and 00003, the incidence of ventricular fibrillation/ventricular tachycardia-related adverse events[18)] was 1.9% in the OPC-61815 16 mg group (3 of 160 subjects; ventricular tachycardia in 3 subjects) and 1.9% in the oral tolvaptan group (3 of 157 subjects; ventricular tachycardia in 2 subjects and ventricular extrasystoles in 1 subject), indicating no marked difference between the 2 groups. A causal relationship to the study drug was denied for these events except for ventricular tachycardia in 1 subject in the OPC-61815 16 mg group. A serious adverse event (ventricular tachycardia) occurred in 1 subject in the oral tolvaptan group, for which a causal relationship to the study drug was denied. One subject in the OPC-61815 16 mg group developed not only ventricular tachycardia on Day 2, but also a hyperkalaemia-related adverse event (muscle spasms) on Day 1. Both events were mild in severity, and a causal relationship to the study drug could not be ruled out for either of the events. While muscle spasms resolved within the same day, ventricular tachycardia was still present at the completion of the study. The remaining 5 subjects did not develop hyperkalaemia-related adverse events. In Study 00004, the incidence of ventricular fibrillation/ventricular tachycardia-related adverse events was 6.7% (3 of 45 subjects; ventricular tachycardia

[18)] MedDRA SMQ "ventricular tachyarrhythmias (narrow)"

in 3 subjects), and none of these subjects developed hyperkalaemia-related adverse events. Pulseless ventricular tachycardia (10-15 seconds) occurred in one of these subjects approximately 4 hours after the start of administration on Day 1 (8 mg), and several minutes later, the same arrhythmia occurred (unknown duration). This ventricular tachycardia event was classified as a serious adverse event, and a causal relationship to the study drug could not be ruled out. OPC-61815 treatment was discontinued, and treatment with landiolol hydrochloride started, and the event resolved by Day 15. The electrocardiogram of this subject taken during hospitalization indicated QT prolongation with negative T wave. No change in serum potassium concentration was observed before or after the onset of ventricular tachycardia, and the event occurred approximately 30 minutes after bolus administration of furosemide 20 mg. Cardiac stress due to rapid increase in urine output and significant reduction in circulatory blood flow was identified as the main cause by the investigator. Ventricular tachycardia events occurring in the remaining 2 subjects (1 subject on 8 mg treatment and 1 subject in the follow-up period) were mild in severity, and a causal relationship to the study drug was denied for both events.

In the pooled data from Studies 00001 and 00003, the incidence of hepatic dysfunction-related adverse events[19)] was 2.5% (4 of 160 subjects) in the OPC-61815 16 mg group and 3.8% (6 of 157 subjects) in the oral tolvaptan group, indicating no difference between the 2 groups. All events were mild in severity and the subjects continued to receive treatment. In Study 00004, the incidence of hepatic dysfunction-related adverse events was 17.8% (8 of 45 subjects; hepatic function abnormal in 5 subjects; drug-induced liver injury, international normalised ratio increased, and hepatic enzyme increased in 1 subject each), indicating a higher incidence than that in the pooled data from Studies 00001 and 00003. In Study 00004, eligible patients were those with heart failure of increasing severity and many patients enrolled in the study had liver function values higher than the upper limit of the normal range, which may have influenced the results. The majority of the events occurred after the completion of treatment (follow-up period), and a causal relationship to the study drug was denied for all events. Except for drug-induced liver injury (moderate) in 1 subject, all events were mild in severity. Hepatic encephalopathy did not occur in any of the clinical studies.

In the pooled data from Studies 00001 and 00003, the incidence of renal impairment-related adverse events[20)] was 3.8% (6 of 160 subjects) in the OPC-61815 16 mg group and 4.5% (7 of 157 subjects) in the oral tolvaptan group, indicating no difference between the 2 groups. All events were either mild or moderate in severity. One subject in the OPC-61815 16 mg group who had blood creatinine increased was the same subject who developed dehydration that resulted in treatment discontinuation. One of the subjects who developed renal impairment led to treatment discontinuation, while other events did not prevent subjects from continuing treatment. In Study 00004, the incidence of renal impairment-related adverse events was 2.2% (1 of 45 subjects, on 8 mg treatment). The events were mild in severity and reported as resolved.

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19) MedDRA SMQ “cholestasis and jaundice of hepatic origin (narrow),” “hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow),” “hepatitis, non-infectious (narrow),” “liver neoplasms, benign (incl cysts and polyps) (narrow),” “liver malignant tumours (narrow),” “liver tumours of unspecified malignancy (narrow),” “liver related investigations, signs and symptoms (narrow),” and “liver-related coagulation and bleeding disturbances (narrow)”

20) MedDRA SMQ “acute renal failure (broad)”; MedDRA high level term (HLT) “renal failure and impairment,” MedDRA PT “renal disorder”

Moreover, the incidence of adverse events related to gout/hyperuricaemia, diabetes mellitus/hyperglycaemia, glaucoma, gastrointestinal haemorrhage, and neoplasm skin did not raise any particular concerns.

The applicant's explanation about the incidence of infusion reaction-related adverse events[21)] caused by OPC-61815 administered as intravenous infusion:
The incidence of infusion reaction-related adverse events in the pooled data from Studies 00001 and 00003 was 8.8% (14 of 160 subjects) in the OPC-61815 16 mg group and 7.0% (11 of 157 subjects) in the oral tolvaptan group, indicating no marked difference between the two groups. Adverse events occurring in ≥2 subjects in the OPC-61815 16 mg group were eczema, rash, infusion site extravasation, and vessel puncture site bruise, and all of these events occurred only in the OPC-61815 16 mg group except for rash. A causal relationship to the study drug was denied for all infusion reaction-related adverse events except for those in 2 subjects in the oral tolvaptan group (injection site phlebitis and infusion related reaction). All events were either mild or moderate in severity, and none of them led to treatment discontinuation. In Study 00004, the incidence of infusion reaction-related adverse events was 13.3% (6 of 45 subjects; eczema and injection site inflammation in 2 subjects each; infusion site swelling and drug eruption in 1 subject each). A causal relationship to the study drug was denied for these events, and all events were either mild or moderate in severity. No shock/anaphylaxis[22)] occurred in the clinical studies for OPC-61815.

The above findings indicated that no particular cautionary statement on infusion reaction-related adverse events is needed for OPC-61815. Risks that are already known from oral tolvaptan are considered to be manageable by providing cautionary statement equivalent to those provided for oral tolvaptan.

PMDA's view:
No particular cautionary statement on infusion reaction-related adverse events is necessary for OPC-61815. It is appropriate at this point that the applicant plans to provide cautionary statements to manage risks that are already known from oral tolvaptan other than those discussed in Sections 7.R.3.1 through 7.R.3.3, equivalent to those provided for oral tolvaptan.

7.R.4 Dosage and administration

7.R.4.1 Usual dosage

The applicant's explanation about the usual dosage of OPC-61815:
OPC-61815 16 mg once daily was proposed as the usual dosage to achieve exposure equivalent to that of tolvaptan 15 mg once daily, the usual dosage of oral tolvaptan [see Section "6.R.1 Rationale for the dosage regimen in the phase III study"]. Study 00003 confirmed the non-inferiority of OPC-61815 16 mg to oral tolvaptan 15 mg in terms of the change from baseline in body weight to final dose administration, the primary efficacy endpoint. Although some adverse events occurred at a higher incidence in the OPC-61815 16 mg

21) MedDRA HLTs "infusion site reactions," "injection site reactions," "administration site reactions NEC"; MedDRA PT "infusion related reaction"
22) MedDRA SMQ "hypersensitivity," "anaphylactic reaction," "severe cutaneous adverse reactions," "drug reaction with eosinophilia and systemic symptoms syndrome"

group than in the oral tolvaptan 15 mg group, this is not considered to be a clinically unacceptable difference. Therefore, OPC-61815 16 mg once daily is appropriate as the usual dosage.

PMDA's view:
On the basis of the study design as well as their efficacy and safety results in the clinical study data submitted, the applicant's explanation is reasonable. PMDA concluded that OPC-61815 16 mg once daily is appropriate as the usual dosage for the treatment of fluid retention in heart failure when treatment with other diuretics including loop diuretics is not sufficiently effective.

7.R.4.2 Patient populations that should start treatment at a low dose

The applicant's explanation about the necessity and method of starting treatment at a low dose:
The package insert of oral tolvaptan has a cautionary statement to the effect that patients should be closely monitored for fluid intake volume as a measure to prevent hypernatraemia, dehydration, and other adverse events, and patients should be instructed to have adequate fluid intake. In Study 00004, a study in patients who have difficulty with or are incapable of oral intake, it was considered difficult for patients to drink water by themselves to ensure adequate fluid intake. To reduce risks caused by the excessive aquaretic effect of OPC-61815 immediately after the start of treatment, it was specified in the protocol that the patients were to start treatment at a starting dose of 8 mg, half the usual dose, and the dose was to be increased to 16 mg in accordance with the dose escalation criteria (Table 29); at the same time, healthcare professionals were to check and adjust the fluid balance, vital signs, and infusion volume frequently at an early stage after the start of treatment and at the time of dose escalation. The dose escalation criteria were specified so that healthcare professionals could determine if the dose is insufficient based on the increase in daily urine volume, body weight, congestive symptoms, and other findings, and confirm that there are no safety concerns. The dose escalation criteria comprise the following with respect to serum sodium concentrations: the concentration at predose should not exceed the upper limit of the normal range, 147 mEq/L, and the increase in the serum sodium concentration should be ≤10 mEq/L in the 24 hours from the start of administration on the preceding day. The latter criterion was established to minimize the risk of osmotic demyelination syndrome associated with rapid increase in serum sodium concentration (*Am J Med*. 2013;126:S5-42, *Harrison's Principles of Internal Medicine*. 5th edition, 2017;p1830 [in Japanese], *Nephrol Dial Transplant.* 2013;29:ii1-39). As a result of dose escalation assessment, 38 subjects continued to receive 8 mg (25 subjects continued at 8 mg, 11 subjects completed treatment earlier due to improvement of symptoms on Day 2, 2 subjects discontinued on Day 2) and 7 subjects underwent dose escalation to 16 mg, and the dose was escalated on Day 2 in all 7 subjects. Of the 25 subjects who continued to receive 8 mg from Day 2 onward, 24 subjects failed to meet dose escalation criterion 1), 8 subjects criterion 4), 1 subject criterion 2), and 1 subject criterion 3) (some subjects failed to meet more than 1 criteria). The efficacy data show that body weight reduction and improvement in congestive symptoms were observed in both subjects continuing with the 8 mg dose and those undergoing dose escalation to 16 mg. The extent of body weight reduction did not differ markedly between subjects continuing with the 8 mg dose and those undergoing dose escalation to 16 mg. However, the maximum response in terms of increase in urine volume and body weight reduction was achieved on the first day of treatment in subjects who remained at the same dose level, while it was achieved postdose on Day 2 in subjects who had dose escalation to 16 mg, thus

suggesting the positive effect of dose escalation to 16 mg in subjects with an inadequate response to 8 mg. The safety data showed no serious adverse events for which a causal relationship to the study drug could not be ruled out, or adverse events leading to study drug treatment discontinuation, except for 1 subject who developed serious ventricular tachycardia on Day 1 after the start of treatment at dose of 8 mg, resulting in treatment discontinuation. Risks associated with the aquaretic effect, increase in blood sodium concentration, increase in blood potassium concentration, and other adverse events of special interest at 8 mg were manageable [see Section "7.R.3 Safety"]. The incidence of adverse events occurring post-escalation (from Day 2 onward) in subjects undergoing dose escalation to 16 mg was 85.7% (6 of 7 subjects). The incidence of adverse events occurring from Day 2 onward in subjects continuing with the 8 mg dose was 76.3% (29 of 38 subjects), lower than the incidence in subjects undergoing dose escalation to 16 mg. However, no adverse events of special interest occurred when treated at 16 mg, and there was no trend towards an obvious increase in the incidence of specific adverse events. Table 39 shows the changes in serum sodium concentration and serum potassium concentration after dose escalation to 16 mg compared with those in subjects who continued to receive 8 mg for at least 2 days. The increase in serum sodium concentration on Day 2 (post-escalation) in subjects undergoing dose escalation to 16 mg is greater than that in subjects continuing with the 8 mg dose, and the difference is similar from Day 3 onward, suggesting there may be a heightened risk of increase in serum sodium concentration associated with dose escalation. Serum potassium concentration data did not indicate there was a heightened risk of increase in serum potassium concentration associated with dose escalation.

Table 39. Time-course for changes from baseline in serum sodium concentration and serum potassium concentration

		Serum sodium concentration (mEq/L)		Serum potassium concentration (mEq/L)	
		Subjects who continued to receive 8 mg	Subjects who underwent dose escalation to 16 mg	Subjects who continued to receive 8 mg	Subjects who underwent dose escalation to 16 mg
Day 1	Predose (baseline)	n = 25 140.9 ± 3.8	n = 7 138.0 ± 1.7	n = 25 3.79 ± 0.40	n = 7 3.63 ± 0.60
	4 hours after start of administration	n = 25 1.4 ± 2.2	n = 7 0.9 ± 1.6	n = 25 0.02 ± 0.26	n = 7 0.01 ± 0.68
	8 hours after start of administration	n = 25 1.6 ± 2.7	n = 7 0.6 ± 2.2	n = 25 0.04 ± 0.31	n = 7 0.19 ± 1.12
Day 2	Predose	n = 25 1.4 ± 2.5	n = 7 1.9 ± 2.7	n = 25 0.12 ± 0.37	n = 7 −0.06 ± 0.59
	4 hours after start of administration	—	n = 7 2.6 ± 4.0	—	n = 7 −0.04 ± 0.64
	8 hours after start of administration	—	n = 7 2.7 ± 4.5	—	n = 7 −0.01 ± 0.69
Day 3		n = 24 1.5 ± 2.8	n = 7s 3.1 ± 4.5	n = 24 0.05 ± 0.51	n = 7 0.14 ± 0.86
Day 4		n = 10 0.3 ± 1.6	n = 3 1.3 ± 0.6	n = 10 0.24 ± 0.40	n = 3 0.67 ± 1.10
Day 5		n = 6 0.5 ± 2.4	n = 2 4, 6[a]	n = 6 0.47 ± 0.61	n = 2 0.7, 1.6[a]
Day 6		n = 6 −2.0 ± 2.4	n = 1 5.0	n = 6 0.53 ± 0.87	n = 1 0.50
Follow-up		n = 25 −1.5 ± 3.7	n = 7 −0.1 ± 3.4	n = 25 0.40 ± 0.60	n = 7 0.70 ± 1.03

Mean ± standard deviation
a, individual values

On the basis of the above, when using OPC-61815 in patients who have difficulty with oral fluid intake, in principle, it is reasonable to start treatment at 8 mg and determine whether dose can be increased to 16 mg according to the dose escalation criteria established in Study 00004 on the following day or later, and an appropriate cautionary statement to this effect should be provided in the package insert. However, the intended patient population for OPC-61815 is assumed to include patients such as those with acute heart failure who have just been taken to the emergency room, and therefore there are cases where obtaining the urine volume measured on the day before treatment would be difficult in clinical practice. Accordingly, of the dose escalation criteria 1) established in Study 00004 (Table 29), the criterion for the case where urine volume on the day before is not available (body weight did not decrease as compared with predose with no improvement in congestive symptoms) should be used. Since body weight and improvement in congestive symptoms are general indicators used to determine the efficacy of diuretics, the package insert (draft) should include a brief statement to the effect that the dose should be increased on the day following the initial administration or later in patients with an insufficient response. As for 2) and 3) of the dose escalation criteria, the package insert (draft) should include a cautionary statement in the "Clinically Significant Adverse Reactions" section to the effect that if serum sodium concentration exceeds the upper limit of the normal range, treatment with OPC-61815 must be immediately discontinued, and in the "Precautions Concerning Dosage and Administration" section a cautionary statement should be included to the effect that if an increase of >10 mEq/L in serum sodium concentration occurs within 24 hours following initiation of OPC-61815 administration, increasing the dose on the day following treatment initiation is not recommended.

To assess the starting dose of OPC-61815 in patients for whom starting treatment with oral tolvaptan 7.5 mg (half the usual dose) is recommended (patients with a serum sodium concentration of <125 mEq/L, patients for whom rapid reduction in circulatory blood flow is considered unfavorable, older adult patients, patients whose serum sodium concentrations are near the high end of the normal range), tolvaptan exposure following administration of OPC-61815 (2, 4, 8, or 16 mg) intravenously or oral tolvaptan (7.5 or 15 mg) was estimated using a PPK model [see Section "6.2.4.1 Population pharmacokinetic analysis"]. These estimated results indicated that OPC-61815 8 mg is the dose equivalent to oral tolvaptan 7.5 mg and is half the recommended clinical dose of OPC-61815, and therefore, it is considered appropriate to provide a cautionary statement to the effect that starting treatment at half the usual dose of OPC-61815 (8 mg) is recommended.

PMDA's view:

To avoid the risks of dehydration, hypernatraemia, and other adverse events associated with the aquaretic effect of tolvaptan, whether treatment should be started at a low dose needs to be evaluated in patients who have difficulty with oral fluid intake, and those who have factors that could potentially increase their susceptibility to developing such adverse events. On the basis of data including the safety at OPC-61815 8 mg, efficacy by the final dose of OPC-61815, and efficacy and safety after dose escalation in Study 00004, PMDA concluded that the following specifications are appropriate for patients who have difficulty with oral fluid intake: treatment should be started at OPC-61815 8 mg while monitoring patients in accordance with the protocol-specified measurement procedure and fluid management based on the infusion volume used in Study 00004; the dose should be increased to 16 mg in accordance with the dose escalation criteria of Study 00004, when

body weight, congestive symptoms, and other data suggest insufficient improvement, and an increase of >10 mEq/L in serum sodium concentration within 24 hours following initiation of OPC-61815 administration is not observed. In addition, PMDA also concluded that the applicant's plan to include the following cautionary statements is appropriate: in patient populations for which starting treatment with oral tolvaptan 7.5 mg (half the usual dose) is deemed preferable (e.g., patients with a serum sodium concentration of <125 mEq/L, patients for whom rapid reduction in circulatory blood flow is considered unfavorable, older adult patients, patients whose serum sodium concentrations are near the high end of the normal range), starting treatment at half the usual dose of OPC-61815 (8 mg) is recommended.

7.R.4.3 Treatment duration

The applicant's explanation about the treatment duration of OPC-61815:

In Study 00003, based on the data from clinical studies of oral tolvaptan, a treatment duration of 5 days was determined to be sufficient to evaluate the change in body weight, and was selected as the treatment duration for the study. Study 00004 was conducted in patients who had difficulty with or were incapable of oral intake, and a maximum treatment duration of 5 days was selected based on factors including the following: situations in which oral intake of diuretics is difficult are not considered to be prolonged given that dyspnea caused by acute phase symptoms of heart failure often resolves within the same day of the start of conventional treatment, and NPPV devices can be removed within 2 to 3 days; the purpose of treatment with diuretic injections is to improve congestive symptoms promptly, and treatment commonly ends within 5 days. Treatment was to be ended when all congestive symptoms resolved and no further improvement in fluid retention was necessary, or the subject became capable of fluid management by oral intake alone. The results of Study 00004 showed that the treatment ended earlier than 5 days due to improvement of symptoms in 34 of 41 subjects (82.9%), excluding 4 subjects whose treatment was discontinued. Of the 34 subjects, the reasons for early completion were "the subject became capable of fluid management by oral intake alone" in 30 (88.2%) and "all congestive symptoms resolved and no further improvement in fluid retention was necessary" in 4 (11.8%). The above results suggest that the duration for which administration of OPC-61815 is required is <5 days in the majority of patients, based on the time frame when fluid management become possible by oral intake alone and treatment can be switched to oral medications in most patients. On the other hand, some patients with severe symptoms may receive intravenous fluid and nutritional supplementation for >5 days. The possibility that OPC-61815 treatment may become necessary for >5 days cannot be ruled out in clinical practice. While there is no experience in treating patients with OPC-61815 for >5 days, given that the efficacy and safety of oral tolvaptan for 7 days have been demonstrated in clinical studies, and that the efficacy of continuous treatment with oral tolvaptan for up to 14 days has been reported, suggesting that tolvaptan treatment for more than 5 days is safe (*Circ J.* 2019;83:1520-7, *Circ J.* 2014;78:844-52), it is unlikely that unacceptable safety-related problem will occur when OPC-61815 is administered for >5 days.

Termination of OPC-61815 treatment should be decided on a comprehensive assessment of body weight reduction, improvement in congestive symptoms, and other factors, when all congestive symptoms have resolved and no further improvement in fluid retention is considered necessary, regardless of the patient's capability for oral intake. If fluid retention has not been improved by OPC-61815, prolonging treatment further

is not expected to be effective; therefore, cautionary statements should be included in the package insert (draft), equivalent to those provided for oral tolvaptan, to the effect that when fluid retention symptoms have resolved treatment should be discontinued; efficacy in preventing recurrence of fluid retention symptoms after their resolution has not been established; if there is no further improvement in fluid retention status, administration of OPC-61815 should not be continued without careful consideration. Additionally, even in cases where continuation of treatment with diuretics is considered to be required to improve fluid retention in patients who have difficulty with oral intake, when the patient has become capable of receiving oral tolvaptan, OPC-61815 should be discontinued considering the burden that infusion imposes on patients, and the patient should be switched to oral tolvaptan treatment [see Section "7.R.4.4 Switch-over from OPC-61815 to oral tolvaptan" for switch-over to oral tolvaptan]. Given that OPC-61815 is an injectable solution for invasive treatment, that it requires reconstitution prior to administration and delivery by intravenous drip infusion over 1 hour, and that daily fluid balance needs to be monitored and infusion volume needs to be adjusted in patients who have difficulty with oral intake, it is unlikely that treatment with OPC-61815 will be continued once body weight has decreased to the targeted weight (body weight when fluid retention is well controlled). Therefore, cautionary statements equivalent to those provided for oral tolvaptan, will not be necessary.

PMDA's view:

OPC-61815 is a symptomatic treatment and its purpose is to improve acute phase symptoms of heart failure associated with the aquaretic effect. Therefore, the duration of treatment with OPC-61815 should be minimized and limited to the time until fluid retention symptoms improve when treatment with other diuretics has not produced adequate response, and whether to continue treatment with OPC-61815 should be determined on an individual basis, from the perspective of improvement of fluid retention such as body weight reduction and improvement of congestive symptoms. Therefore, PMDA concluded that the applicant's plan to include the following cautionary statements in the package insert, equivalent to those provided for oral tolvaptan, is appropriate: treatment with OPC-61815 should be discontinued when fluid retention symptoms have resolved; efficacy in preventing recurrence of fluid retention symptoms after their resolution has not been established; and if there is no further improvement in fluid retention status, administration of OPC-61815 should not be continued without careful consideration. Generally, patients who have become capable of oral medication intake are expected to be switched from OPC-61815 treatment to oral tolvaptan; however, OPC-61815 may also be used in some patients who are capable of oral intake [see Section "7.R.1 Clinical positioning"]. The possibility that a patient who requires continuous tolvaptan treatment is assessed as needing OPC-61815 rather than oral tolvaptan, depending on the patient's condition, cannot be denied. On the basis of this and other possibilities, when body weight has decreased to the targeted weight (body weight when fluid retention is well controlled), administration of OPC-61815 should not be continued without careful consideration, and a statement to this effect should be provided, equivalent to those provided for oral tolvaptan. The appropriateness of the above conclusion by PMDA will be finalized taking into account the comments from the Expert Discussion.

7.R.4.4 Switch-over from OPC-61815 to oral tolvaptan

The applicant's explanation about switch-over from OPC-61815 to oral tolvaptan:

Switching over from oral tolvaptan to OPC-61815 may be considered in patients who experience worsening of heart failure condition during treatment with oral tolvaptan, leading to the situation where oral intake is either difficult or impossible, and in patients in whom absorption of an oral drug has deteriorated due to intestinal edema, making oral tolvaptan less effective or ineffective. When switching to OPC-61815, based on the dose (usual or half) of oral tolvaptan prior to switching, the corresponding dose level can be determined for OPC-61815 (usual or half); however, in some cases such as when the patient's condition has worsened, the dose of OPC-61815 may be determined according to the patient's condition rather than being based on the dose of oral tolvaptan. On the other hand, when a patient treated with OPC-61815 has become capable of oral intake of tolvaptan and determined to be suitable for fluid retention management with oral tolvaptan, the patient may be switched from OPC-61815 to oral tolvaptan. In this case, it is appropriate to select the dose of oral tolvaptan that is expected to produce a level of efficacy and safety similar to that of OPC-61815 prior to switching, and therefore a switch from OPC-61815 16 mg to oral tolvaptan 15 mg, or a switch from OPC-61815 8 mg to oral tolvaptan 7.5 mg is recommended. For both cases, the corresponding doses of OPC-61815 and oral tolvaptan can be estimated easily by healthcare professionals. A statement to the effect that tolvaptan exposure at OPC-61815 16 mg is equivalent to that at oral tolvaptan 15 mg will be included in the package insert, while no particular cautionary statement regarding switch over of treatment is considered necessary.

PMDA's view:

The following explanation by the applicant is reasonable: switching over from oral tolvaptan to OPC-61815 may be considered in patients who experience worsening of heart failure condition, leading to the situation where oral intake is either difficult or impossible, and in patients for whom oral tolvaptan shows diminished efficacy; and switching over from OPC-61815 to oral tolvaptan may be considered when a patient treated with OPC-61815 has become capable of oral intake of tolvaptan. When a patient is switched from oral tolvaptan to OPC-61815 because oral intake is difficult or impossible, it is appropriate to start with OPC-61815 8 mg, a dose generally recommended for patients who have difficulty with oral fluid intake. Even when a patient is switched from oral tolvaptan to OPC-61815 for reasons other than difficulty or incapability of oral intake, a suitable dose should be selected after assessing the patient's condition and considering the information contained in the package insert of the drug to be switched to rather than switching to an equivalent dose automatically. Therefore, PMDA concluded that the applicant's plan to provide information on tolvaptan exposure at OPC-61815 16 mg and at oral tolvaptan 15 mg in the package insert, without providing particular cautionary statements regarding switch over of treatment is reasonable.

On the basis of the discussions in Sections 7.R.4.1 through 7.R.4.4, PMDA considers that the dosage and administration and related cautionary statements in the package insert should be as follows. The above issues will be finalized taking into account the comments from the Expert Discussion.

Dosage and Administration

The usual adult dosage is 16 mg of tolvaptan sodium phosphate once daily administered as an intravenous infusion over 1 hour.

Precautions Concerning Dosage and Administration (excerpted) (Underline denotes additions to the proposed text; strikethrough denotes deletions from the proposed text)

- When OPC-61815 is administered to patients who have difficulty with ~~fluid management by~~ oral fluid intake, treatment should be started at 8 mg, half the usual dose. The dose ~~should~~ may be increased to 16 mg on the following day or later if the patient's response to treatment has been inadequate. However, if there is an increase of >10 mEq/L in serum sodium concentration within 24 hours after start of OPC-61815 administration, ~~it is not recommended to~~ do not increase the dose on the following day. ~~The maximum dose should be 16 mg once daily.~~
- For patients with a serum sodium concentration of <125 mEq/L, patients for whom rapid reduction in circulatory blood flow is considered unfavorable, older adult patients, and patients whose serum sodium concentrations are near the high end of the normal range, starting treatment at half the usual dose of OPC-61815 (8 mg) is recommended.
- Treatment with OPC-61815 should be discontinued when fluid retention symptoms have resolved. Efficacy in preventing recurrence of fluid retention symptoms after their resolution has not been established.

Important Precautions (excerpted)

- If there is no further improvement in fluid retention status, administration should not be continued without careful consideration.
- When body weight has decreased to the targeted weight (body weight when fluid retention is well controlled), administration of OPC-61815 should not be continued without careful consideration.

7.R.5 Indication and patient population

The applicant's explanation about the rationale for the indication and patient population of OPC-61815:
The efficacy of OPC-61815 16 mg is not inferior to that of oral tolvaptan 15 mg in patients with heart failure with fluid retention who had an inadequate response to loop and other diuretics in the clinical study of OPC-61815 [see Section "7.R.2.1 Appropriateness of the design of Study 00003 and efficacy of OPC-61815"], and OPC-61815 has acceptable safety in view of efficacy demonstrated [see Section "7.R.3 Safety"]. Therefore, the indication for OPC-61815 should be the same as that for oral tolvaptan, "treatment of fluid retention in heart failure when treatment with other diuretics including loop diuretics is not sufficiently effective."

Oral tolvaptan is contraindicated in patients who are unable to sense thirst or who have difficulty with fluid intake and patients with hepatic encephalopathy who have difficulty maintaining an adequate fluid intake, because such patients are at an increased risk for hypernatraemia and dehydration because of their inability to take fluids orally. In Study 00004, which was conducted in patients who had difficulty with or were incapable of oral intake, eligible patients were presumably unable to take adequate fluid by drinking; therefore, the study was designed to start treatment at 8 mg, half the usual dose, to prevent risks associated with an excessive aquaretic effect. Healthcare professionals were to check and adjust the fluid balance, vital signs, and infusion volume frequently. Subjects actually enrolled in Study 00004 included patients who were incapable of swallowing solids or drinking water due to severe dyspnea, patients who wanted to avoid taking oral

medications and drinking water whenever possible to prevent aspiration risks, patients who could not drink water when thirsty at the desired timing due to being placed on NPPV or on oxygen therapy. The study suggested the efficacy of OPC-61815 in these patients, and OPC-61815 has acceptable safety if appropriate cautionary statement is provided [see Sections "7.R.2.2 Appropriateness of the design of Study 00004 and efficacy of OPC-61815" and "7.R.3 Safety"]; therefore, OPC-61815 can also be used for treating patients who have difficulty with oral fluid intake. The inclusion criteria for Study 00004 include "patients who are unable to sense thirst"; however, information on the presence/absence of thirst was not collected, making it impossible to identify the number of patients who were unable to sense thirst. Because of inability to take fluids orally, patients with hepatic encephalopathy, a patient population excluded from Study 00004, may also be considered to be equivalent to "patients who have difficulty with oral fluid intake." Therefore, it is considered that "patients who are unable to sense thirst or who have difficulty with fluid intake" and "patients with hepatic encephalopathy who have difficulty maintaining an adequate fluid intake" can be included in the intended patient population of OPC-61815, although oral tolvaptan is contraindicated in these patients, provided that the patient's fluid balance is closely managed by healthcare professionals, equivalent to that implemented in Study 00004. The above indicated that the package insert (draft) should include cautionary statements to the effect that when OPC-61815 is administered to patients who have difficulty with oral fluid intake, treatment should be started at 8 mg, half the usual dose, with the dose being increased if the response is not adequate, and provided an increase of >10 mEq/L in serum sodium concentration within 24 hours following initiation of OPC-61815 administration is not observed. Additionally, based on the protocol-specified procedure for monitoring in Study 00004, the following should also be included in the cautionary statements to ensure suitable management of fluid balance:

- At an early stage after the start of treatment or at the time of dose escalation of OPC-61815, dehydration, hypernatraemia, and other adverse drug reactions associated with excessive diuresis may occur.
- The urine volume and water intake (including infusion volume) should be monitored at the following approximate time points: every hour up to 2 hours after the start of administration and every 2 hours thereafter up to 8 hours after the start of administration; after dose escalation, at 4 hours and 8 hours after the start of administration. The infusion volume should be adjusted based on the fluid balance. If the patient continues to receive treatment, the fluid balance should be examined every day.
- The patient's condition should be monitored through frequent measurement of body weight, blood pressure, pulse rate, and other parameters.
- When the dose is escalated, serum sodium concentration should be measured at least at 4 to 6 hours and 8 to 12 hours after the start of administration.

PMDA's view:

Study 00003, which was conducted in patients with congestive heart failure who had an inadequate response to other diuretics such as loop diuretics, demonstrated the non-inferiority of OPC-61815 to oral tolvaptan in terms of efficacy in patients who are capable of oral intake, as well as acceptable safety. Study 00004, which was conducted in patients with congestive heart failure who were assessed as having difficulty with or being incapable of oral intake, demonstrated the efficacy of OPC-61815 as well as acceptable safety when patients were monitored in accordance with the protocol-specified procedure. Therefore, PMDA concluded that the

indication of OPC-61815 for the present application should be “treatment of fluid retention in heart failure when treatment with other diuretics including loop diuretics is not sufficiently effective,” equivalent to that for oral tolvaptan, while the intended patient population should include patients who have difficulty with or are incapable of oral fluid intake provided that fluid management based on appropriate monitoring and adjustment of infusion volume is implemented by healthcare professionals.

In view of the discussion in Section 7.R.3, the applicant explained that for patients who have difficulty with or are incapable of oral fluid intake, the package insert (draft) should include a cautionary statement to the effect that the patient’s fluid balance should be monitored and managed in accordance with the protocol-specified procedure for monitoring in Study 00004. While the applicant’s approach is generally reasonable, it is appropriate to provide a cautionary statement to the effect that after dose escalation, serum potassium concentration should be measured at time intervals equivalent to those implemented for Study 00004 as well as those implemented for serum sodium concentration.

The appropriateness of PMDA’s conclusion above will be finalized taking into account the comments from the Expert Discussion.

7.R.6 Post-marketing investigations

The applicant’s explanation about the post-marketing investigations for OPC-61815:

The applicant plans to conduct a general use-results survey (observation period, 2 weeks from the start of treatment; target sample size, 1300 patients as the safety analysis set) on hypernatraemia, rapid increase in serum sodium concentration/osmotic demyelination syndrome, dehydration, and hyperkalaemia, which are listed as important identified risks in the safety specifications included in the risk management plan (draft), as an additional pharmacovigilance activity to confirm the incidence and the effect of risk factors (capability of oral fluid intake, fluid balance, and predose serum sodium concentration) in clinical use. The target sample size is the number of patients required to detect increased risks for hypernatraemia, dehydration, and hyperkalaemia in a population with risk factors, and the sample size allows estimation of the incidence of rapid increase in serum sodium concentration at an acceptable level of accuracy. Of the safety specifications, the following items do not constitute concerns that require further investigation after the market launch of OPC-61815, and routine pharmacovigilance activities should be performed: thrombosis/thromboembolism, renal failure/renal impairment, acute hepatic failure/hepatic dysfunction, shock/anaphylaxis, excessive decrease in blood pressure/ventricular fibrillation/ventricular tachycardia, gout/hyperuricaemia, dizziness, diabetes mellitus/hyperglycaemia, syncope/loss of consciousness, drug interaction (coadministration with CYP3A4 inhibitors), glaucoma, gastrointestinal haemorrhage, neoplasm skin (basal cell carcinoma/malignant melanoma).

PMDA’s view:

The major activity of OPC-61815 is the same as that of oral tolvaptan; therefore, in addition to the safety specifications listed by the applicant, the following items that were listed by the applicant as the safety specifications in the risk management plan for oral tolvaptan should also be listed as safety specifications in

the risk management plan for OPC-61815 and investigated based on the post-marketing data for oral tolvaptan and that for OPC-61815: thirst, hepatic encephalopathy, patients with a serum sodium concentration of <125 mEq/L, effects on mid- to long-term prognosis of heart failure, patients with renal impairment, and coadministration with conventional heart failure drugs. On the basis of the incidence of adverse events of special interest in the clinical studies for OPC-61815, and the fact that frequent confirmation of fluid balance and adjustment of infusion volume by healthcare professionals are considered to be required in patients who have difficulty with oral fluid intake, additional pharmacovigilance activities should be performed on risks associated with the aquaretic effect (e.g., thirst, thrombosis/thromboembolism, dizziness, syncope/loss of consciousness, excessive decrease in blood pressure/ventricular fibrillation/ventricular tachycardia) to identify risk factors, including their occurrence and fluid management status in clinical use. Identification of safety specifications, adequacy of risk classification, and the appropriateness of pharmacovigilance activities and risk minimization activities will be finalized in accordance with the "Risk Management Plan Guidance" (PFSB/SD Notification No. 0411-1, and PFSB/ELD Notification No. 0411-2, dated April 11, 2012), taking into account the comments from the Expert Discussion.

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 5.3.5.1-01) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that OPC-61815 has efficacy in the treatment of fluid retention in heart failure when treatment with other diuretics including loop diuretics is not sufficiently effective, and that OPC-61815 has acceptable safety in view of its benefits. OPC-61815 is an aquaretic mediated by the V_2-receptor and is administered by intravenous infusion. OPC-61815 is clinically meaningful because it makes a new treatment option available to improve fluid retention for patients with heart failure who have difficulty with or are incapable of oral intake and patients with heart failure who are capable of taking oral medications but for whom intravenous treatment is considered appropriate. PMDA considers that dosage and administration, the details of cautionary statements in the package insert, and post-marketing investigations should be subject to further discussions.

PMDA has concluded that OPC-61815 may be approved if OPC-61815 is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 3, 2022

Product Submitted for Approval

Brand Name	Samtasu for I.V. Infusion 8 mg Samtasu for I.V. Infusion 16 mg
Non-proprietary Name	Tolvaptan Sodium Phosphate
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	March 22, 2021

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 Clinical positioning

OPC-61815 is clinically meaningful because it makes a new treatment option available for patients with heart failure who have fluid retention despite treatment with other diuretics such as loop diuretics and have difficulty with or are incapable of taking oral medications, and patients with heart failure who are capable of taking oral medications but in whom intravenous treatment is considered appropriate. The expert advisors supported the PMDA's conclusion.

1.2 Safety

The expert advisors commented that whether the cautionary statements sufficiently address the risks associated with an increase in blood potassium concentration requires further assessment taking the following issues into account. PMDA asked the applicant to explain the issues:

- When an increase in blood potassium concentration is detected, whether any change caused by the increase is found in the electrocardiogram at the same time
- Whether decline in renal function (especially eGFR <60 mL/min/1.73 m^2) can affect the development of risks associated with an increase in blood potassium concentration induced by OPC-61815

The applicant's explanation:

In the OPC-61815 16 mg group in the pooled data from Studies 00001 and 00003, and in Study 00004, of the 21 subjects at 28 time points that indicated high blood potassium concentration, electrocardiograms were measured in 9 subjects at 12 time points on the same day. No electrocardiogram abnormalities (e.g., tented T wave, missing P wave, QRS prolongation) were found among these subjects. Table 40 shows the incidence of events related to an increase in blood potassium concentration by baseline renal function (eGFR) in the OPC-61815 16 mg group in the pooled data from Studies 00001 and 00003, and in Study 00004. The incidence of events related to an increase in blood potassium concentration tended to be higher in the eGFR <60 mL/min/1.73 m^2 group than in the eGFR ≥60 mL/min/1.73 m^2 group.

Table 40. Incidence of events related to an increase in blood potassium concentration by baseline renal function (eGFR) (safety analysis set)

	Pooled data from Studies 00001 and 00003						00004 (N = 45)		
	≥60		≥30 and <60		<30				
	OPC-61815 16 mg (N = 33)	Oral tolvaptan (N = 25)	OPC-61815 16 mg (N = 98)	Oral tolvaptan (N = 96)	OPC-61815 16 mg (N = 29)	Oral tolvaptan (N = 36)	≥60 (N = 13)	≥30 and <60 (N = 24)	<30 (N = 8)
Hyperkalaemia-related adverse events	6.1 (2)	4.0 (1)	9.2 (9)	3.1 (3)	10.3 (3)	0 (0)	0 (0)	4.2 (1)	0 (0)
Clinically significant increase in serum potassium concentration[a]	6.1 (2)	4.0 (1)	16.3 (16)	9.4 (9)	10.3 (3)	13.9 (5)	0 (0)	0 (0)	0 (0)

Incidence, % (n)

a, When graded on a 5-point scale (Grade 0 [≤ULN], Grade 1 [>ULN and ≤5.5 mEq/L], Grade 2 [>5.5 mEq/L and ≤6 mEq/L], Grade 3 [>6 mEq/L and ≤7 mEq/L], and Grade 4 [>7 mEq/L]), "clinically significant" was defined as worsening by ≥2 grades if the event was rated as ≤Grade 1 at baseline, and as worsening by ≥1 grade if the event was rated as ≥Grade 2 at baseline.

In light of the above, hyperkalaemia will be defined as a clinically significant adverse reaction in the package insert, as proposed in the discussion in Review Report (1), and a statement will be included to the effect that patients whose serum potassium concentrations exceed the normal range or near the high end of the normal range require particular caution. In addition, taking into account the comments from PMDA, it was decided to add cautionary statements to the effect that patients should be monitored closely by measuring serum potassium concentration at the same intervals as those in the clinical studies, and that patients with renal impairment (eGFR <60 mL/min/1.73 m^2) may be at an increased risk for hyperkalaemia.

PMDA concluded that the applicant's action is appropriate based on the presented data, and the expert advisors finally supported the PMDA's conclusion.

The expert advisors also commented that information on the differences between OPC-61815 and oral tolvaptan with respect to the incidence and onset time of events related to an increase in blood sodium concentration or blood potassium concentration should be provided in an appropriate manner using information materials such as materials for healthcare professionals, and the applicant took appropriate action.

1.3 Dosage and administration

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown in Section "7.R.4 Dosage and administration" in Review Report (1).

In view of the above, PMDA concluded that the dosage and administration and cautionary statements to be included in the "Precautions Concerning Dosage and Administration" section of the package insert should be as shown below.

Dosage and Administration

The usual adult dosage is 16 mg of tolvaptan sodium phosphate once daily administered as an intravenous infusion over 1 hour.

Precautions Concerning Dosage and Administration (excerpted)

- When OPC-61815 is administered to patients who have difficulty with oral fluid intake, treatment should be started at 8 mg, half the usual dose. The dose may be increased to 16 mg on the following day or later if the patient's response to treatment has been inadequate. However, if there is an increase of >10 mEq/L in serum sodium concentration within 24 hours after start of OPC-61815 administration, do not increase the dose on the following day.
- For patients with a serum sodium concentration of <125 mEq/L, patients for whom rapid reduction in circulatory blood flow is considered unfavorable, older adult patients, and patients whose serum sodium concentrations are near the high end of the normal range, starting treatment at half the usual dose of OPC-61815 (8 mg) is recommended.
- Treatment with OPC-61815 should be discontinued when fluid retention symptoms have resolved. Efficacy in preventing recurrence of fluid retention symptoms after their resolution has not been established.

Important Precautions (excerpted)

- If there is no further improvement in fluid retention status, administration should not be continued without careful consideration.
- When body weight has decreased to the targeted weight (body weight when fluid retention is well controlled), administration of OPC-61815 should not be continued without careful consideration.

1.4 Indication and patient population

The indication for the present application should be the same as that for oral tolvaptan, "treatment of fluid retention in heart failure when treatment with other diuretics including loop diuretics is not sufficiently effective." It is not necessary to contraindicate OPC-61815 in patient populations in which oral tolvaptan is contraindicated, i.e., "patients who are unable to sense thirst or who have difficulty with fluid intake" and "patients with hepatic encephalopathy who have difficulty maintaining an adequate fluid intake," provided that appropriate cautionary statement is provided regarding the treatment of patients who have difficulty with oral

fluid intake. The expert advisors supported this conclusion by PMDA. The expert advisors commented that a statement to the effect that when treating patients who have difficulty with oral fluid intake, OPC-61815 should be administered under the condition that fluid management can also be implemented as necessary by securing venous access, etc. to ensure that treatment can be performed safely.

In view of the above, PMDA concluded that the indication and cautionary statements to be included in the "Precautions Concerning Indication" section of the package insert should be as shown below:

Indication

Treatment of fluid retention in heart failure when treatment with other diuretics including loop diuretics is not sufficiently effective

Precautions Concerning Patients with Specific Backgrounds

- Patients who have difficulty with oral fluid intake

The precautions below should be followed to ensure suitable management of fluid balance. Note that at an early stage after the start of treatment or at the time of dose escalation of OPC-61815, dehydration, hypernatraemia, and other adverse drug reactions associated with excessive diuresis may occur.

- Fluid management should be performed with an infusion solution, etc.
- The urine volume and water intake (including infusion volume) should be monitored at the following approximate time points: every hour up to 2 hours after the start of administration and every 2 hours thereafter up to 8 hours after the start of administration; after dose escalation, at 4 hours and 8 hours after the start of administration. The infusion volume should be adjusted based on the fluid balance. If the patient continues to receive treatment, the fluid balance should be examined every day.
- The patient's condition should be monitored through frequent measurement of body weight, blood pressure, pulse rate, and other parameters.
- When the dose is escalated, serum sodium concentration and serum potassium concentration should be measured at least at 4 to 6 hours and 8 to 12 hours after the start of administration.

1.5 Risk management plan (draft)

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for OPC-61815 should include the safety specification presented in Table 41, the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 42, and that the applicant should conduct a general use-results survey presented in Table 43.

Table 41. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Thirst • Hypernatraemia • Rapid increase in serum sodium concentration/osmotic demyelination syndrome • Dehydration • Thrombosis/thromboembolism • Renal failure/renal impairment • Acute hepatic failure/hepatic dysfunction • Shock/anaphylaxis • Excessive decrease in blood pressure/ventricular fibrillation/ventricular tachycardia • Gout/hyperuricaemia • Dizziness • Hyperkalaemia • Diabetes mellitus/hyperglycaemia • Syncope/loss of consciousness • Hepatic encephalopathy • Glaucoma	• Drug interaction (coadministration with CYP3A4 inhibitors) • Gastrointestinal haemorrhage • Neoplasm skin (basal cell carcinoma/malignant melanoma)	• Patients with a serum sodium concentration of <125 mEq/L • Effects on mid- to long-term prognosis of heart failure • Patients with renal impairment who have fluid retention associated with heart failure • Coadministration with conventional heart failure drugs in patients with fluid retention associated with heart failure
Efficacy specification		
Not applicable		

Table 42. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate information material for healthcare professionals (Material 1: Before prescribing Samtasu for I.V. Infusion) • Organize and disseminate information material for patients and their families (Material 2: For patients receiving Samtasu for I.V. Infusion and their families or caregivers)

Table 43. Outline of general use-results survey (draft)

Objective	Investigation of safety in clinical use
Survey method	Continuous registry
Population	Patients who are treated with OPC-61815
Observation period	14 days
Registration period	For 3 years after the completion of early post-marketing phase vigilance
Planned sample size	1600 patients (number of patients subject to safety analysis)
Main survey items	Items including patient characteristics, status of treatment with OPC-61815, concomitant therapy (diuretics other than OPC-61815, concomitant drugs other than diuretics, nonpharmacological therapy), status of fluid balance, serum sodium concentration, serum potassium concentration, and adverse events

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition. Since the product is classified as 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

Treatment of fluid retention in heart failure when treatment with other diuretics including loop diuretics is not sufficiently effective

Dosage and Administration

The usual adult dosage is 16 mg of tolvaptan sodium phosphate once daily administered as an intravenous infusion over 1 hour.

Approval Condition

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

Appendix

List of Abbreviations

A→B	apical-to-basolateral
ACE	Angiotensin converting enzyme
ACP	Acid phosphatase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
ARB	Angiotensin II receptor blocker
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from zero to infinity
AUC_{0-last}	Area under the plasma concentration-time curve from zero to the time of last measurement
AUC_{0-t}	Area under the plasma concentration-time curve from zero to time t
B→A	basolateral-to-apical
BCRP	Breast cancer resistance protein
BSEP	Bile salt export pump
cAMP	Cyclic adenosine monophosphate
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Total body clearance
CM	Cimetidine
C_{max}	Maximum plasma concentration
C_{trough}	Trough plasma concentration
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
DPH	Diphenhydramine
eGFR	Estimated glomerular filtration rate
HEK	Human embryonic kidney cells
HeLa	Human endocervical carcinoma cell line
hERG	Human ether a-go-go related gene
HPLC	High performance liquid chromatography
HPLC-UV	HPLC-Ultraviolet spectroscopy
IC_{50}	Half maximal inhibitory concentration
ICH Q1E Guidelines	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Q1E Guidelines: “Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated June 3, 2003)
ICH S1 Guidelines	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use S1 Guidelines: “Guidelines on the Need for Carcinogenicity Studies of Pharmaceuticals” (PAB/ELD Notification No. 315 of the Evaluation and Licensing Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated April 14, 1997)
IR	Infrared spectroscopy
K_i	Inhibition constant

LC-MS/MS	Liquid chromatography coupled with tandem mass spectrometry
LLC-PK1	Lewis lung carcinoma pork kidney cell line
MATE	Multidrug and toxin extrusion
MDCK	Madin-Darby canine kidney
MedDRA HLT	Medical Dictionary for Regulatory Activities High level Term
MedDRA PT	Medical Dictionary for Regulatory Activities Preferred Term
MedDRA SMQ	Medical Dictionary for Regulatory Activities standardised MedDRA queries
mRNA	Messenger ribonucleic acid
MS	Mass spectrometry
NCI ODWG	National Cancer Institute Organ Dysfunction Working Group
NMR	Nuclear magnetic resonance spectroscopy
NPPV	Noninvasive positive pressure ventilation
NYHA	New York Heart Association
NZW	New Zealand White
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OOT	Out of trend
OPC-61815	Tolvaptan sodium phosphate
PAP	Prostatic acid phosphatase
P_{app}	Apparent permeability coefficient
PBPK	Physiologically-based pharmacokinetics
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetic
PV	Process validation
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT Interval
RH	Relative humidity
Samtasu for I.V. Infusion	Samtasu for I.V. Infusion 8 mg Samtasu for I.V. Infusion 16 mg
SD	Sprague-Dawley
SGLT2	Sodium glucose cotransporter 2
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
Study 00001	Study 263-102-00001
Study 00003	Study 263-102-00003
Study 00004	Study 263-102-00004
$t_{1/2}$	Elimination half-life
t_{max}	Time of maximum plasma concentration
TRACP-5b	Tartrate resistant acid phosphatase-5b
ULN	Upper limit of normal
UV-A	Ultraviolet A
UV-VIS	Ultraviolet-visible spectroscopy
V_{1a}-receptor	Vasopressin V_{1a} receptor
V_{1b}-receptor	Vasopressin V_{1b} receptor
V_2-receptor	Vasopressin V_2 receptor

V_z	Volume of distribution during terminal phase