Report on the Deliberation Results

March 3, 2014

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

[Brand name]	(a) Samsca Tablets 7.5 mg (b) Samsca Tablets 15 mg (c) Samsca Tablets 30 mg
[Non-proprietary name]	Tolvaptan (JAN*)
[Name of applicant]	Otsuka Pharmaceutical Co., Ltd.
[Date of application]	May 30, 2013

[Results of deliberation]
In the meeting held on February 24, 2014, the First Committee on New Drugs concluded that applications for partial changes for Samsca Tablets 7.5 mg and 15 mg and a new drug application for Samsca Tablets 30 mg may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

Since Samsca has been designated as an orphan drug for the indication of autosomal dominant polycystic kidney disease, its re-examination period is 10 years for the indication and the dosage and administration proposed in the current application. With respect to Samsca Tablets 30 mg, the drug product is classified as a powerful drug, and the product is not classified as a biological product or a specified biological product.

[Conditions for approval]
(a) and (b) to be used for slowing the progression of autosomal dominant polycystic kidney disease in patients with an increased kidney volume and a rapid rate of kidney volume increase,
The applicant is required to:

1. Take necessary measures prior to marketing to ensure that Samsca is prescribed only by physicians who fully understand the treatment of autosomal dominant polycystic kidney disease and the risks of Samsca and who comply with the proper use of Samsca with regard to selection of eligible patients and periodic monitoring of liver function and serum sodium concentrations and that medical institutions/pharmacies verify that Samsca has been prescribed by a relevant physician, prior to dispensing Samsca.
2. Conduct a post-marketing surveillance study, which will cover all patients treated with Samsca, until data from a specific number of patients are collected, in order to collect data on the safety and efficacy of Samsca as early as possible and to take necessary measures to ensure the proper use of Samsca. Periodically report the collected results.

(c)
The applicant is required to:

1. Take necessary measures prior to marketing to ensure that Samsca is prescribed only by physicians who fully understand the treatment of autosomal dominant polycystic kidney disease and the risks of Samsca and who comply with the proper use of Samsca with regard to selection of eligible patients and periodic

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monitoring of liver function and serum sodium concentrations and that medical institutions/pharmacies verify that Samsca has been prescribed by a relevant physician, prior to dispensing Samsca.

2. Conduct a post-marketing surveillance study, which will cover all patients treated with Samsca, until data from a specific number of patients are collected, in order to collect data on the safety and efficacy of Samsca as soon as possible and to take necessary measures to ensure the proper use of Samsca. Periodically report the collected results.

(Underline denotes new additions.)

**Japanese Accepted Name (modified INN)*

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Review Report

February 7, 2014
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	(a) Samsca Tablets 7.5 mg (b) Samsca Tablets 15 mg (c) Samsca Tablets 30 mg		
[Non-proprietary name]	Tolvaptan		
[Name of applicant]	Otsuka Pharmaceutical Co., Ltd.		
[Date of application]	May 30, 2013		
[Dosage form/Strength]	Each tablet contains 7.5 mg, 15 mg, or 30 mg of Tolvaptan		
[Application classification]			
	(a) and (b):	Prescription drug	(4) Drugs with new indications and (6) Drugs with new dosages
	(c):	Prescription drug	(4) Drugs with new indications, (6) Drugs with new dosages, and (8) Drugs with additional dosage forms
[Items warranting special mention]	Orphan drug (Designation No. 193 [18 yaku], PFSB/ELD Notification No. 0811002 dated August 11, 2006)		
[Reviewing office]	Office of New Drug II		

Review Results

February 7, 2014

[Brand name]	(a) Samsca Tablets 7.5 mg (b) Samsca Tablets 15 mg (c) Samsca Tablets 30 mg
[Non-proprietary name]	Tolvaptan
[Name of applicant]	Otsuka Pharmaceutical Co., Ltd.
[Date of application]	May 30, 2013

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of Samsca in slowing the progression of autosomal dominant polycystic kidney disease in patients who have an already-large and rapidly increasing kidney volume has been demonstrated. Given that the benefits of Samsca is considered to outweigh the risks such as adverse reactions (hepatic dysfunction) in patients with an increased kidney volume and a rapid rate of kidney volume increase and that appropriate monitoring for serious hepatic dysfunction and hypernatremia is required, it is necessary to prepare a system under which Samsca is prescribed only by physicians with adequate knowledge about autosomal dominant polycystic kidney disease and Samsca, thereby ensuring the proper use of Samsca. The occurrence of adverse events such as hepatic dysfunction, dehydration associated with aquaresis, an increase in serum sodium levels including central pontine myelinolysis, and hyperkalaemia, and the long-term safety and efficacy of Samsca, etc. need to be further investigated via post-marketing surveillance.

As a result of its review, PMDA has concluded that Samsca may be approved for the Indication and the Dosage and Administration as shown below, with the following conditions.

[Indications]

(a)

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

(b)

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

(c)

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.

(Underline denotes new additions proposed in the current application and double underline denotes additions proposed as of September 13, 2013 after the submission of the current application.)

[Dosage and Administration]

(a)

・ For the treatment of fluid retention in heart failure

The usual adult dosage of Tolvaptan is 15 mg once daily administered orally.

・ For the treatment of fluid retention in hepatic cirrhosis

The usual adult dosage of Tolvaptan is 7.5 mg once daily administered orally.

・ For slowing the progression of autosomal dominant polycystic kidney disease

The usual initial adult dosage of Tolvaptan is 60 mg per day as a split-dose oral regimen of 45 mg/15 mg (morning/evening). When Tolvaptan is tolerated at 60 mg per day for ≥1 week, the dose may be increased to 90 mg (60 mg/30 mg) per day and then to 120 mg (90 mg/30 mg) per day in a step-wise manner with a ≥1-week interval between titrations. The dose may be adjusted, as appropriate, based on tolerability, but the maximum dose should not exceed 120 mg per day.

(b)

・ For the treatment of fluid retention in heart failure

The usual adult dosage of Tolvaptan is 15 mg once daily administered orally.

・ For slowing the progression of autosomal dominant polycystic kidney disease

The usual initial adult dosage of Tolvaptan is 60 mg per day as a split-dose oral regimen of 45 mg/15 mg (morning/evening). When Tolvaptan is tolerated at 60 mg per day for ≥1 week, the initial dose may be increased to 90 mg (60 mg/30 mg) per day and then to 120 mg (90 mg/30 mg) per day in a step-wise manner with a ≥1-week interval between titrations. The dose may be adjusted, as appropriate, based on tolerability, but the maximum dose should not exceed 120 mg per day.

(c)

The usual initial adult dosage of Tolvaptan is 60 mg per day as a split-dose oral regimen of 45 mg/15 mg (morning/evening). When Tolvaptan is tolerated at 60 mg per day for ≥1 week, the initial dose may be increased to 90 mg (60 mg/30 mg) per day and then to 120 mg (90 mg/30 mg) per day in a step-wise manner with a ≥1-week interval between titrations. The dose may be adjusted, as appropriate, based on tolerability, but the maximum dose should not exceed 120 mg per day.

(Underline denotes new additions proposed in the current application and double underline denotes additions proposed as of September 13, 2013 after the submission of the current application.)

[Conditions for approval]

(a) and (b) to be used for slowing the progression of autosomal dominant polycystic kidney disease in patients with an increased kidney volume and a rapid rate of kidney volume increase

The applicant is required to:

1. Take necessary measures prior to marketing to ensure that Samsca is prescribed only by physicians who fully understand the treatment of autosomal dominant polycystic kidney disease and the risks of Samsca and who comply with the proper use of Samsca with regard to selection of eligible patients and periodic monitoring of liver function and serum sodium concentrations and that medical institutions/pharmacies verify that Samsca has been prescribed by a relevant physician, prior to dispensing Samsca.
2. Conduct a post-marketing surveillance study, which will cover all patients treated with Samsca, until data from a specific number of patients are collected, in order to collect data on the safety and efficacy of Samsca as early as possible and to take necessary measures to ensure the proper use of Samsca. Periodically report the collected results.

(c)

The applicant is required to:

1. Take necessary measures prior to marketing to ensure that Samsca is prescribed only by physicians who fully understand the treatment of autosomal dominant polycystic kidney disease and the risks of Samsca and who comply with the proper use of Samsca with regard to selection of eligible patients and periodic monitoring of liver function and serum sodium concentrations and that medical institutions/pharmacies verify that Samsca has been prescribed by a relevant physician, prior to dispensing Samsca.
2. Conduct a post-marketing surveillance study, which will cover all patients treated with Samsca, until data from a specific number of patients are collected, in order to collect data on the safety and efficacy of Samsca as early as possible and to take necessary measures to ensure the proper use of Samsca. Periodically report the collected results.

(Underline denotes new additions.)

Review Report (1)

November 21, 2013

I. Product Submitted for Registration

[Brand name]	(a) Samsca Tablets 7.5 mg (b) Samsca Tablets 15 mg (c) Samsca Tablets 30 mg
[Non-proprietary name]	Tolvaptan
[Name of applicant]	Otsuka Pharmaceutical Co., Ltd.
[Date of application]	May 30, 2013
[Dosage form/Strength]	(a), (b), and (c): Each tablet contains 7.5 mg, 15 mg, or 30 mg of Tolvaptan

[Proposed indication]

(a) and (b):

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

Slowing of the progression of autosomal dominant polycystic kidney disease.

(c):

Slowing of the progression of autosomal dominant polycystic kidney disease.

(Underline denotes new additions.)

[Proposed dosage and administration]

(a) and (b):

For the treatment of fluid retention in heart failure

The usual adult dosage of Tolvaptan is 15 mg once daily administered orally.

For slowing the progression of autosomal dominant polycystic kidney disease

The usual initial adult dosage of Tolvaptan is 60 mg per day as a split-dose oral regimen of 45 mg/15 mg (morning/evening). When Tolvaptan is tolerated at 60 mg per day for ≥1 week, the initial dose may be increased to 90 mg (60 mg/30 mg) per day and then to 120 mg (90 mg/30 mg) per day in a step-wise manner with a ≥1-week interval between titrations. The dose may be adjusted, as appropriate, based on tolerability, but the maximum dose should not exceed 120 mg per day.

(c):

The usual initial adult dosage of Tolvaptan is 60 mg per day as a split-dose oral regimen of 45 mg/15 mg (morning/evening). When Tolvaptan is tolerated at 60 mg per day for ≥1 week, the initial dose may be increased to 90 mg (60 mg/30 mg) per day and then to 120 mg (90 mg/30 mg) per day in a step-wise manner with a ≥1-week interval between titrations. The dose may be adjusted, as appropriate, based on tolerability, but the maximum dose should not exceed 120 mg per day.

(Underline denotes new additions.)

II. Summary of the Submitted Data and Outline of Review

The data submitted in the application and the outline of a review by the Pharmaceuticals and Medical

Devices Agency (PMDA) are as follows.

The current applications have been submitted for new indications, new dosages, and an additional dosage form, and the data packages submitted include "data relating to quality," "non-clinical data" from primary pharmacodynamic studies only, and "clinical data." As a result of its review of the additional dosage form, PMDA found no major problems. Thus, this report contains a review of the new indications and new dosages only.

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

Tolvaptan is a nonpeptide vasopressin V_2-receptor antagonist synthesized by Otsuka Pharmaceutical Co., Ltd. and reduces renal cyst growth by inhibiting vasopressin-stimulated increases in intracellular cyclic AMP in polycystic kidney disease. It also produces aquaresis by inhibiting vasopressin-stimulated water reabsorption in the collecting duct of the kidney.

In Japan, tolvaptan was developed by Otsuka Pharmaceutical Co., Ltd. and Samsca Tablets 15 mg was approved for the indication of treatment of "fluid retention in heart failure when treatment with other diuretics including loop diuretics is not sufficiently effective" (fluid retention in heart failure) in October 2010 and a new 7.5-mg tablet dosage form was approved for this indication in February 2013. An additional indication of treatment of "fluid retention in hepatic cirrhosis when treatment with other diuretics including loop diuretics is not sufficiently effective" (fluid retention in hepatic cirrhosis) and its dosage were approved for Samsca ablets 7.5 mg in September 2013.

Outside Japan, tolvaptan was approved for "the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH)" in the US in May 2009 and for "the treatment of adult patients with hyponatraemia secondary to SIADH" in the EU in August 2009. As of October 2013, tolvaptan has been approved for varying indications in 41 countries or regions.

For the indication of autosomal dominant polycystic kidney disease, a new drug application, based primarily on the results from a multinational clinical trial (including Japan), was filed in the US in [redacted] 20[redacted]. Now, also in Japan, applications for partial changes for Samsca Tablets 7.5 mg and 15 mg to obtain approval for an additional indication of "slowing of the progression of autosomal dominant polycystic kidney disease" and its dosage and a new drug application for a new 30-mg tablet dosage form for this indication etc. were submitted. FDA issued a complete response letter that indicated its decision not to approve the application in [redacted] 20[redacted] [see "3.(iii).B.(3).4) Details of regulatory review in the US" for details].

In Japan, tolvaptan has been designated as an orphan drug with the intended indication of "slowing of the progression of polycystic kidney disease" (Designation No. 193 [18 yaku], PFSB/ELD Notification No. 0811002 dated August 11, 2006).

2. Non-clinical data

2.(i) Summary of pharmacology studies

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

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

2.(i).A.(1).1) Effects on cells cultured from the renal cysts of patients with autosomal dominant polycystic kidney disease (Attached document 4.2.1.1-09)

Primary cell cultures of renal cysts from patients with autosomal dominant polycystic kidney disease (ADPKD) were pretreated with tolvaptan (10^{-12} to 10^{-7} mol/L) and then incubated with vasopressin (10^{-9} mol/L). The number of cells after 48 hours of incubation and intracellular cyclic AMP (cAMP) levels, extracellular signal-regulated kinase (ERK) activity, and B-rapidly accelerated fibrosarcoma (B-Raf) activity after 15 minutes incubation were assessed. Tolvaptan caused a concentration-dependent inhibition of vasopressin-induced cell proliferation and intracellular cAMP production. Tolvaptan also concentration-dependently inhibited vasopressin-induced activation of intracellular B-Raf and ERK, which are downstream of cAMP and involved in cell proliferation.

2.(i).A.(1).2) Effects in animal models of polycystic kidney disease

Three different animal models of polycystic kidney disease (PKD), each caused by different genes, (DBA/2:FG-*pcy* mice, PCK rats, $Pkd2^{WS25/-}$ mice) were used. Animals were fed tolvaptan in their diet to investigate the inhibitory effects of tolvaptan on PKD.

2.(i).A.(1).2).(a) Effects in DBA/2:FG-*pcy* mice (Attached documents 4.2.1.1-01 to 4.2.1.1-03)

Male DBA/2:FG-*pcy* mice (5 weeks of age) were maintained on a diet containing 0.1% tolvaptan until 29 weeks of age and kidney volumes (left kidneys) evaluated by magnetic resonance imaging (MRI) and renal function parameters (urinary albumin excretion and blood urea nitrogen [BUN]) in these animals were compared with those in animals maintained on a tolvaptan-free diet (control group) (n = 15/group). A significant increase in kidney volume and renal cysts were detected in the control group compared with normal controls without *pcy* mutations, i.e. DBA/2JJcl mice (normal group), from 4 weeks of age (before drug treatment) and the kidney volume was maximal at 16 to 20 weeks of age. There were significant differences in kidney volume growth between the tolvaptan and control groups at 12 weeks of age and thereafter, and the inhibitory effect of tolvaptan was sustained until the end of the study. Urine volume was high and urine osmolality was low in the tolvaptan group compared with the control group throughout the study period. Regarding renal function, increases in urinary albumin excretion and BUN were observed in both the tolvaptan and control groups. Although urinary albumin excretion was significantly low in the tolvaptan group compared with the control group, there were no significant differences in BUN between the tolvaptan and control groups. By 29 weeks of age, 9 of 15 animals in the control group and 3 of 15 animals in the tolvaptan group died.

Male DBA/2:FG-*pcy* mice (5 weeks of age) were maintained on a diet containing 0.01%, 0.03%, 0.1%, or 0.3% tolvaptan until 15 weeks of age and controls were maintained on a tolvaptan-free diet (n = 14/group).

Diets containing 0.03% to 0.3% tolvaptan dose-dependently inhibited increases in kidney weight, renal cystic volume, fibrotic volume, and proliferating cell nuclear antigen (PCNA)-positive cells, a measure of cell proliferation. Regarding renal function, tolvaptan dose-dependently inhibited increases in urinary neutrophil gelatinase-associated lipocalin (NGAL) at 14 to 15 weeks of age. No apparent increases in urinary albumin excretion, serum creatinine, or BUN were observed in all groups including the control group. Dietary administration of tolvaptan increased urine volume and decreased urine osmolality; the increases in urine volume were significant in animals fed diets containing 0.03% to 0.3% tolvaptan and the decreases in urine osmolality were significant in animals fed diets containing 0.01% to 0.3% tolvaptan. The inhibitory effects of tolvaptan on kidney weight and renal cystic volume and its aquaretic effect were almost maximal in animals fed a diet containing 0.1% tolvaptan, and the serum tolvaptan concentration at necropsy (in the morning) was 146.0 ng/mL. Tolvaptan also reduced renal cAMP and ERK activity in a dose-dependent manner. When male DBA/2:FG-*pcy* mice (7 weeks of age) were maintained on a diet containing 0.1% tolvaptan for 2 weeks, the mean serum tolvaptan concentrations were 177.9 ng/mL in the morning, 49.3 ng/mL in the evening, and 467.5 ng/mL at night, showing diurnal variation (n = 3).

2.(i).A.(1).2).(b) Effects in PCK rats (Attached document 4.2.1.1-04)

Male and female PCK rats (3 weeks of age) were maintained on a diet containing 0.01%, 0.03%, or 0.1% tolvaptan until 10 weeks of age and kidney weight, renal cystic volume, renal fibrotic volume, renal function, and urine volume in these animals were compared with those in animals fed a tolvaptan-free diet (control group) (n = 10/sex/group). Kidney weight, renal cystic volume, and renal fibrotic volume were significantly small in the overall tolvaptan group compared with the control group. Mitotic Index (% of PCNA-positive cells out of 500 renal medullary epithelial cells) and Apoptotic Index (% of TUNEL-positive cells out of 500 renal medullary epithelial cells) determined by Terminal Transferase dUTP Nick End Labeling (TUNEL) assay were also significantly small. Although tolvaptan dose-dependently increased urine volume and decreased renal cAMP, no increases in renal function parameters (BUN and plasma creatinine) were observed in all groups including the control group. PCK rats develop not only renal cysts but also hepatic cysts, but tolvaptan had no effects on liver weight.

2.(i).A.(1).2).(c) Effects in Pkd2$^{WS25/-}$ mice (Attached document 4.2.1.1-07)

Male and female Pkd2$^{WS25/-}$ mice (4 weeks of age) were maintained on a diet containing 0.01%, 0.03%, or 0.1% tolvaptan until 16 weeks of age and controls were maintained on a tolvaptan-free diet (n = 9-12/sex/group). Kidney weight and renal fibrotic volume were significantly small and renal cystic volume also tended to be small in the overall tolvaptan group compared with the control group. Mitotic Index and Apoptotic Index were also significantly small. Tolvaptan dose-dependently increased urine volume. Effects on renal function parameters were not dose-dependent, but BUN was significantly low in the overall tolvaptan group compared with the control group. No significant reduction in renal cAMP was observed in the overall tolvaptan group.

2.(i).A.(1).2).(d) Effects of Tolvaptan administered by oral gavage (Attached documents 4.2.1.1-05 and 4.2.1.1-06)

Male PCK rats (5 weeks of age) were orally gavaged with 10 mg/kg of tolvaptan once daily or twice daily until 13 weeks of age (n = 10/group). Although urine volume was significantly large in animals treated with tolvaptan compared with controls treated with vehicle, tolvaptan did not reduce kidney weight, renal cystic volume, renal fibrotic volume, or renal cAMP.

Male Sprague-Dawley (SD) rats (8 weeks of age) were orally gavaged with 10 mg/kg of tolvaptan once daily or twice daily or fed a diet containing 0.01% or 0.1% tolvaptan, and the duration of aquaretic effect was compared (n = 5/group). On Day 7, a diet containing 0.1% tolvaptan caused a significant increase in urinary excretion rate and a significant decrease in urine osmolality throughout 24 hours while once-daily or twice-daily oral gavage of 10 mg/kg of tolvaptan caused a significant increase in urinary excretion rate only for the first 4 hours after administration and a significant decrease in urine osmolality only for 8 hours after administration.

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

The applicant explained the pharmacological effects of tolvaptan as follows:

Vasopressin is thought to stimulate cell proliferation and cystogenesis via intracellular cAMP production and B-Raf and ERK activation. Tolvaptan was considered to inhibit renal cyst growth by inhibiting vasopressin-induced, intracellular cAMP-mediated signaling and kidney-cyst cell proliferation via V_2-receptor inhibition. In addition, tolvaptan has been reported to inhibit vasopressin-induced, cAMP-dependent, cystic fibrosis transmembrane conductance regulator (CFTR) activation in cultured human ADPKD cystic cells (Reif GA et al. *Am J Physiol Renal Physiol.* 2011;301:F1005-13). It is known that the expansion of individual cysts is determined by both cell proliferation and cyst fluid secretion via CFTR activation (Belibi FA et al. *Kidney Int.* 2004;66:964-73), suggesting that inhibition of cAMP-dependent cyst fluid secretion also plays a role in the inhibition of cyst growth by tolvaptan. In studies using animal models of PKD, dietary administration of tolvaptan reduced kidney weight (kidney volume) and inhibited renal cyst growth in three different animal models, i.e. DBA/2:FG-*pcy* mice, PCK rats, and $Pkd2^{WS25/-}$ mice.

PMDA asked the applicant to explain differences in pathology between ADPKD patients and different animal models and the suitability of the animal models for use in studies to support efficacy in ADPKD patients.

The applicant explained as follows:

Although three different animal models of PKD used for the evaluation of the effect of tolvaptan all develop cystic kidneys and renal dysfunction as ADPKD patients do, there are some differences as to the disease gene, concurrent liver enlargement, and the sites for cyst formation in the kidney. The disease genes in spontaneous PKD animal models, DBA/2:FG-*pcy* mice and PCK rats, are *Nphp3* and *Pkhd1*, respectively, and like ADPKD patients, DBA/2:FG-*pcy* mice and PCK rats develop PKD and worsen renal function. Meanwhile, unlike ADPKD patients, DBA/2:FG-*pcy* mice do not develop liver enlargement, and in PCK rats, the renal cysts develop relatively focally in ascending loops of Henle, distal tubules, and

collecting ducts (Takahashi H et al. *J Am Soc Nephrol.* 1991;1:980-9. Lager DJ et al. *Kidney Int.* 2001;59:126-36). The PKD gene in a genetically modified animal model, $Pkd2^{WS25/-}$ mice, is *Pkd2*, which is the same as the ADPKD gene. Also, $Pkd2^{WS25/-}$ mice develop PKD, worsen renal function, and show liver enlargement as a complication, which relatively resembles human ADPKD. Although diffuse renal cysts are observed, a detailed investigation has not been conducted on the sites for renal cyst formation (Wu G et al. *Cell.* 1998;93:177-88), and *Pkd2* is responsible for only approximately 15% of human ADPKD cases. Therefore, it is difficult to identify a suitable animal model for use in studies to support efficacy in ADPKD patients, from a pathophysiological standpoint.

No marked increases in renal function parameters were observed in the control group compared with the normal group for DBA/2:FG-*pcy* mice and PCK rats used in primary pharmacodynamic studies. PMDA asked the applicant to explain its reasons.

The applicant explained as follows:
In a dose response study in DBA/2:FG-*pcy* mice (Attached document 4.2.1.1-02), at necropsy at 15 weeks of age when the kidney volume reaches almost maximal, increases in kidney weight and urinary NGAL excretion were observed while urinary albumin excretion, BUN, and serum creatinine all increased slightly (≤2-fold increases vs. the normal group). In a dietary administration study in PCK rats (Attached document 4.2.1.1-04), at necropsy at 10 weeks of age, renal cysts were detected, but BUN was almost normal. In a chronic administration study in DBA/2:FG-*pcy* mice (Attached document 4.2.1.1-01), urinary albumin excretion increased significantly at 19 weeks of age and thereafter, and BUN significantly increased from early on and rose to ≥2-fold of that in the normal group at 23 weeks of age and thereafter. It has been reported that marked increases in BUN and serum creatinine were noted also in PCK rats, starting from 25 weeks of age (Mason SB et al. *Anat Rec (Hoboken).* 2010;293:1279-88). Basically, kidney enlargement is followed by deterioration of renal function in these models. However, it is considered that as necropsy was performed at a relatively early stage of disease in these studies submitted in the application, renal function parameters did not increase even in the control group compared with the normal group.

PMDA asked the applicant to explain why tolvaptan showed no dose-dependent effects on some endpoints in dietary administration studies in PCK rats and $Pkd2^{WS25/-}$ mice.

The applicant explained as follows:
In a dietary administration study of tolvaptan in PCK rats, tolvaptan showed significant inhibitory effects on renal cystic volume etc., and for most of the endpoints, a diet containing 0.03% tolvaptan and a diet containing 0.1% tolvaptan had almost comparable effects. Thus, the results suggested that tolvaptan may have produced a maximal effect at ≥0.03%. On the other hand, BUN was almost normal in the control group in this study, indicating that the animals were at an early stage in disease progression. Based on the above, the applicant considered that tolvaptan showed no clear dose-dependent effects on the endpoints such as kidney weight, renal cystic volume, mitotic index, apoptotic index, and renal cAMP in PCK rats because a maximal effect was achieved at the relatively low dose and animals were evaluated from 3

through 10 weeks of age at an early stage of disease and the disease progression was small. Also for $Pkd2^{WS25/-}$ mice, it has been reported that the disease slowly progresses at 4 to 12 months of age and that the disease progression is different between males and females (Doctor RB et al. *Nephrol Dial Transplant.* 2010;25:3496-504. Stroope A et al. *Am J Pathol.* 2010;176:1282-91). However, $Pkd2^{WS25/-}$ mice were evaluated from 4 through 16 weeks of age in the study, indicating that these animals may have been at a relatively early stage in disease progression. Thus, since there were individual differences or variation in disease progression between the groups and since changes were small for some of the endpoints such as apoptosis and fibrosis, etc. at 16 weeks of age, it might have been too early to adequately assess dose-dependent effects of tolvaptan on the endpoints such as renal cystic volume, Mitotic index, Apoptotic index, and renal cAMP.

PMDA considers as follows:
Although no animal model completely recapitulates human ADPKD, tolvaptan concentration-dependently inhibited renal-cyst cell proliferation and reduced kidney volume and renal cyst growth in three different animal models of PKD caused by different genes, showing that tolvaptan has the potential to inhibit renal cyst growth also in ADPKD patients. On the other hand, since studies using animal models of PKD failed to show that tolvaptan slowed the worsening of renal function, the submitted results from primary pharmacodynamic studies have not clearly shown the possibility that tolvaptan slows the worsening of renal function. However, it can be presumed that pathological changes in kidney tissue have no small effects on renal function. Also, it has been suggested that tolvaptan, which inhibits pathological changes in PKD, may slow the progression of ADPKD, including the decline of renal function in humans.

3. Clinical data

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

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

Plasma concentrations of tolvaptan and its metabolites DM-4103 and DM-4107 were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The lower limits of quantification for tolvaptan, DM-4103, and DM-4107 in plasma were all 2 ng/mL in Trial 156-[redacted]-001, and those in other studies were 5 ng/mL, 12.5 ng/mL, and 12.5 ng/mL, respectively.

Unless otherwise specified, pharmacokinetic parameters are expressed as the mean ± standard deviation (SD).

3.(i).A.(1) Bioequivalence

The 15-mg and 30-mg clinical trial tablets were used in Japanese clinical trials (Trial 156-[redacted]-001, Trial 156-[redacted]-003), a multinational clinical trial in which Japanese patients with ADPKD participated (Trial 156-[redacted]-251), and a foreign dose-finding trial (Trial 156-[redacted]-249). The 15-mg, 30-mg, and 60-mg clinical trial tablets were used in a foreign dose-finding trial (Trial 156-[redacted]-248). For foreign studies on food effect etc., the 60-mg clinical tablet, which was demonstrated to be bioequivalent to the 30-mg clinical tablet in a foreign human bioequivalence (BE) study (Trial 156-[redacted]-233), was used in Trial 156-[redacted]-256, and the

90-mg clinical tablet, which was demonstrated to be bioequivalent to the foreign 30-mg tablet[1] in a foreign human BE study (Trial 156-[redacted]-295), was used in Trial 156-[redacted]-295. The bioequivalence between the 15-mg clinical tablet and the 15-mg approved tablet and the bioequivalence between the 30-mg clinical tablet and the to-be-marketed 30-mg tablet were demonstrated by dissolution testing, in accordance with "Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms" (PMSB/ELD Notification No.67 dated February 14, 2000, the Guideline was partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012) ("BE Guideline for Formulation Changes").

3.(i).A.(1).1) BE study for the 15-mg, 30-mg, and 60-mg clinical trial tablets (Trial 156-[redacted]-233, Attached document 5.3.5.4-01)

A 6-treatment, 3-period crossover study was conducted in 30 foreign healthy adult subjects to determine the bioequivalence among the 15-mg, 30-mg, and 60-mg clinical trial tablets (with a 4-day washout period between treatments). Single doses of four 15-mg tablets (reference formulation) or one 60-mg tablet (test formulation), four 15-mg tablets (reference formulation) or two 30-mg tablets (test formulation), and two 30-mg tablets (reference formulation) or one 60-mg tablet (test formulation) were administered in the fasted state. The upper and lower bounds of the 90% confidence intervals for the geometric mean ratios of the maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve from time zero to the last sampling time (AUC_t) for the test formulation vs. the reference formulation all fell within the BE range as specified in "Guideline for Bioequivalence Studies of Generic Products" (PMSB/ELD Notification No. 487 dated December 22, 1997, the Guideline was partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012) (hereinafter, "BE Guideline for Generic Products"); the bioequivalence among the 15-mg, 30-mg, and 60-mg clinical trial tablets was established.

3.(i).A.(1).2) BE study for the foreign 30-mg tablet and the 90-mg clinical tablet (Trial 156-[redacted]-295, Attached document 5.3.1.2-01)

A 2-treatment, 2-period crossover study was conducted in 44 foreign healthy adult subjects to determine the bioequivalence between the foreign 30-mg tablet and the 90-mg clinical tablet (with a 4-day washout period between treatments). A single dose of three 30-mg tablets (reference formulation) or one 90-mg tablet (test formulation) was administered in the fasted state. The upper and lower bounds of the 90% confidence intervals for the geometric mean ratios of the C_{max} and AUC_t for one 90-mg tablet vs. three 30-mg tablets fell within the BE interval as specified in the BE Guideline for Generic Products and the bioequivalence between the foreign 30-mg tablet and the 90-mg clinical tablet was established.

3.(i).A.(2) Food effect

3.(i).A.(2).1) Food effect study of the 60-mg tablet (Trial 156-[redacted]-256, Attached document 5.3.1.1-01)

A 2-treatment, 2-period crossover study was conducted in 14 foreign healthy adult subjects (with a 4-day washout period between treatments). A single oral dose of the 60-mg clinical tablet was administered in the fasted state or after a meal. Following a single oral dose of the 60-mg tablet in the fasted and fed states, the

[1] Only shape and debossed markings are different between the foreign 30-mg tablet and the to-be-marketed 30-mg tablet.

median times to reach C_{max} (t_{max}) were both 2.00 hours, the C_{max} values were 430 ± 150 and 603 ± 223 ng/mL, respectively, the AUC_t values were 3500 ± 1440 and 3670 ± 1440 ng·h/mL, respectively, and the terminal-phase elimination half-lives ($t_{1/2,z}$) were 7.1 ± 2.6 and 4.3 ± 1.3 hours, respectively. The geometric mean ratios of the C_{max} and AUC_t of tolvaptan for fed administration vs. fasted administration [90% CIs] were 1.40 [1.17-1.67] and 1.06 [0.97-1.16], respectively.

3.(i).A.(2).2) Food effect study of the 90-mg tablet (Trial 156-[redacted]-295, Attached document 5.3.1.2-01)

A 2-treatment, 2-period crossover study was conducted in 14 foreign healthy adult subjects (with a 4-day washout period between treatments). A single oral dose of the 90-mg clinical tablet was administered in the fasted state or after a meal. Following a single oral dose of the 90-mg tablet in the fasted and fed states, the median t_{max} values of tolvaptan were both 2.00 hours, the C_{max} values were 539 ± 243 and 1050 ± 443 ng/mL, respectively, the AUC_t values were 5970 ± 2440 and 5850 ± 2730 ng·h/mL, respectively, and the $t_{1/2,z}$ values were 9.8 ± 4.8 and 5.4 ± 1.2 hours, respectively. The geometric mean ratios of the C_{max} and AUC_t of tolvaptan for fed administration vs. fasted administration [90% CIs] were 1.960 [1.726-2.226] and 0.968 [0.912-1.026], respectively.

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

PMDA considers as follows:

No data directly comparing the bioavailability between the approved 7.5-mg or 15-mg tablet and the to-be-marketed 30-mg tablet have been presented. However, the bioequivalence between the 15-mg clinical tablet and the approved 15-mg tablet and the bioequivalence between the 30-mg clinical tablet and the to-be-marketed 30-mg tablet have been demonstrated by dissolution testing in accordance with the BE Guideline for Formulation Changes, and the 15-mg clinical tablet has been demonstrated to be bioequivalent to the 30-mg clinical tablet in a human BE study. Thus, there is no problem with introducing the to-be-marketed 30-mg tablet to clinical practice.

Concerning the effect of food on the pharmacokinetics of tolvaptan, since the effect of food on the C_{max} tended to be greater with increasing dose and since 15 mg to 90 mg of tolvaptan will be administered at one time under the claimed indication, the package insert should include the results of food effect studies of tolvaptan 60 mg and 90 mg as well as the results of a food effect study of tolvaptan 15 mg, which was conducted in support of prior regulatory approval.

Based on the above, PMDA requested the applicant to include the information on food effect following administration of 60 mg and 90 mg of tolvaptan in the package insert, and the applicant responded appropriately.

3.(ii) Summary of clinical pharmacology studies

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

The results from 1 Japanese and 3 foreign studies in ADPKD patients and 1 foreign study in subjects with varying degrees of renal function were submitted as the evaluation data. The main study results are

described below.

3.(ii).A.(1) Pharmacokinetics and pharmacodynamics in ADPKD patients

3.(ii).A.(1).1) Japanese dose-finding study (Trial 156-[redacted]-001, Attached document 5.3.4.2-01)

Eighteen Japanese patients with ADPKD were assigned to 2 groups and received a single oral dose of 15 mg of tolvaptan in Period I, a single oral dose of 30 mg of tolvaptan in Period II, and either multiple oral doses of 15 mg of tolvaptan twice daily (BID) (morning and evening) (15 + 15 mg) or multiple oral doses of 30 mg of tolvaptan once daily (QD) (morning) (30 + 0 mg) for 5 days in Period III. A 1- to 3-week washout period was included between the treatments, but a 4- to 6-week washout period was applied to subjects weighing <50 kg, taking account of the volume of collected blood. The pharmacokinetic parameters of tolvaptan and its major metabolites following a single dose administration or a 5-day multiple-dose administration of tolvaptan (after a morning dose) were as shown in Table 1.

Table 1. Pharmacokinetic parameters of Tolvaptan and its major metabolites following single and multiple doses of Tolvaptan (Adapted from submitted data)

Dose (mg)	Day	n	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_t (ng·h/mL)	$t_{1/2,z}$ (h)
Tolvaptan (A single dose)						
15	1	18	181.12 ± 50.39	1.00	816.71 ± 303.29	4.18 ± 1.36
30	1	18	374.59 ± 149.65	1.00	1941.24 ± 1019.29	4.57 ± 1.07
DM-4103						
15	1	18	103.06 ± 24.18	24.00	2971.25 ± 653.48	50.72 ± 39.13
30	1	18	258.23 ± 71.31	24.00	7727.61 ± 2321.30	62.73 ± 30.58
DM-4107						
15	1	18	63.44 ± 19.62	4.00	859.49 ± 223.26	7.49 ± 1.76
30	1	18	121.86 ± 39.39	4.00	1789.10 ± 488.71	7.97 ± 2.25
Dose (mg)	Day	n	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{24h} (ng·h/mL)	$t_{1/2,z}$ (h)
Tolvaptan (Multiple doses)						
15 + 15 [b]	1	9	202.58 ± 91.30	1.00	1510.82 ± 722.52	—
	5	9	205.09 ± 71.63	1.00	1460.20 ± 524.57	4.36 ± 0.77
30 + 0	1	9	339.01 ± 77.55	1.00	1532.37 ± 671.76	—
	5	9	359.19 ± 139.59	1.00	1665.31 ± 875.23	5.00 ± 1.47
DM-4103						
15 + 15 [b]	1	9	418.54 ± 98.34	16.00	7213.53 ± 1806.62	—
	5	9	1489.74 ± 339.21	7.90	29880.20 ± 6244.60	198.28 ± 72.14
30 + 0	1	9	319.11 ± 109.12	12.00	5919.09 ± 1912.11	—
	5	9	1033.54 ± 290.50	10.00	20771.98 ± 4863.17	266.03 ± 264.82
DM-4107						
15 + 15 [b]	1	9	129.07 ± 28.90	11.00	1784.53 ± 413.27	—
	5	9	152.51 ± 36.17	10.00	2588.17 ± 727.46	15.89 ± 4.09
30 + 0	1	9	116.43 ± 32.58	4.00	1446.29 ± 281.98	—
	5	9	143.18 ± 20.24	4.00	1903.00 ± 319.70	14.49 ± 4.60

Mean ± SD; —, Not calculated; a, Median; b, 15 mg BID (Pharmacokinetic parameters after morning doses were calculated.)

AUC_{24h}, Area under the plasma concentration-time curve from time 0 to 24 hours post-dose

With respect to pharmacodynamic endpoints, the time course of urine osmolality by dosing regimen was as shown in Figure 1. The area under urine osmolality-time curve from time zero to 28 hours post-dose (urine osmolality $AUC_{0\text{-}28h}$) by dosing regimen was as shown in Table 2. Regardless of dosing regimen, urine

osmolality $AUC_{0\text{-}28h}$ was reduced from baseline on Day 1. A greater reduction in urine osmolality $AUC_{0\text{-}28h}$ was observed on Day 5 in Period III in the 15 + 15 mg multiple dose group than in the 30 + 0 mg multiple dose group.

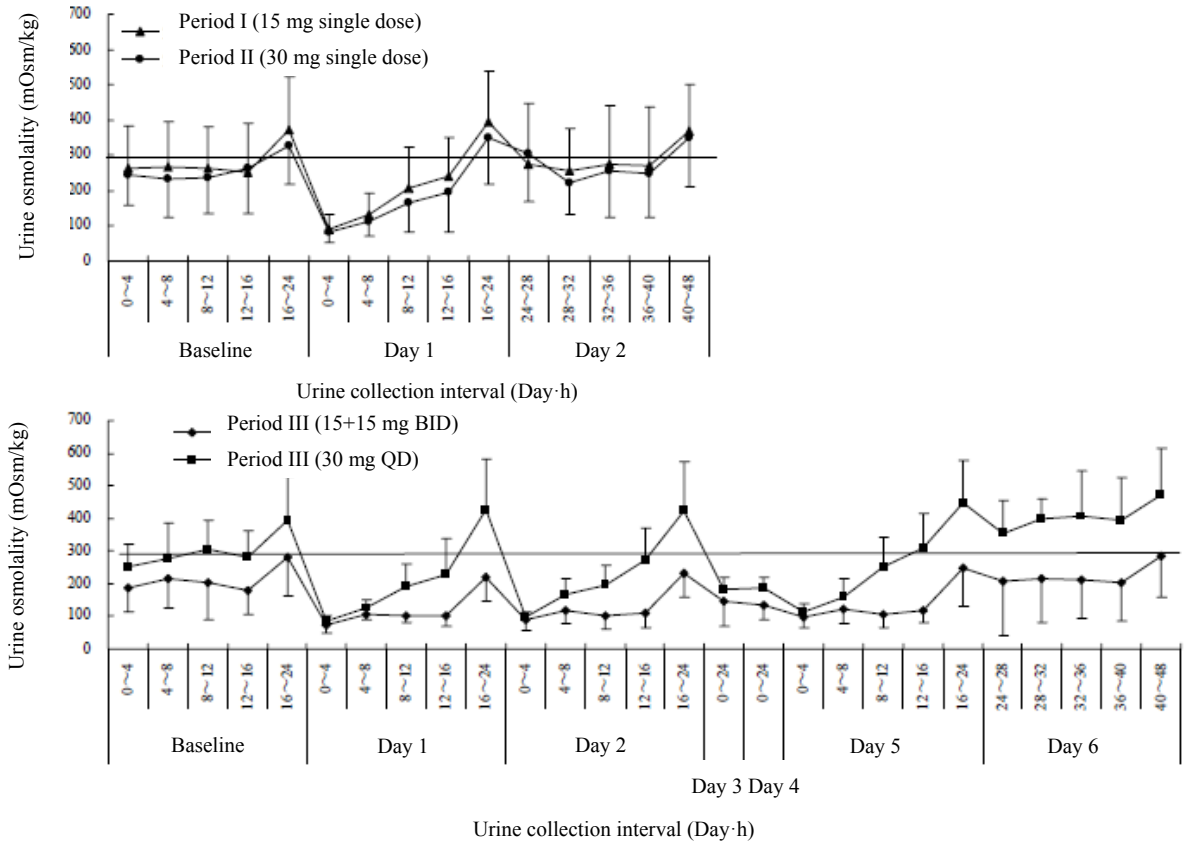

Figure 1. Time course of urine osmolality by dosing regimen

Table 2. Urine osmolality $AUC_{0\text{-}28h}$ by dosing regimen (Adapted from submitted data)

Urine osmolality $AUC_{0\text{-}28h}$ (mOsm/kg·h)	Interval (h)	15 mg single dose (Period I) N = 18	30 mg single dose (Period II) N = 18	15 + 15 mg multiple doses (Period III) N = 9	30 + 0 mg multiple doses (Period III) N = 9
Baseline	0-28 [a]	8229.6 ± 3123.8	7502.2 ± 2315.2	6124.9 ± 2441.6	8637.8 ± 1741.0
Day 1	0-28 [b]	6944.4 ± 2826.1	6256.4 ± 2329.8	3647.6 ± 980.7	6332.4 ± 1926.7
Day 5	0-28 [c]	—	—	4592.4 ± 1961.7	8332.4 ± 2175.2

Mean ± SD; a, 0-24 h at baseline＋0-4 h at baseline; b, 0-24 h on Day 1＋0-4 h on Day 2;
C, 0-24 h on Day 5＋0-4 h on Day 6

Following single doses of 15 and 30 mg of tolvaptan, the changes from baseline in 24-hour urine volume were 1929.8 ± 834.6 (mean ± SD) and 2217.9 ± 629.8 mL, respectively. Following 5-day administration of 15 + 15 mg and 30 + 0 mg of tolvaptan, the changes from baseline in 24-hour urine volume were 2451.2 ± 719.0 and 2085.4 ± 485.9 mL, respectively, on Day 1 and 1656.4 ± 645.9 and 793.9 ± 709.1 mL, respectively, on Day 5.

3.(ii).A.(1).2) Foreign single dose-finding study (Trial 156-[redacted]-248, Attached document 5.3.4.2-02)

Following ascending single oral doses of 15, 30, 60, and 120 mg of tolvaptan administered on Days 1, 4, 7, and 10, respectively, to 8 foreign patients with ADPKD, the C_{max} values of tolvaptan were 146 ± 35.4, 263 ± 74.5, 481 ± 177, and 917 ± 237 ng/mL, respectively, the AUC_t values were 686 ± 258, 1520 ± 698, 3280 ± 1400, and 6900 ± 2790 ng·h/mL, respectively, the median t_{max} values were 1, 1, 1.5, and 1.5 hours, respectively, and the $t_{1/2,z}$ values were 4.5 ± 2.7, 4.3 ± 1.3, 5.1 ± 1.0, and 5.6 ± 2.0 hours, respectively.

With respect to pharmacodynamic endpoints, the time course of urine osmolality by dose was as shown in Figure 2, and urine osmolality $AUC_{0\text{-}28h}$ by dose was as shown in Table 3.

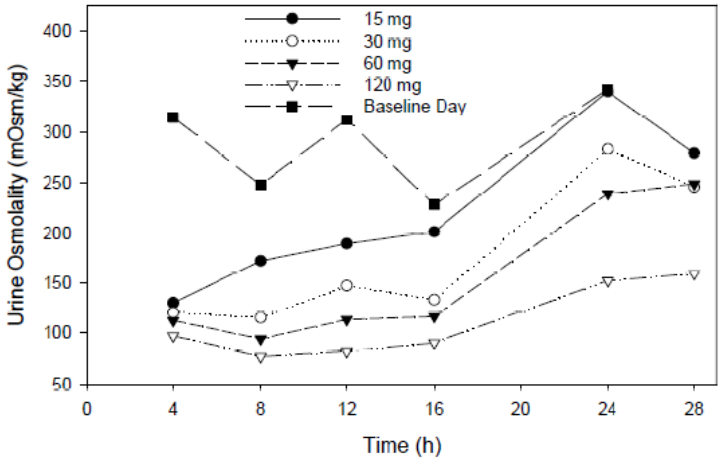

Figure 2. Time course of urine osmolality by dose (Tolvaptan group)

Table 3. Urine osmolality $AUC_{0\text{-}28h}$ by dose (Adapted from submitted data)

Urine osmolality $AUC_{0\text{-}28h}$ (mOsm/kg·h)	Tolvaptan N = 8	Placebo N = 3
Baseline	8412 ± 1538	8346 ± 1876
Day 1 (15 mg or placebo)	6615 ± 1108	8788 ± 3988
Day 4 (30 mg or placebo)	5313 ± 671	7918 ± 2451
Day 7 (60 mg or placebo)	4663 ± 807	7653 ± 966
Day 10 (120 mg or placebo)	3251 ± 539	7653 ± 817

Mean ± SD

Following administration of 15, 30, 60, and 120 mg of tolvaptan, the changes from baseline (8412 ± 1538 mOsm/kg·h) in urine osmolality $AUC_{0\text{-}28h}$ were -1796.5 ± 1111.2, -3099.0 ± 1515.6, -3749.0 ± 1763.7, and -5161.0 ± 1682.9 mOsm/kg·h, respectively, and the changes from baseline in 24-hour urine volume were 1568.75 ± 845.42, 3547.13 ± 1470.46, 4629.38 ± 2194.67, and 6546.25 ± 2826.42 mL, respectively.

3.(ii).A.(1).3) Foreign multiple dose-finding study (Trial 156-[redacted]-249, Attached document 5.3.4.2-03)

Multiple oral doses of 30 + 0 mg, 15 + 15 mg, 30 mg (morning) + 15 mg (evening) (30 + 15 mg), and 30 mg BID (morning and evening) (30 + 30 mg) of tolvaptan were administered for 5 days in 37 foreign

patients with ADPKD. The pharmacokinetic parameters of tolvaptan after morning doses on Days 1 and 5 were as shown in Table 4.

Table 4. Pharmacokinetic parameters following multiple oral doses of Tolvaptan in foreign patients with ADPKD (Adapted from submitted data)

Dose (mg)	Day	n	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{24h} (ng·h/mL)	$t_{1/2,z}$ (h)
Tolvaptan (Multiple doses)						
30 + 0 [b]	1	9	312 ± 205	2.00	1950 ± 1490	—
	5	9	330 ± 230	1.98	2140 ± 1620	4.3 ± 1.2
15 + 15 [b]	1	9	201 ± 88.5	8.97	1650 ± 774	—
	5	9	190 ± 60.5	9.00	1890 ± 1070	6.2 ± 3.3
30 + 15 [b]	1	9	262 ± 55.1	1.00	2270 ± 1650	—
	5	9	269 ± 69.2	0.98	2770 ± 2020	6.4 ± 3.7
30 + 30 [b]	1	10	335 ± 135	2.00	2900 ± 1340	—
	5	10	295 ± 122	5.47	2990 ± 1640	4.7 ± 1.8

Mean ± SD; —, Not calculated;
a, Median; b, A morning dose + an evening dose (Pharmacokinetic parameters after morning doses were calculated.)
AUC_{24h}, Area under the plasma concentration-time curve from time 0 to 24 hours post-dose

With respect to pharmacodynamic endpoints, urine osmolality $AUC_{0\text{-}28h}$ values at baseline and on Day 5 were as shown in Table 5.

Table 5. Urine osmolality $AUC_{0\text{-}28h}$ (Adapted from submitted data)

Urine osmolality $AUC_{0\text{-}28h}$ (mOsm/kg·h)	**15 + 15 mg N = 9**	**30 + 0 mg N = 9**	**30 + 15 mg N = 9**	**30 + 30 mg N = 10**
Baseline	8331.6 ± 3686.6	10881.3 ± 6408.9	9412.9 ± 3431.8	8054.0 ± 5422.7
Day 5	4871.6 ± 1672.4	6322.7 ± 3060.4	4942.2 ± 1796.9	4216.0 ± 1863.7

Mean ± SD

The changes from baseline in 24-hour urine volume on Day 5 in the tolvaptan 30 + 0 mg, 15 + 15 mg, 30 + 15 mg, and 30 + 30 mg groups were 1799.67 ± 569.36, 1954.44 ± 1271.07, 2273.89 ± 1514.50, and 1764.00 ± 1241.04 mL, respectively.

3.(ii).A.(1).4) Foreign dose-finding study (Trial 156-[redacted]-250, Attached document 5.3.5.2-01)

When 30 to 120 mg of tolvaptan were orally administered as a split dose BID for 4 years to 46 foreign patients with ADPKD who had participated in Trial 156-[redacted]-248 and Trial 156-[redacted]-249, pharmacodynamic endpoints were assessed.

The study consisted of a titration phase and a fixed-dose phase. Dosage regimens used in the titration period (from Day 1 through Month 2) were split doses of 15 + 15 mg; 30 + 15 mg; 45 mg (morning) + 15 mg (evening) (hereinafter, "45 + 15 mg"); 60 mg (morning) + 30 mg (evening) (hereinafter, "60 + 30 mg"); and 90 mg (morning) + 30 mg (evening) (hereinafter, "90 + 30 mg"). Subjects were initiated on a split dose of 30 + 15 mg and up- or down-titrated based on tolerability in the titration period. Based on efficacy and tolerability data from the titration period, subjects were randomly allocated to tolvaptan 45 + 15 mg or 60 + 30 mg for up to Month 36 in the fixed-dose period.

The pharmacodynamic endpoint of the time course of urine osmolality was as shown in Table 6. The proportions of subjects with urine osmolality >300 mOsm/kg at baseline in the titration period and Weeks 1, 2, 3, and 4 (45 + 15 mg and 90 + 30 mg) were 76%, 36%, 30%, 23%, 58%, and 15%, respectively, Prior to First Dose, 67%, 16%, 2.3%, 2.3%, 7.1%, and 0%, respectively, Prior to Second Dose, and 62%, 8.9%, 7.0%, 2.3%, 8.3%, and 0%, respectively, Prior to Bedtime. The mean urine osmolality for the total population was maintained at <300 mOsm/kg throughout the fixed-dose period.

Table 6. Time course of urine osmolality (mOsm/kg) in titration period (Adapted from submitted data)

	N	Prior to First dose	Prior to Second dose	Prior to bedtime
Baseline	45	467 ± 227	455 ± 237	438 ± 207
Week 1 (30 + 15 mg)	45	276 ± 143	191 ± 108	170 ± 106
Week 2 (45 + 15 mg)	43	264 ± 104	154 ± 66	163 ± 75
Week 3 (60 + 30 mg)	43	239 ± 122	140 ± 70	136 ± 110
Week 4 (45 + 15 mg)	14	300 ± 99	175 ± 85	206 ± 109
(90 + 30 mg)	27	174 ± 98	136 ± 58	108 ± 28

Mean ± SD

3.(ii).A.(1).5) Multinational phase III trial (TEMPO) (Trial 156-[redacted]-251, Attached document 5.3.5.1-01)

When 60 to 120 mg of tolvaptan were orally administered as a split dose BID for 3 years to 1445 patients with ADPKD (including 177 Japanese patients), pharmacodynamic endpoints were assessed.

The trial consisted of a titration phase and a maintenance phase. In the titration period (up to 3 weeks after the initiation of treatment with tolvaptan), tolvaptan was initiated at 45 + 15 mg and then titrated to 60 + 30 mg and 90 + 30 mg if tolerated, and the maintenance phase began at the highest dose tolerated.

The pharmacodynamic endpoint of the proportions of subjects with urine osmolality <300 mOsm/kg during the study period (Week 3 through Month 36) in the overall trial population and Japanese subgroup were as shown in Table 7.

Table 7. Proportion of subjects with trough urine osmolality <300 mOsm/kg (Adapted from submitted data)

	Overall trial population				Japanese subgroup			
	N	Tolvaptan	N	Placebo	N	Tolvaptan	N	Placebo
Baseline	899	130 (14.46)	472	71 (15.04)	114	15 (13.16)	58	7 (12.07)
Week 3/End of Titration	896	766 (85.49)	470	113 (24.04)	112	83 (74.11)	57	16 (28.07)
Month 12	797	626 (78.54)	446	106 (23.77)	98	72 (73.47)	58	15 (25.86)
Month 24	749	580 (77.44)	415	92 (22.17)	91	70 (76.92)	55	12 (21.82)
Month 36	710	538 (75.77)	402	91 (22.64)	90	66 (73.33)	52	9 (17.31)

n (%)

3.(ii).A.(1).6) Study investigating the effect of maximally tolerated doses on renal function (Trial 156-[redacted]-284, Attached document 5.3.4.2-05)

Tolvaptan was initiated at 45 + 15 mg and then titrated weekly to 60 + 30 mg and then 90 + 30 mg in 29 foreign ADPKD patients with an estimated glomerular filtration rate determined by the Modified Diet in Renal Disease (MDRD) equation ($eGFR_{MDRD}$) of >60 mL/min/1.73 m^2, ≥30 and ≤60 mL/min/1.73 m^2, or <30 mL/min/1.73 m^2. For the pharmacodynamic endpoints of measured glomerular filtration rate (mGFR), effective renal plasma flow, and filtration fraction, the changes and percent changes from baseline to final treatment visit or post-treatment visit (3 weeks after the last dose) were as shown in Table 8.

Table 8. mGFR, effective renal plasma flow, and filtration fraction (Adapted from submitted data)

$eGFR_{MDRD}$ (mL/min/1.73 m^2)	>60 N = 9	≥30 and ≤60 N = 9	<30 N = 9 [a]
mGFR (mL/min)			
Baseline	112.3 ± 20.3	66.3 ± 20.3	29.3 ± 10.6
Final treatment visit	104.3 ± 22.7	60.1 ± 16.6	28.6 ± 10.0
Change from baseline	-8.0 ± 9.1	-6.2 ± 6.2	-0.7 ± 1.5
Percent change from baseline	-7.4 ± 8.7	-8.4 ± 6.8	-2.1 ± 5.5
Post-treatment visit	112.3 ± 23.1	64.8 ± 18.1	26.9 ± 9.3
Change from baseline	0.1 ± 4.9	-1.5 ± 4.0	-1.2 ± 3.0
Percent change from baseline	-0.3 ± 4.8	-1.4 ± 5.2	-2.6 ± 12.4
Effective renal plasma flow (mL/min)			
Baseline	335.9 ± 56.0	222.8 ± 57.2	98.1 ± 30.1
Final treatment visit	319.0 ± 77.6	211.7 ± 47.0	96.4 ± 28.6
Change from baseline	-16.9 ± 36.4	-11.1 ± 18.4	-1.7 ± 5.1
Percent change from baseline	-5.7 ± 11.7	-4.0 ± 7.5	-1.1 ± 6.1
Post-treatment visit	340.2 ± 77.8	214.3 ± 48.1	91.5 ± 23.8
Change from baseline	4.3 ± 30.2	-8.4 ± 17.7	-1.3 ± 10.3
Percent change from baseline	0.7 ± 8.1	-2.9 ± 6.9	-0.2 ± 12.9
Filtration fraction			
Baseline	0.335 ± 0.029	0.296 ± 0.022	0.303 ± 0.030
Final treatment visit	0.330 ± 0.024	0.283 ± 0.023	0.293 ± 0.029
Change from baseline	-0.005 ± 0.017	-0.013 ± 0.016	-0.010 ± 0.014
Percent change from baseline	-1.372 ± 5.145	-4.235 ± 5.253	-3.265 ± 4.358
Post-treatment visit	0.333 ± 0.030	0.301 ± 0.031	0.289 ± 0.035
Change from baseline	-0.003 ± 0.018	0.005 ± 0.015	-0.016 ± 0.023
Percent change from baseline	-0.640 ± 5.605	1.714 ± 4.891	-5.323 ± 6.899

Mean ± SD;
Final treatment, Day 21 (± 1 day) or within 1 week after treatment with maximally tolerated dose;
a, As 1 subject in the $eGFR_{MDRD}$ <30 group used a diuretic (bumetanide) after the last dose of study drug, this subject was excluded from post-treatment analyses (N = 8 included in post-treatment analyses).

3.(ii).A.(1).7) Population pharmacokinetic analysis of ADPKD patients (Trial 156-[redacted]-296, Attached document 5.3.3.5-01)

Using plasma tolvaptan concentration data (1067 subjects, 6437 observations) obtained from clinical pharmacology studies in ADPKD patients (Trial 156-[redacted]-001, Trial 156-[redacted]-248, Trial 156-[redacted]-249, Trial 156-[redacted]-260, Trial 156-[redacted]-284, Trial 156-[redacted]-285), a clinical pharmacology study in subjects with varying degrees of renal function (Trial 156-[redacted]-282), open-label, safety studies (Trial 156-[redacted]-250, Trial 156-[redacted]-002), and the TEMPO trial (Trial 156-[redacted]-251), a population pharmacokinetic (PPK) analysis was

performed. The distribution of the major baseline characteristics of patients included in the PPK analysis was as follows: gender (male, 541 subjects; female, 526 subjects); age, 40 [18, 79] years (median [min., max.] ; the same shall apply hereinafter); body weight, 77.1 [38.0, 162.9] kg; Body mass index (BMI), 25.4 [15.4, 54.7] kg/m^2; eGFR, 72.2 [9.8, 144.7] mL/min/1.73m^2; geographic region (Japan, 136 subjects; non-Japan, 931 subjects); CYP3A4 inhibitor coadministration (Yes, 161 observations; No, 6276 observations); and CYP3A4 inducer coadministration (Yes, 165 observations; No, 6272 observations). A 1-compartment model with first-order absorption was chosen as the pharmacokinetic base model. The effects of gender, age, body weight, BMI, and geographic region were investigated as potential covariates on pharmacokinetic parameters, and the effects of eGFR, CYP3A4 inhibitor coadministration, and CYP3A4 inducer coadministration were investigated as potential covariates on apparent total body clearance (CL/F) only. As a result, CYP3A4 inhibitors, BMI, and eGFR as covariates on CL/F, geographic region and age as covariates on apparent volume of distribution (Vc/F), and gender as a covariate on absorption rate constant (K_a) were included in the model. The inter-individual coefficient of variation (CV%) was 43% for CL/F, 34% for Vc/F, and 67% for K_a. With respect to the population mean pharmacokinetic parameters, CL/F was reduced with CYP3A4 inhibitor coadministration, higher BMI, and lower eGFR, Vc/F was reduced with Japan (geographic region) and increasing age, and women had higher K_a than men.

3.(ii).A.(2) Clinical pharmacology study in subjects with renal impairment (Trial 156-[redacted]-282, Attached document 5.3.3.3-01)

Following a single oral dose of 60 mg of tolvaptan in foreign subjects with creatinine clearance (CLcr) calculated from the 24-hour urinary excretion of creatinine and serum creatinine of >60 mL/min, ≥30 and ≤60 mL/min, and <30 mL/min (12 subjects each), the C_{max} values of tolvaptan were 417 ± 150, 621 ± 241, and 535 ± 183 ng/mL, respectively, the AUC_t values were 3530 ± 1570, 6470 ± 3090, and 6690 ± 3550 ng·h/mL, respectively, the $t_{1/2,z}$ values were 10.1 ± 8.3, 9.2 ± 3.3, and 9.1 ± 2.8 hours, respectively, and values of the fraction unbound were 1.0 ± 0.3%, 0.6 ± 0.1%, and 1.2 ± 0.8%, respectively. Urine osmolality from 24 to 48 hours post-dose was 409.3 ± 206.7, 355.4 ± 137.6, and 224.8 ± 53.8 mOsm/kg, respectively, and the changes from baseline in 24-hour urine volume were 4247 ± 1673, 2704 ± 1375, and 1089 ± 785 mL, respectively.

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

3.(ii).B.(1) Pharmacokinetics of Tolvaptan in ADPKD patients

PMDA considers as follows:

The pharmacokinetics of tolvaptan in ADPKD patients have been determined by PPK analysis using blood tolvaptan concentration data obtained from clinical studies in Japanese and foreign ADPKD patients, or other means. There have been no pharmacokinetic concerns specific to ADPKD patients.

However, it is assumed that ADPKD patients have varying degrees of renal function, and the results of Trial 156-[redacted]-282 and PPK analysis have shown that tolvaptan exposure increases in subjects with impaired renal function compared with those with normal renal function. The concentration of tolvaptan unbound to

plasma proteins increased approximately 2-fold in subjects with CLcr <30 mL/min compared with those with CLcr >60 mL/min in Trial 156-[redacted]-282. Given that the multinational phase III trial (TEMPO) included only patients with CLcr ≥60 mL/min prior to randomization and that tolvaptan has never been administered at doses higher than the maximum dose of 120 mg/day to Japanese ADPKD patients, the levels of exposure experienced by Japanese ADPKD patients may be exceeded if tolvaptan is administered to patients with severe renal impairment. Based on the above, from a pharmacokinetic point of view, at least, the package insert should advise that tolvaptan exposure may increase in patients with severe renal impairment and that the dose should be reduced in patients with severe renal impairment. Use of tolvaptan in patients with significantly advanced renal impairment will continue to be discussed in the clinical section [see "3.(iii).B.(3).3) Use of tolvaptan in dialysis patients and patients with significantly advanced renal impairment"].

3.(ii).B.(2) CYP3A4 inhibitor coadministration

As with the precautions in the package insert for the approved indications, the proposed package insert recommends avoiding the use of tolvaptan with CYP3A4 inhibitors and advises that if tolvaptan has to be used with CYP3A4 inhibitors, reducing the dose of tolvaptan or starting tolvaptan at a lower dose, etc. should be considered. PMDA asked the applicant to explain the appropriate starting and maximum doses of tolvaptan when tolvaptan has to be used with CYP3A4 inhibitors in ADPKD patients.

The applicant explained as follows:

In a drug-drug interaction trial with ketoconazole in healthy adult subjects (Trial 156-[redacted]-201), which was submitted in support of prior regulatory approval, ketoconazole, a strong CYP3A4 inhibitor, caused a 3.5-fold and 5.4-fold increase in tolvaptan C_{max} and AUC, respectively. Thus, the dose of tolvaptan should be reduced to approximately one-fourth to one-fifth when coadministered with strong CYP3A4 inhibitors. In addition, tolvaptan can be administered as the commercial or to-be-marketed 7.5-, 15-, and 30-mg tablet formulations and their fragments broken along the score line. Based on the above, it will be advised in the "Precautions for Dosage and Administration" section of the draft package insert that the dose of tolvaptan should be reduced to one-fourth when coadministered with strong CYP3A4 inhibitors.

Although no drug-drug interaction studies with moderate CYP3A4 inhibitors have been conducted, the extent of increase in tolvaptan exposure when coadministered with moderate CYP3A4 inhibitors was predicted from the extent of increase in tolvaptan exposure when coadministered with a strong CYP3A4 inhibitor, ketoconazole. According to the US Food and Drug Administration (FDA)'s draft guidance on drug interaction studies, "Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations," a strong CYP3A4 inhibitor is defined as an inhibitor that causes ≥80% decrease in clearance, and a moderate CYP3A4 inhibitor is defined as an inhibitor that causes 50% to 80% decrease in clearance. Although the effects of different drugs classified as moderate inhibitors on tolvaptan exposure are not considered all the same, taking account of the extent of decrease in clearance that meets the criteria of strong or moderate inhibitors and the extent of increase in tolvaptan exposure when coadministered with ketoconazole, the appropriate dose of tolvaptan when coadministered with

moderate CYP3A4 inhibitors is approximately one-half to one-third of the usual dose. In addition, tolvaptan can be administered as the commercial or to-be-marketed 7.5-, 15-, and 30-mg tablet formulations and their fragments broken along the score line. Based on the above, it will be advised in the "Precautions for Dosage and Administration" section of the draft package insert that the dose of tolvaptan should be reduced to one-half when coadministered with moderate CYP3A4 inhibitors.

Although there seems little need to reduce the dose of tolvaptan to as low as one-half when coadministered with weak CYP3A4 inhibitors, it is considered difficult to strictly distinguish moderate CYP3A4 inhibitors from weak CYP3A4 inhibitors based on the information from the package inserts etc. Therefore, the "Precautions for Dosage and Administration" section of the draft package insert will include a precautionary statement that the dose of tolvaptan should be reduced to one-half when coadministered with weak CYP3A4 inhibitors.

PMDA considered as follows:
Since coadministration with ketoconazole resulted in marked increase in tolvaptan exposure, tolvaptan exposure is expected to increase when coadministered with CYP3A4 inhibitors. To what extent tolvaptan exposure increases when tolvaptan is coadministered with hepatic CYP3A4 inhibitors other than ketoconazole has not been determined, and tolvaptan has never been administered at doses higher than the maximum dose of 120 mg/day to Japanese ADPKD patients. Therefore, in principle, use of tolvaptan with CYP3A4 inhibitors should be avoided. However, as tolvaptan will be given continuously and chronically to ADPKD patients, specific recommendations for dose reduction should be provided, assuming the situation where tolvaptan has to be used with CYP3A4 inhibitors temporarily. It is appropriate to make recommendations for dose reduction of tolvaptan when coadministered with strong CYP3A4 inhibitors and with weak or moderate CYP3A4 inhibitors, based on the effects of CYP3A4 inhibitors on tolvaptan exposure.
Therefore, PMDA accepted the applicant's explanation.

3.(iii) Summary of clinical efficacy and safety

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

As the evaluation data, the results from 2 Japanese phase II studies (including 1 long-term extension study), 2 Japanese phase III studies (2 long-term extension studies), 4 foreign phase I studies, 4 foreign phase II studies (including 1 long-term extension study), and 1 multinational phase III study (including Japan's participation) were submitted [see "3.(i) Summary of biopharmaceutic studies and associated analytical methods" and "3.(ii) Summary of clinical pharmacology studies" for pharmacokinetics and pharmacodynamics and BE]. As the reference data, the results from 4 foreign clinical studies were submitted. The main study results are described below.

3.(iii).A.(1) Phase I studies

3.(iii).A.(1).1) Food effect study of the 60-mg tablet in foreign healthy adult subjects (Trial 156-[redacted]-256, Attached document 5.3.1.1-01 [redacted])

A 2-treatment, 2-period crossover study was conducted in foreign healthy adult subjects at 1 site in the US. A single oral dose of the 60-mg tablet was administered after a meal or in the fasted state (with a 4-day washout period between treatments).

Fourteen subjects were enrolled into the study, and all of them completed the study. Adverse events occurred in 4 subjects after fed administration (headache NOS and abrasion NOS; urticaria NOS; headache NOS, dry throat, and meteorism; balance impaired NOS, headache NOS, and nasal congestion [1 subject each]) and 6 subjects after fasted administration (constipation and xerosis; diarrhoea NOS; headache NOS, venipuncture site contusion, and dermatitis NOS; dry eye NOS; venipuncture site pain; headache NOS [1 subject each]). There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation.

3.(iii).A.(1).2) BE and food effect study in foreign healthy adult subjects (Trial 156-[redacted]-295, Attached document 5.3.1.2-01 [redacted])

A 2-treatment, 2-period crossover study (Part 1 [BE assessment] and Part 2 [food effect assessment]) was conducted in foreign healthy adult subjects at 1 site in the US (with a 4-day washout period between treatments).

In Part 1, a single dose of three 30-mg tablets or one 90-mg tablet was administered in the fasted state on Days 1 and 5. In Part 2, a single dose of one 90-mg tablet was administered in the fasted state or after a meal on Days 1 and 5.

Part 1 enrolled 44 subjects, of whom 43 subjects completed the study. The incidences of adverse events were 38.6% (17 of 44 subjects) after administration of three 30-mg tablets and 43.2% (19 of 44 subjects) after administration of one 90-mg tablet. Adverse events reported by at least 2 subjects after administration of either three 30-mg tablets or one 90-mg tablet were thirst (11 subjects after administration of three 30-mg tablets and 13 subjects after administration of one 90-mg tablet), pain in extremity (1 subject and 3 subjects, respectively), dizziness (0 subjects and 4 subjects, respectively), headache (1 subject and 2 subjects, respectively), and polyuria (15 subjects and 15 subjects, respectively).

Part 2 enrolled 14 subjects and all of them completed the study. The incidences of adverse events were 50.0% (7 of 14 subjects) after fed administration and 57.1% (8 of 14 subjects) after fasted administration. Adverse events reported by at least 2 subjects after either fed or fasted administration were thirst (1 subject after fed administration and 5 subjects after fasted administration) and polyuria (6 subjects and 8 subjects, respectively).

In either Part 1 or 2, there were no deaths, serious adverse events, or adverse events leading to study drug

discontinuation.

3.(iii).A.(1).3) BE study for the 15-mg, 30-mg, and 60-mg tablets in foreign healthy adult subjects (Trial 156-[redacted]-233, Attached document 5.3.5.4-01 [redacted])

A study was conducted in foreign healthy adult subjects at 1 site in the US to determine the bioequivalence of a single oral dose of 60 mg of tolvaptan given as the 15-, 30-, and 60-mg tablets in the fasted state using a 6-treatment, 3-period crossover design and to assess potential drug interactions between tolvaptan 60 mg and lovastatin 80 mg in Period 4 (with a 4-day washout period between treatment).

The study enrolled 30 subjects, of whom 27 subjects completed the study. The incidences of adverse events were 100.0% (29 of 29 subjects) after administration of four 15-mg tablets, 100.0% (30 of 30 subjects) after administration of two 30-mg tablets, 100.0% (30 of 30 subjects) after administration of one 60-mg tablet, and 100.0% (27 of 27 subjects) after coadministration with lovastatin. Adverse events reported by at least 2 subjects after any of the treatments were thirst (28 subjects after administration of four 15-mg tablets, 28 subjects after administration of two 30-mg tablets, 29 subjects after administration of one 60-mg tablet, and 27 subjects after coadministration with lovastatin), decreased appetite NOS (3 subjects, 3 subjects, 0 subjects, and 0 subjects, respectively), dizziness (1 subject, 0 subjects, 0 subjects, and 2 subjects, respectively), headache NOS (1 subject, 1 subject, 2 subjects, and 3 subjects, respectively), micturition urgency (2 subjects, 0 subjects, 1 subject, and 0 subjects, respectively), pollakiuria (29 subjects, 29 subjects, 29 subjects, and 27 subjects, respectively), and nasal congestion (0 subjects, 0 subjects, 2 subjects, and 0 subjects, respectively).

There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation during the study period.

3.(iii).A.(1).4) Clinical pharmacology study in foreign subjects with renal impairment (Trial 156-[redacted]-282, Attached document 5.3.3.3-01 [redacted])

An open-label, uncontrolled study was conducted in subjects with renal impairment at 2 sites in the US (Target number of subjects, 12 subjects per group stratified by renal function, a total of 36 subjects). A single oral dose of 60 mg of tolvaptan was administered in the fasted state.

The study enrolled 37 subjects (12 subjects in the CLcr <30 mL/min group, 12 subjects in the CLcr ≥30 and ≤60 mL/min group, 13 subjects in the CLcr >60 mL/min group), and all of them completed the study. The incidences of adverse events were 83.3% (10 of 12 subjects) in the CLcr <30 mL/min group, 66.7% (8 of 12 subjects) in the CLcr ≥30 and ≤60 mL/min group, and 61.5% (8 of 13 subjects) in the CLcr >60 mL/min group. Adverse events reported by at least 2 subjects in any group were diarrhoea (2 subjects in the CLcr <30 mL/min group, 0 subjects in the CLcr ≥30 and ≤60 mL/min group, and 0 subjects in the CLcr >60 mL/min group), dry mouth (1 subject, 3 subjects, and 1 subject, respectively), thirst (3 subjects, 4 subjects, and 3 subjects, respectively), hypoglycaemia (2 subjects, 0 subjects, and 0 subjects, respectively), and pollakiuria (1 subject, 4 subjects, and 4 subjects, respectively).

There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation.

3.(iii).A.(2) Phase II studies

3.(iii).A.(2).1) Japanese dose-finding study (Trial 156-[redacted]-001, Attached document 5.3.4.2-01 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label, ascending dose trial was conducted in Japanese patients with ADPKD at 1 site in Japan to evaluate the pharmacokinetics, pharmacodynamics, and safety of tolvaptan (Target number of subjects, 9 subjects per group, a total of 18 subjects). Subjects received single oral doses of 15 and 30 mg of tolvaptan, followed by multiple oral doses of tolvaptan 15 mg BID (morning and evening) (15 + 15 mg) or 30 mg QD (morning) (30 + 0 mg) for 5 days.

In Group I, subjects received a single dose of 15 mg of tolvaptan in Period I, a single dose of 30 mg of tolvaptan in Period II, and multiple doses of tolvaptan 15 + 15 mg in Period III. In Group II, subjects received a single dose of 15 mg of tolvaptan in Period I, a single dose of 30 mg of tolvaptan in Period II, and multiple doses of tolvaptan 30 + 0 mg in Period III (with a 1- to 3-week washout period between treatments, but a 4- to 6-week washout for subjects weighing <50 kg). In order to inhibit parathyroid hormone secretion, calcium 300 mg (containing vitamin D 100 IU) was administered BID from 3 days prior to the initiation of study drug until the following day of the last dose in each Period.

Key inclusion criteria were: patients who have been diagnosed with ADPKD by imaging and who are ≥20 and <60 years of age. Key exclusion criteria were: male patients with serum creatinine >1.4 mg/dL or female patients with serum creatinine >1.2 mg/dL; and patients with renal disease other than ADPKD and its signs (e.g., symptomatic nephrolithiasis, urine protein measurement of +2 or more, a history of nephrectomy).

Since all of 18 randomized subjects (9 subjects in Group I, 9 subjects in Group II) received study drug and the pharmacodynamic endpoints were measured for all the subjects, 18 subjects were included in the safety and pharmacodynamic analyses. No subjects discontinued the trial.

Total kidney volumes at baseline were 1106.4 ± 876.5 (mean ± SD) mL in Group I and 1587.9 ± 677.8 mL in Group II.

The primary pharmacodynamic endpoint was urine osmolality. The time course of urine osmolality and urine osmolality $AUC_{0\text{-}28h}$ by dosing regimen were as described in "3.(ii).A.(1).1) Japanese dose-finding study".

Regarding safety, the incidences of adverse events were 66.7% (6 of 9 subjects) in Group I and 66.7% (6 of 9 subjects) in Group II, and adverse events reported by at least 2 subjects in either Group were nausea (2 subjects in Group I and 0 subjects in Group II), thirst (2 subjects and 2 subjects, respectively),

nasopharyngitis (1 subject and 2 subjects, respectively), and headache (4 subjects and 0 subjects, respectively).

There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation.

3.(iii).A.(2).2) Foreign single dose-finding study (Trial 156-[redacted]-248, Attached document 5.3.4.2-02 [redacted])

A randomized, double-blind, ascending dose trial was conducted in foreign patients with ADPKD at 1 site in the US to evaluate the pharmacokinetics, pharmacodynamics, and safety of single ascending doses of tolvaptan (target number of subjects, a total of 9-21 subjects; subjects were randomized in a 2:1 ratio to receive either tolvaptan or placebo). Single ascending doses of 15, 30, 60, and 120 mg of tolvaptan or placebo were orally administered in the fasted state.

In the tolvaptan group, tolvaptan was initiated at 15 mg and single ascending doses of 30, 60, and 120 mg were administered as tolerated (with a 72-hour washout period between dosings). In order to inhibit parathyroid hormone secretion, vitamin D and calcium were administered from 3 days prior to the initiation of study drug until Day 11.

Key inclusion criteria were: patients who have been diagnosed with ADPKD by imaging and who are ≥18 and <55 years of age. Key exclusion criteria were: male patients with serum creatinine >1.4 mg/dL or female patients with serum creatinine >1.2 mg/dL, whom the investigator and the medical monitor have decided to exclude from the trial; patients with serum creatinine >1.8 mg/dL; patients with significant renal disease other than ADPKD; and patients with symptomatic nephrolithiasis, urine protein >2 g/day, or a history of nephrectomy, etc.

Since all of 11 randomized subjects (8 subjects in the tolvaptan group, 3 subjects in the placebo group) received study drug and had baseline and post-baseline urine osmolality measurements, 11 subjects were included in the safety and pharmacodynamic analyses. No subjects discontinued the trial and all subjects completed the trial.

Right kidney volumes at baseline were 520.7 ± 224.6 mL in the tolvaptan group and 1012.5 ± 429.2 mL in the placebo group, and left kidney volumes at baseline were 739.5 ± 616.9 and 1114.0 ± 135.8 mL, respectively.

The primary pharmacodynamic endpoint was urine osmolality. The time course of urine osmolality and urine osmolality $AUC_{0\text{-}28h}$ by dose level were as described in "3.(ii).A.(1).2) Foreign single dose-finding study".

Regarding safety, the incidences of adverse events were 50.0% (4 of 8 subjects) after administration of tolvaptan 15 mg, 25.0% (2 of 8 subjects) after administration of tolvaptan 30 mg, 25.0% (2 of 8 subjects)

after administration of tolvaptan 60 mg, 37.5% (3 of 8 subjects) after administration of tolvaptan 120 mg, and 66.7% (2 of 3 subjects) after administration of placebo, and adverse events reported by at least 2 subjects after any of the treatments were dry mouth (3 subjects after administration of tolvaptan 15 mg, 0 subjects after administration of tolvaptan 30 mg, 1 subject after administration of tolvaptan 60 mg, 1 subject after administration of tolvaptan 120 mg, and 0 subjects after administration of placebo), somnolence (0 subjects, 0 subjects, 1 subject, 2 subjects, and 0 subjects, respectively), and dizziness (0 subjects, 0 subjects, 1 subject, 0 subjects, and 2 subjects, respectively).

There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation.

3.(iii).A.(2).3) Foreign multiple dose-finding study (Trial 156-[redacted]-249, Attached document 5.3.4.2-03 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, parallel-group trial was conducted in foreign patients with ADPKD at 1 site in the US to evaluate the pharmacokinetics, pharmacodynamics, and safety of multiple doses of tolvaptan (target sample size, 6-12 subjects per group, a total of 18-48 subjects). Tolvaptan 15 + 15 mg, tolvaptan 30 + 0 mg, tolvaptan 30 mg (morning) + 15 mg (evening) (30 + 15 mg), or tolvaptan 30 mg BID (morning and evening) (30 + 30 mg) was orally administered for 5 days. In order to inhibit parathyroid hormone secretion, vitamin D and calcium were administered from 3 days prior to the initiation of study drug until Day 6.

Key inclusion criteria were: patients who have been diagnosed with ADPKD by imaging and who are ≥18 and <60 years of age; and total kidney volume ≥600 mL for patients ≤30 years of age and ≥1000 mL for patients >30 years of age were preferred. Key exclusion criteria were: male patients with serum creatinine >1.4 mg/dL or female patients with serum creatinine >1.2 mg/dL, whom the investigator and the medical monitor have decided to exclude from the trial; patients with serum creatinine >1.8 mg/dL; patients with significant renal disease other than ADPKD; and patients with symptomatic nephrolithiasis, urine protein >2 g/day, or a history of nephrectomy, etc.

Since all of 37 randomized subjects (9 subjects in the 15 + 15 mg group, 9 subjects in the 30 + 0 mg group, 9 subjects in the 30 + 15 mg group, 10 subjects in the 30 + 30 mg) received study drug and had baseline and post-baseline urine osmolality measurements, all 37 subjects were included in the safety and pharmacodynamic analyses. No subjects discontinued the trial.

Total kidney volumes at baseline in the 15 + 15 mg, 30 + 0 mg, 30 + 15 mg, and 30 + 30 mg groups were 1435.0 ± 1138.0, 1027.4 ± 231.0, 1913.5 ± 1248.0, and 1741.1 ± 973.5 mL, respectively.

The primary pharmacodynamic endpoint was urine osmolality. Urine osmolality $AUC_{0\text{-}28h}$ at baseline and on Day 5 were as described in "3.(ii).A.(1).3) Foreign multiple dose-finding study".

Regarding safety, the incidences of adverse events were 66.7% (6 of 9 subjects) in the 15 + 15 mg group,

88.9% (8 of 9 subjects) in the 30 + 0 mg group, 44.4% (4 of 9 subjects) in the 30 + 15 mg group, and 30.0% (3 of 10 subjects) in the 30 + 30 mg group, and adverse events reported by at least 2 subjects in any group were dry mouth (3 subjects in the 15 + 15 mg group, 4 subjects in the 30 + 0 mg group, 1 subject in the 30 + 15 mg group, and 3 subjects in the 30 + 30 mg group), fatigue (1 subject, 4 subjects, 0 subjects, and 0 subjects, respectively), dizziness (0 subjects, 2 subjects, 1 subject, and 0 subjects, respectively), and dysgeusia (0 subjects, 2 subjects, 1 subject, and 0 subjects, respectively).

There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation.

3.(iii).A.(2).4) Foreign dose-finding/long-term treatment study (Trial 156-[redacted]-250, Attached document 5.3.5.2-01 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, long-term extension study was conducted in foreign patients with ADPKD who had participated in Trial 156-[redacted]-248 and Trial 156-[redacted]-249 at 11 sites in the US to evaluate the long-term safety of tolvaptan (target sample size, approximately 50 subjects). Tolvaptan 30 to 120 mg was orally administered as a split dose BID for 4 years.

The study consisted of a titration phase, a fixed-dose phase, and an extension phase. Dose regimens used in the titration period (from Day 1 through Month 2) were: 15 + 15 mg, 30 + 15 mg, 45 mg (morning) + 15 mg (evening) (45 + 15 mg), 60 mg (morning) + 30 mg (evening) (60 + 30 mg), and 90 mg (morning) + 30 mg (evening) (90 + 30 mg). Subjects were initiated on a split dose of 30 + 15 mg and titrated in weekly intervals. Subjects who could tolerate the dose were up-titrated to the next higher dose and subjects who were unable to tolerate the dose were down-titrated to the previous dose or discontinued study drug as appropriate. Based on urine osmolality and tolerability data from the titration period, the maximal tolerated dose (the highest dose tolerated by a cumulative >50% of the subjects) was 60 + 30 mg and the minimum effective dose (the lowest dose at which most subjects had urine osmolality <300 mOsm/kg) was 45 + 15 mg. Thus, tolvaptan 45 + 15 mg and 60 + 30 mg were chosen as doses for the fixed-dose period, and subjects were randomized to one of the two doses for up to Month 36. When participating in the extension period after the fixed-dose period, subjects had a 4- to 12-month off-treatment period and then received tolvaptan at the same doses for another 12 months. During the fixed-dose and extension periods, subjects on 60 + 30 mg were allowed to down-titrate to 45 + 15 mg temporarily or continuously, at the discretion of the sponsor and the investigator.

Key inclusion criteria were: ADPKD patients who have participated in Trial 156-[redacted]-248 and Trial 156-[redacted]-249. Besides, only subjects who had completed the Month 36 visit were to be allowed to enter the extension period. Key exclusion criteria were: patients with eGFR <30 mL/min on Day 1 or the first day of the extension period; and patients who plan to undergo renal replacement therapy during the extension period.

All of 46 subjects who entered the titration period and who received study drug entered the fixed-dose period and were randomized to tolvaptan 45 + 15 mg (22 subjects) or 60 + 30 mg (24 subjects). All of the

46 subjects were included in the analyses of efficacy and safety in the titration and fixed-dose phases. During the fixed-dose period, 7 subjects discontinued the trial (4 subjects in the 45 + 15 mg group and 3 subjects in the 60 + 30 mg group); the reasons for discontinuation were adverse events (2 subjects and 1 subject, respectively), lost to follow-up (1 subject and 1 subject, respectively), the withdrawal criteria met (1 subject and 0 subjects, respectively), and consent withdrawal (0 subjects and 1 subject, respectively). Of the 39 subjects who completed the fixed-dose period, 35 subjects entered the extension period and were assigned to the 45 + 15 mg group (17 subjects) or the 60 + 30 mg group (18 subjects) and included in the analyses of efficacy and safety in the extension phase. All of the 35 subjects completed the extension period.

In the fixed-dose period, 84.8% of subjects (39 of 46 subjects) (81.8% [18 of 22 subjects] and 87.5% [21 of 24 subjects], respectively) were treated for 961 to 1095 days. In the extension period, all subjects were treated for 1326 to 1460 days, and 31.4% of subjects (11 of 35 subjects) (23.5% [4 of 17 subjects] and 38.9% [7 of 18 subjects], respectively) were treated for >1460 days.

Total kidney volume at baseline in the titration period was 1581.7 ± 878.9 mL.

The results of the efficacy endpoint were as shown below. The time course of urine osmolality and the proportion of subjects with urine osmolality >300 mOsm/kg were as described in “3.(ii).A.(1).4) Foreign dose-finding study”.

Based on analysis of self-reported tolerability, 30 + 15 mg, 45 + 15 mg, 60 + 30 mg, and 90 + 30 mg were not tolerable in 4.3% (2 of 46 subjects), 0% (0 of 43 subjects), 36.4% (16 of 44 subjects), and 25.0% (7 of 28 subjects) of subjects, respectively.

Total kidney volumes at baseline in the fixed-dose period were 1566 ± 730 mL in the 45 + 15 mg group and 1596 ± 1012 mL in the 60 + 30 mg group, and the percent changes from baseline in the two groups were as shown in Figure 3.

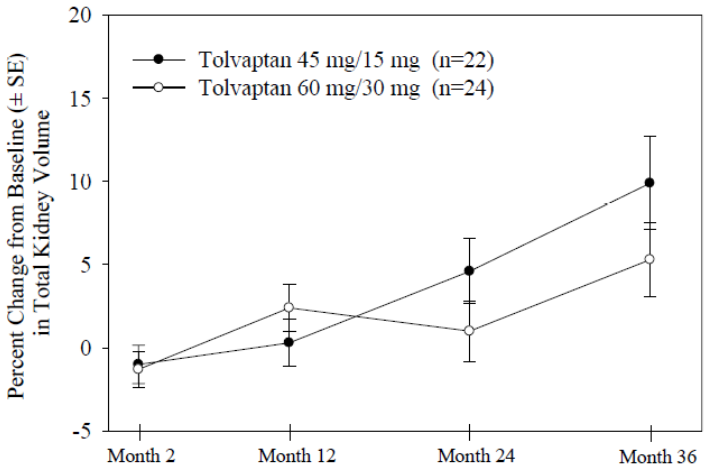

Figure 3. Percent change from baseline to Month 36 in total kidney volume

Regarding safety, the incidence of adverse events occurred during the titration period was 100% (46 of 46 subjects), and adverse events reported by ≥10% of subjects were pollakiuria (47.8% [22 of 46 subjects]), thirst (41.3% [19 of 46 subjects]), nocturia (23.9% [11 of 46 subjects]), polyuria (21.7% [10 of 46 subjects]), fatigue (19.6% [9 of 46 subjects]), dizziness (13.0% [6 of 46 subjects]), upper respiratory tract infection (10.9% [5 of 46 subjects]), sinusitis (10.9% [5 of 46 subjects]), renal pain (10.9% [5 of 46 subjects]), headache (10.9% [5 of 46 subjects]), and dry skin (10.9% [5 of 46 subjects]).

The incidences of adverse events occurred during the fixed-dose period were 100.0% (22 of 22 subjects) in the 45 + 15 mg group and 100.0% (24 of 24 subjects) in the 60 + 30 mg group, and adverse events reported by ≥10% of subjects in either group were renal pain (45.5% in the 45 + 15 mg group and 37.5% in the 60 + 30 mg group), dizziness (27.3% and 12.5%, respectively), fatigue (18.2% and 20.8%, respectively), polyuria (27.3% and 8.3%, respectively), nocturia (22.7% and 8.3%, respectively), back pain (18.2% and 12.5%, respectively), abdominal pain (9.1% and 20.8%, respectively), upper respiratory tract infection (4.5% and 25.0%, respectively), urinary tract infection (4.5% and 25.0%, respectively), oedema peripheral (13.6% and 12.5%, respectively), headache (13.6% and 12.5%, respectively), thirst (4.5% and 20.8%, respectively), dyspnoea (4.5% and 20.8%, respectively), dry eye (13.6% and 8.3%, respectively), abdominal distension (13.6% and 8.3%, respectively), chest pain (13.6% and 8.3%, respectively), bronchitis (13.6% and 8.3%, respectively), hypertension (13.6% and 8.3%, respectively), sinusitis (9.1% and 12.5%, respectively), arthralgia (9.1% and 12.5%, respectively), diarrhoea (4.5% and 16.7%, respectively), anaemia (13.6% and 4.2%, respectively), palpitations (13.6% and 4.2%, respectively), insomnia (4.5% and 12.5%, respectively), and pollakiuria (0% and 12.5%, respectively).

The incidences of adverse events occurred during the extension period were 94.1% (16 of 17 subjects) in the 45 + 15 mg group and 88.9% (16 of 18 subjects) in the 60 + 30 mg group, and adverse events reported by ≥10% of subjects in either group were anaemia (5.9% and 11.1%, respectively), diarrhoea (23.5% and 0%, respectively), vomiting (11.8% and 0%, respectively), fatigue (11.8% and 5.6%, respectively), influenza like illness (0% and 11.1%, respectively), thirst (17.6% and 44.4%, respectively), sinusitis

(11.8% and 11.1%, respectively), polydipsia (29.4% and 0%, respectively), arthralgia (11.8% and 0%, respectively), dizziness (23.5% and 0%, respectively), nocturia (47.1% and 5.6%, respectively), pollakiuria (17.6% and 22.2%, respectively), polyuria (17.6% and 27.8%, respectively), renal pain (11.8% and 11.1%, respectively), and hypertension (11.8% and 11.1%, respectively).

No deaths occurred in the titration, fixed-dose, or extension period.

Serious adverse events occurred in 1 subject receiving 60 + 30 mg of tolvaptan during the titration period (abdominal pain, pelvic pain, ovarian cyst ruptured, urinary tract infection, and pituitary tumour benign). During the fixed-dose period, serious adverse events occurred in 3 subjects in the 45 + 15 mg group (cholelithiasis; pituitary tumour benign; renal pain [1 subject each]) and 8 subjects in the 60 + 30 mg group (dyspnoea, rash, transient ischaemic attack, and atrial fibrillation; abdominal pain; uterine leiomyoma; malignant melanoma in situ; pyelonephritis; polycystic liver; atrial fibrillation; epiploic appendagitis, chest pain, tachycardia, and renal pain [1 subject each]). One subject in the 45 + 15 mg group experienced a serious adverse event (hepatic cyst ruptured) during the extension period.

Adverse events leading to study drug discontinuation were reported by 3 subjects in the 45 + 15 mg group (eye swelling; pituitary tumour benign; renal failure acute [1 subject each]) and 1 subject in the 60 + 30 mg group (transient ischaemic attack) during the fixed-dose period, and there were no adverse events leading to study drug discontinuation during the titration or extension period.

3.(iii).A.(2).5) Study investigating the effect of maximally tolerated doses on renal function (Trial 156-[redacted]-284, Attached document 5.3.4.2-05 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in foreign patients with ADPKD at 1 site in the Netherlands to investigate the effect of maximally tolerated doses of tolvaptan on mGFR, effective renal plasma flow, and filtration fraction (target sample size, 6-12 subjects per group stratified by renal function, a total of up to 36 subjects). Oral doses of tolvaptan were titrated over 3 weeks.

A starting daily tolvaptan dose of 45 + 15 mg was to be up-titrated weekly to 60 + 30 mg, then to 90 + 30 mg, as tolerated.

Key inclusion criteria were: patients with a diagnosis of ADPKD based on Ravine's criteria (Ravine D et al. *Lancet.* 1994;343:824-7) and $eGFR_{MDRD}$ based on the mean of two creatinine measurements (one of the two measurements may have been obtained within 3 months prior to trial participation) of >60 mL/min/1.73 m^2, ≥30 and ≤60 mL/min/1.73 m^2, or <30 mL/min/1.73 m^2, who are ≥18 and <70 years of age. Key exclusion criteria were: patients undergoing renal replacement therapy (e.g. dialysis, renal transplant); and patients with current evidence of significant renal disease other than ADPKD, e.g. glomerulonephritis, renal cancer, and single kidney.

Since all of 29 enrolled and randomized subjects (10 subjects in the $eGFR_{MDRD}$ >60 mL/min/1.73 m^2 group,

10 subjects in the $eGFR_{MDRD}$ ≥30 and ≤60 mL/min/1.73 m^2 group, and 9 subjects in the $eGFR_{MDRD}$ <30 mL/min/1.73 m^2 group) received study drug, all 29 subjects were included in the safety analysis and 27 of the 29 subjects with post-baseline renal function test values (9 subjects, 9 subjects, and 9 subjects, respectively) were included in the pharmacodynamic analysis. Two subjects discontinued the trial (1 subject in the $eGFR_{MDRD}$ >60 mL/min/1.73 m^2 group, 1 subject in the $eGFR_{MDRD}$ ≥30 and ≤60 mL/min/1.73 m^2 group) due to the occurrence of adverse events.

$eGFR_{MDRD}$ values at screening in the $eGFR_{MDRD}$ >60 mL/min/1.73 m^2 group, $eGFR_{MDRD}$ ≥30 and ≤60 mL/min/1.73 m^2 group, and $eGFR_{MDRD}$ <30 mL/min/1.73 m^2 group were 84.2 ± 14.9, 45.7 ± 8.5, and 19.8 ± 4.4 mL/min/1.73 m^2, respectively.

The primary pharmacodynamic endpoints were mGFR, effective renal plasma flow, and filtration fraction. The changes and percent changes from baseline to final treatment visit or post-treatment visit (3 weeks after the final dose) were as described in "3.(ii).A.(1).6) Study investigating the effect of maximally tolerated doses on renal function".

Regarding safety, the incidences of adverse events were 100.0% (10 of 10 subjects) in the $eGFR_{MDRD}$ >60 mL/min/1.73 m^2 group, 100.0% (10 of 10 subjects) in the $eGFR_{MDRD}$ ≥30 and ≤60 mL/min/1.73 m^2 group, and 100.0% (9 of 9 subjects) in the $eGFR_{MDRD}$ <30 mL/min/1.73 m^2 group, and adverse events reported by at least 5 subjects in any group were dry mouth (6 subjects in the $eGFR_{MDRD}$ >60 mL/min/1.73 m^2 group, 5 subjects in the $eGFR_{MDRD}$ 30-60 mL/min/1.73 m^2 group, and 5 subjects in the $eGFR_{MDRD}$ <30 mL/min/1.73 m^2 group), thirst (10 subjects, 10 subjects, and 8 subjects, respectively), nocturia (8 subjects, 6 subjects, and 6 subjects, respectively), and polyuria (10 subjects, 9 subjects, and 7 subjects, respectively).

No deaths were reported.

Serious adverse events occurred in 1 subject (polyuria) in the $eGFR_{MDRD}$ >60 mL/min/1.73 m^2 group and 1 subject (angina pectoris) in the $eGFR_{MDRD}$ <30 mL/min/1.73 m^2 group. Adverse events leading to treatment discontinuation occurred in 1 subject (polyuria) in the $eGFR_{MDRD}$ >60 mL/min/1.73 m^2 group and 1 subject (dry mouth) in the $eGFR_{MDRD}$ ≥30 and ≤60 mL/min/1.73 m^2 group.

3.(iii).A.(3) Phase III study

3.(iii).A.(3).1) Multinational phase III trial (TEMPO) (Trial 156-[redacted]-251, Attached document 5.3.5.1-01 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, parallel-group trial was conducted in ADPKD patients at 129 sites in 15 countries including Japan to evaluate the efficacy of tolvaptan (target sample size, 1200-1500 subjects [the original calculation for the trial], 1400 subjects [a calculation redesigned during the trial[2] as prescribed]). Tolvaptan or placebo was orally administered BID for up to 36 months.

[2] As prescribed, a blinded sample size re-calculation was conducted when 1000 subjects were enrolled ([redacted], 20[redacted]) and suggested that a total sample size of 1400 would be required.

The trial consisted of a titration phase (up to 3 weeks from the initiation of study treatment) and a maintenance phase (from the end of the titration phase until up to 36 months from the initiation of study treatment). In the titration period, tolvaptan was initiated at 60 mg/day orally (45 mg [morning]/15 mg [evening] BID) and then up-titrated weekly to 90 mg/day (60 mg [morning]/30 mg [evening]) first and to 120 mg/day (90 mg [morning]/30 mg [evening]) next if tolerated. If a subject could not tolerate a given dose, the titration phase was over for that subject, and the maintenance phase began at the highest dose tolerated. During the maintenance period, the investigator was allowed to choose to up-titrate subjects, with medical monitor approval, if a change in clinical status, lifestyle, or concomitant treatment suggested a possibility that a higher dose may be tolerated. From a safety standpoint, subjects were allowed to down-titrate at any time, at the discretion of the investigator.

Key inclusion criteria were: CLcr ≥60 mL/min within 31 days prior to randomization; total kidney volume ≥750 mL by magnetic resonance imaging (MRI) at randomization and a rapid estimated rate of kidney volume increase (excluding those meeting volumetric criteria solely due to six or fewer predominant cysts); ≥ regional legal age of maturity (18 years in Europe/the US, 20 years in Japan) and ≤50 years; and a diagnosis of ADPKD.[3]

In this trial, subjects were allocated to tolvaptan or placebo on a 2:1 basis by stratified randomization method in each region independently (3 regions of North and South Americas; Japan; and Europe and the rest of the world). Stratification factors include (i) the presence or absence of hypertension at baseline (systolic blood pressure >139 mmHg and/or diastolic blood pressure >89 mmHg or anti-hypertensive treatment), (ii) renal function at baseline (CLcr <80 mL/min or ≥80 mL/min by the Cockcroft-Gault equation), and (iii) total kidney volume at baseline (<1000 mL or ≥1000 mL).

3.(iii).A.(3).1).(a) Overall results of the trial

Of 1445 randomized subjects (961 subjects in the tolvaptan group and 484 subjects in the placebo group), 1444 subjects who received at least one dose of study drug (961 subjects and 483 subjects, respectively) were included in the safety analysis. Of whom, 1307 subjects with baseline and post-baseline total kidney volume measurements (842 subjects and 465 subjects, respectively) were included in the analysis of the primary efficacy endpoint. Of whom, 1277 subjects for whom total kidney volume was measured during the period from the first dosing day to the 14th day of the last dose of study drug (819 subjects and 458 subjects, respectively) were included in the primary analysis for the primary efficacy endpoint. All of the 1445 randomized subjects were included in the analysis of the composite secondary efficacy endpoint. The number of subjects who discontinued the trial was 288 (221 subjects and 67 subjects, respectively), and the reasons for discontinuation were adverse events (148 subjects and 24 subjects, respectively), consent withdrawal (50 subjects and 30 subjects, respectively), lost to follow-up (15 subjects and 8 subjects,

[3] For patients with a family history of ADPKD, several cysts in each kidney (3 if by sonography or 5 if by CT or MRI); For patients without a family history of ADPKD, 10 cysts in each kidney by any radiologic method and exclusion of other cystic kidney diseases (multiple simple renal cysts, renal tubular acidosis, cystic dysplasia of the kidney, multicystic kidney, multilocular cysts of the kidney, medullary cystic kidney, acquired cystic disease of the kidney).

respectively), withdrawal criteria met (4 subjects and 0 subjects, respectively), the investigator's decision (3 subjects and 4 subjects, respectively), and protocol deviations (1 subject and 1 subject, respectively).

At baseline, the percentages of subjects with hypertension in the tolvaptan and placebo groups were 79.6% and 78.9%, respectively, the percentages of subjects with CLcr <80 mL/min were 25.2% and 26.9%, respectively, the percentages of subjects with total kidney volume <1000 mL were 20.5% and 20.9%, respectively, and the total kidney volumes were 1704.8 ± 921.27 and 1667.5 ± 873.11 mL, respectively.

The percentages of subjects treated with study drug for 36 months were 77.2% (742 of 961 subjects) in the tolvaptan group and 86.5% (418 of 483 subjects) in the placebo group. At Month 36, the daily doses in the tolvaptan group were 0 mg[4] in 2 of 742 subjects (0.3%), 60 mg in 179 of 742 subjects (24.1%), 90 mg in 157 of 742 subjects (21.2%), and 120 mg in 404 of 742 subjects (54.4%). Tolvaptan exposure during the trial period was 2334.5 subject-years.

3.(iii).A.(3).1).(a).i) Efficacy

The primary efficacy endpoint was the rate of total kidney volume change from baseline. As a result of the primary analysis of the primary endpoint, the annualized rates of change in total kidney volume (estimated slopes)[5] were 2.80%/year in the tolvaptan group and 5.51%/year in the placebo group; there was a significant difference between the treatments ($P < 0.0001$, derived from testing the treatment-by-time interaction using a linear mixed effect model with treatment, time, treatment-by-time interaction, and baseline total kidney volume as fixed effects, and intercept and time as random effects).

Among the secondary efficacy endpoints, the incidence rates of secondary composite events of new or worsening hypertension (changes in blood-pressure category [normotensive (systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg), low-pre-hypertensive (120-129 mmHg and 80-84 mmHg, respectively), high-pre-hypertensive (130-139 mmHg and 85-89 mmHg, respectively), hypertensive (>139 mmHg and >89 mmHg, respectively)]), initiation or increasing doses of anti-hypertensive medication), clinically significant renal pain (requiring medical intervention), new or worsening albuminuria (changes in category based on urine albumin/creatinine ratio), and worsening renal function (a 25% reduction in reciprocal serum creatinine from Week 3 or End of Titration) were 43.94 events/100 subject-years of follow-up in the tolvaptan group and 50.04 events/100 subject-years of follow-up in the placebo group. The hazard ratio for tolvaptan vs. placebo (two-sided 95% CI for hazard ratio)[6] was 0.865 (0.775-0.965); there was a significant treatment difference ($P = 0.0095$, proportional rates/means model). Kaplan-Meier plots of the cumulative hazard functions of the time to multiple (recurrent) secondary composite events were as shown in Figure 4.

[4] 0 mg reflects no dose taken during the majority of the time period, due to treatment interruption etc.

[5] A regression model was fitted to the log-transformed total kidney volumes for each subject and the exponential function of the regression coefficient was obtained. Time variable used in the regression was equal to (MRI date − baseline MRI date)/365.25.

[6] Calculated by applying a proportional rates/means model including treatment as a factor to the analysis of time to multiple (recurrent) events of the secondary composite endpoint.

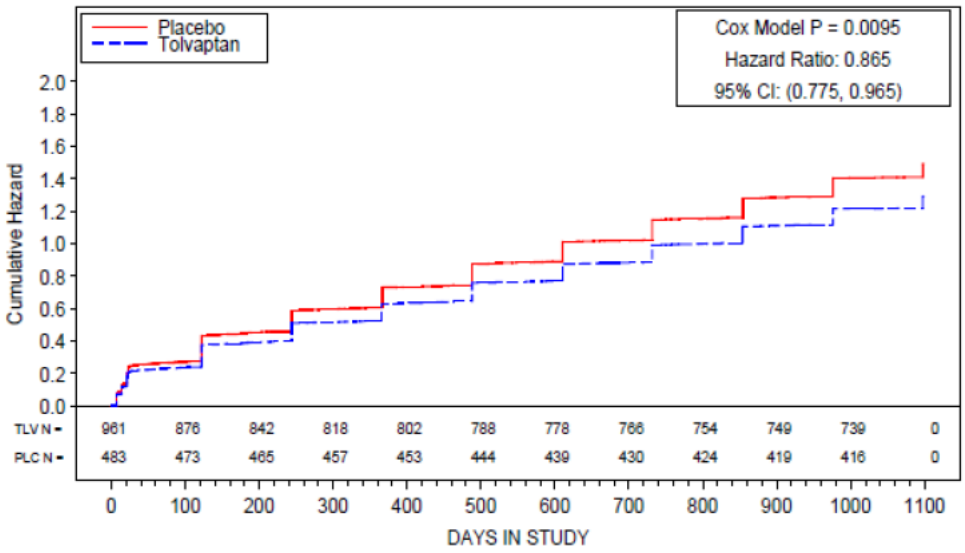

Figure 4. Cumulative hazard function of time to multiple (recurrent) secondary composite events: Overall trial population

The results of between-treatment comparison of the time to multiple (recurrent) events for the components of the secondary composite endpoint were as shown in Table 9.

Table 9. Results of between-treatment comparison of time to multiple (recurrent) events for components of secondary composite endpoint: Overall trial population (Adapted from submitted data)

	Tolvaptan	Placebo
New or worsening hypertension	N = 961	N = 483
No. of events/100 subject-years of follow-up	30.74	32.05
Hazard ratio (Two-sided 95% CI) *	0.942 (0.814-1.090)	
Clinically significant renal pain	N = 961	N = 483
No. of events/100 subject-years of follow-up	4.73	7.30
Hazard ratio (Two-sided 95% CI) *	0.642 (0.466-0.887)	
New or worsening albuminuria	N = 961	N = 483
No. of events/100 subject-years of follow-up	8.17	7.75
Hazard ratio (Two-sided 95% CI) *	1.037 (0.837-1.284)	
Worsening renal function	N = 917	N = 476
No. of events/100 subject-years of follow-up	1.85	4.84
Hazard ratio (Two-sided 95% CI) *	0.386 (0.263-0.566)	

* Calculated using a proportional rates/means model including treatment as a factor

The main results of other secondary efficacy endpoints were as follows. The slopes of reciprocal serum creatinine from Week 3 or End of Titration were -2.609 $(mg/mL)^{-1}$/year in the tolvaptan group and -3.812 $(mg/mL)^{-1}$/year in the placebo group, and similar results were obtained also for CLcr calculated using the Cockcroft-Gault equation, $eGFR_{MDRD}$, and eGFR calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation ($eGFR_{CKD-EPI}$).

The main results of the pharmacodynamic endpoints were as follows. The mean serum creatinine

concentrations at baseline and post-treatment (at Follow-up visit 2, 14-42 days after the end of study treatment) were 1.05 and 1.21 mg/dL, respectively, in the tolvaptan group and 1.04 and 1.27 mg/dL, respectively, in the placebo group. The mean changes from baseline to post-treatment were 0.16 mg/dL in the tolvaptan group and 0.23 mg/dL in the placebo group. The mean changes from baseline to post-treatment in plasma cystatin C were 0.14 mg/L in the tolvaptan group and 0.16 mg/L in the placebo group. The changes from baseline to Month 36 in trough urine osmolality and the proportion of subjects with urine osmolality <300 mOsm/kg during the trial period were as described in "3.(ii).A.(1).5) Multinational phase III trial (TEMPO)".

3.(iii).A.(3).1).(a).ii) Safety

The incidences of adverse events were 97.9% (941 of 961 subjects) in the tolvaptan group and 97.1% (469 of 483 subjects) in the placebo group, and events occurring in ≥5% of subjects in either group were as shown in Table 10.

Table 10. Adverse events occurring in ≥5% of subjects in either group: Overall trial population (Adapted from submitted data)

MedDRA System Organ Class Preferred Term (MedDRA/J version 14.1)	Tolvaptan N = 961 n (%)	Placebo N = 483 n (%)
Blood and lymphatic system disorders		
Anaemia	27 (2.8)	24 (5.0)
Gastrointestinal disorders		
Abdominal pain	62 (6.5)	32 (6.6)
Abdominal pain upper	63 (6.6)	42 (8.7)
Constipation	81 (8.4)	12 (2.5)
Diarrhoea	128 (13.3)	53 (11.0)
Dry mouth	154 (16.0)	60 (12.4)
Dyspepsia	76 (7.9)	16 (3.3)
Nausea	98 (10.2)	57 (11.8)
Vomiting	79 (8.2)	40 (8.3)
General disorders and administration site conditions		
Asthenia	57 (5.9)	27 (5.6)
Fatigue	131 (13.6)	47 (9.7)
Oedema peripheral	81 (8.4)	46 (9.5)
Pyrexia	45 (4.7)	42 (8.7)
Thirst	531 (55.3)	99 (20.5)
Infections and infestations		
Bronchitis	58 (6.0)	33 (6.8)
Gastroenteritis	54 (5.6)	21 (4.3)
Influenza	75 (7.8)	38 (7.9)
Nasopharyngitis	211 (22.0)	111 (23.0)
Sinusitis	53 (5.5)	23 (4.8)
Upper respiratory tract infection	82 (8.5)	42 (8.7)
Urinary tract infection	81 (8.4)	61 (12.6)
Investigations		
Blood creatinine increased	135 (14.0)	71 (14.7)
Metabolism and nutrition disorders		
Appetite decreased	69 (7.2)	5 (1.0)

Polydipsia	100 (10.4)	17 (3.5)
Musculoskeletal and connective tissue disorders		
Arthralgia	69 (7.2)	28 (5.8)
Back pain	133 (13.8)	88 (18.2)
Myalgia	50 (5.2)	16 (3.3)
Pain in extremity	42 (4.4)	27 (5.6)
Nervous system disorders		
Dizziness	109 (11.3)	42 (8.7)
Headache	241 (25.1)	121 (25.1)
Psychiatric disorders		
Insomnia	55 (5.7)	21 (4.3)
Renal and urinary disorders		
Haematuria	75 (7.8)	68 (14.1)
Nocturia	280 (29.1)	63 (13.0)
Pollakiuria	223 (23.2)	26 (5.4)
Polyuria	368 (38.3)	83 (17.2)
Renal pain	260 (27.1)	171 (35.4)
Respiratory, thoracic and mediastinal disorders		
Cough	77 (8.0)	38 (7.9)
Vascular disorders		
Hypertension	310 (32.3)	174 (36.0)

The incidences of adverse events for which a causal relationship to study drug could not be ruled out were 88.6% (851 of 961 subjects) in the Tolvaptan group and 62.5% (302 of 483 subjects) in the placebo group, and events occurring in ≥5% of subjects in either group were thirst (54.6% and 19.3%, respectively), polyuria (38.1% and 16.6%, respectively), nocturia (29.1% and 12.6%, respectively), pollakiuria (23.2% and 5.2%, respectively), dry mouth (15.8% and 11.6%, respectively), headache (13.4% and 9.1%, respectively), polydipsia (10.4% and 3.5%, respectively), blood creatinine increased (9.9% and 9.9%, respectively), fatigue (9.8% and 4.8%, respectively), dizziness (7.5% and 4.6%, respectively), appetite decreased (5.7% and 0.2%, respectively), constipation (5.4% and 0.6%, respectively), and renal pain (4.8% and 5.4%, respectively).

No deaths were reported.

The incidences of serious adverse events were 18.4% (177 of 961 subjects) in the tolvaptan group and 19.7% (95 of 483 subjects) in the placebo group, and events occurring in ≥0.5% of subjects in either group were as shown in Table 11.

Table 11. Serious adverse events occurring in ≥0.5% of subjects in either group: Overall trial population (Adapted from submitted data)

MedDRA System Organ Class Preferred Term (MedDRA/J version 14.1)	Tolvaptan N = 961 n (%)	Placebo N = 483 n (%)
General disorders and administration site conditions		
Chest pain	8 (0.8)	2 (0.4)
Infections and infestations		
Appendicitis	1 (0.1)	4 (0.8)
Pyelonephritis	5 (0.5)	5 (1.0)
Renal cyst infection	6 (0.6)	4 (0.8)
Urinary tract infection	1 (0.1)	3 (0.6)
Investigations		
Alanine aminotransferase increased	9 (0.9)	2 (0.4)
Aspartate aminotransferase increased	9 (0.9)	2 (0.4)
Nervous system disorders		
Headache	5 (0.5)	0 (0.0)
Renal and urinary disorders		
Nephrolithiasis	2 (0.2)	3 (0.6)
Renal cyst haemorrhage	3 (0.3)	4 (0.8)
Renal pain	1 (0.1)	4 (0.8)
Vascular disorders		
Hypertension	1 (0.1)	3 (0.6)

The incidences of serious adverse events for which a causal relationship to study drug could not be ruled out were 5.1% (49 of 961 subjects) in the Tolvaptan group and 2.7% (13 of 483 subjects) in the placebo group, and events occurring in ≥0.5% of subjects in either group were alanine aminotransferase (ALT) increased (0.8% and 0.4%, respectively) and aspartate aminotransferase (AST) increased (0.8% and 0.4%, respectively).

The incidences of adverse events leading to study drug discontinuation were 15.0% (144 of 961 subjects) in the tolvaptan group and 4.3% (21 of 483 subjects) in the placebo group, and events occurring in ≥0.5% of subjects in either group were fatigue (0.5% and 0%, respectively), thirst (0.6% and 0.2%, respectively), hepatic function abnormal (0.6% and 0%, respectively), nocturia (0.9% and 0.2%, respectively), pollakiuria (1.6% and 0%, respectively), polyuria (4.0% and 0%, respectively), and renal pain (0.2% and 0.6%, respectively).

3.(iii).A.(3).1).(b) Results from Japanese subgroup

The trial was conducted at 30 sites in Japan between [redacted] 20[redacted] and [redacted] 20[redacted] (target sample size [Japanese subjects], 180 subjects).

All of 177 randomized Japanese patients (118 subjects in the tolvaptan group and 59 subjects in the placebo group) received at least one dose of study drug and were included in the analyses of safety and the composite secondary efficacy endpoint. Of whom, 169 subjects with baseline and post-baseline total

kidney volume measurements (111 subjects and 58 subjects, respectively) were included in the analysis of the primary efficacy endpoint. Of whom, 164 subjects for whom total kidney volume was measured during the period from the first dosing day to the 14th day of the last dose of the study drug (106 subjects and 58 subjects, respectively) were included in the primary analysis of the primary efficacy endpoint. Thirty subjects (26 subjects and 4 subjects, respectively) discontinued the trial, and the reasons for discontinuation were adverse events (17 subjects and 1 subject, respectively), consent withdrawal (8 subjects and 2 subjects, respectively), lost to follow-up (0 subjects and 1 subject, respectively), and withdrawal criteria met (1 subject and 0 subjects, respectively).

At baseline, the percentages of subjects with hypertension in the tolvaptan and placebo groups were 72.0% and 76.3%, respectively, the percentages of subjects with CLcr <80 mL/min were 39.8% and 40.7%, respectively, the percentages of subjects with total kidney volume <1000 mL were 22.9% and 23.7%, respectively, and the total kidney volumes were 1455.9 ± 559.16 and 1567.4 ± 638.34 mL, respectively.

The percentages of subjects treated with study drug for 36 months were 78.8% (93 of 118 subjects) in the tolvaptan group and 93.2% (55 of 59 subjects) in the placebo group. At Month 36, the daily doses in the tolvaptan group were 0 mg[7] in 0 of 93 subjects (0%), 60 mg in 22 of 93 subjects (23.7%), 90 mg in 25 of 93 subjects (26.9%), and 120 mg in 46 of 93 subjects (49.5%). Tolvaptan exposure during the trial period was 292.6 subject-years.

3.(iii).A.(3).1).(b).i) Efficacy

As a result of the primary analysis for the primary endpoint, the annualized rates of change in total kidney volume (estimated slopes)[8] were 1.27%/year in the tolvaptan group and 5.04%/year in the placebo group.

Among the secondary efficacy endpoints, the incidence rates of secondary composite events of worsening renal function, clinically significant renal pain, new or worsening hypertension, and new or worsening albuminuria were 40.98 events/100 subject-years of follow-up in the tolvaptan group and 51.87 events/100 subject-years of follow-up in the placebo group, and the hazard ratio for tolvaptan vs. placebo (two-sided 95% CI for hazard ratio)[9] was 0.771 (0.552-1.078). Kaplan-Meier plots of the cumulative hazard functions of the time to multiple (recurrent) secondary composite events were as shown in Figure 5.

[7] 0 mg reflects no dose taken during the majority of the time period, due to treatment interruption etc.

[8] A regression model was fitted to the log-transformed total kidney volumes for each subject and the exponential function of the regression coefficient was obtained. Time variable used in the regression was equal to (MRI date − baseline MRI date)/365.25.

[9] Calculated by applying a proportional rates/means model including treatment as a factor to the analysis of time to multiple (recurrent) events of the secondary composite endpoint.

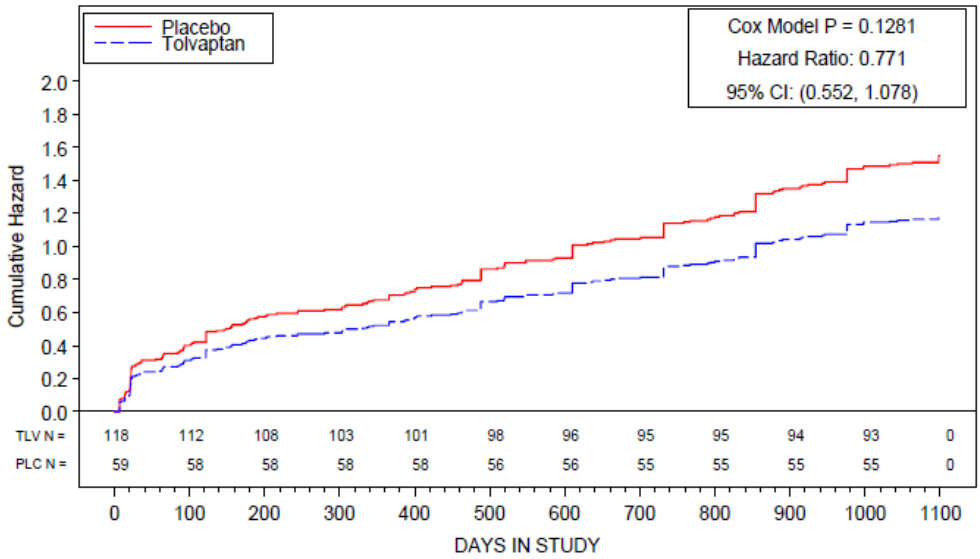

Figure 5. Cumulative hazard function of time to multiple (recurrent) secondary composite events: Japanese subgroup

The results of between-treatment comparison of the time to multiple (recurrent) events for the components of the secondary composite endpoint were as shown in Table 12.

Table 12. Results of between-treatment comparison of time to multiple (recurrent) events for components of secondary composite endpoint: Japanese subgroup (Adapted from submitted data)

	Tolvaptan	Placebo
New or worsening hypertension	N = 118	N = 59
No. of events/100 subject-years of follow-up	28.32	31.83
Hazard ratio (Two-sided 95% CI) *	0.863 (0.548-1.360)	
Clinically significant renal pain	N = 118	N = 59
No. of events/100 subject-years of follow-up	2.33	2.95
Hazard ratio (Two-sided 95% CI) *	0.767 (0.238-2.467)	
New or worsening albuminuria	N = 118	N = 59
No. of events/100 subject-years of follow-up	9.00	8.84
Hazard ratio (Two-sided 95% CI) *	0.994 (0.560-1.763)	
Worsening renal function	N = 116	N = 59
No. of events/100 subject-years of follow-up	1.33	8.25
Hazard ratio (Two-sided 95% CI) *	0.167 (0.057-0.491)	

* Calculated using a proportional rates/means model including treatment as a factor.

The main results of other secondary efficacy endpoints were as follows. The slopes of reciprocal serum creatinine from Week 3 or End of Titration were -4.837 $(mg/mL)^{-1}$/year in the tolvaptan group and -6.279 $(mg/mL)^{-1}$/year in the placebo group, and similar results were obtained also for CLcr calculated using the Cockcroft-Gault equation, $eGFR_{MDRD}$, and $eGFR_{CKD-EPI}$.

The main results of the pharmacodynamic endpoints were as follows. The mean serum creatinine concentrations at baseline and post-treatment (at Follow-up visit 2, 14-42 days after the end of study treatment) were 0.97 and 1.13 mg/dL, respectively, in the tolvaptan group and 1.01 and 1.29 mg/dL, respectively, in the placebo group. The mean changes from baseline to post-treatment were 0.15 mg/dL in

the tolvaptan group and 0.27 mg/dL in the placebo group. The mean changes from baseline to post-treatment in plasma cystatin C were 0.15 mg/dL in the tolvaptan group and 0.22 mg/dL in the placebo group. The change from baseline to Month 36 in trough urine osmolality and the proportion of subjects with urine osmolality <300 mOsm/kg during the trial period were as described in "3.(ii).A.(1).5) Multinational phase III trial (TEMPO)".

3.(iii).A.(3).1).(b).ii) Safety

The incidences of adverse events were 99.2% (117 of 118 subjects) in the tolvaptan group and 100.0% (59 of 59 subjects) in the placebo group, and events occurring in ≥5% of subjects in either group were as shown in Table 13.

Table 13. Adverse events occurring in ≥5% of subjects in either group: Japanese subgroup (Adapted from submitted data)

MedDRA System Organ Class Preferred Term (MedDRA/J version 14.1)	Tolvaptan N = 118 n (%)	Placebo N = 59 n (%)
Blood and lymphatic system disorders		
Iron deficiency anaemia	4 (3.4)	3 (5.1)
Cardiac disorders		
Palpitations	10 (8.5)	0 (0.0)
Eye disorders		
Dry eye	6 (5.1)	1 (1.7)
Gastrointestinal disorders		
Abdominal discomfort	7 (5.9)	2 (3.4)
Abdominal bloating	7 (5.9)	4 (6.8)
Abdominal pain	10 (8.5)	6 (10.2)
Abdominal pain upper	16 (13.6)	7 (11.9)
Colitis	0 (0.0)	3 (5.1)
Constipation	19 (16.1)	4 (6.8)
Dental caries	3 (2.5)	3 (5.1)
Diarrhoea	15 (12.7)	10 (16.9)
Dyspepsia	7 (5.9)	1 (1.7)
Gastrooesophageal reflux disease	11 (9.3)	4 (6.8)
Gingivitis	3 (2.5)	3 (5.1)
Haemorrhoids	6 (5.1)	1 (1.7)
Nausea	16 (13.6)	5 (8.5)
Toothache	1 (0.8)	5 (8.5)
Vomiting	12 (10.2)	3 (5.1)
General disorders and administration site conditions		
Chest discomfort	0 (0.0)	3 (5.1)
Chest pain	6 (5.1)	3 (5.1)
Fatigue	13 (11.0)	2 (3.4)
Malaise	12 (10.2)	1 (1.7)
Oedema	6 (5.1)	2 (3.4)
Oedema peripheral	7 (5.9)	6 (10.2)
Pyrexia	13 (11.0)	9 (15.3)
Thirst	106 (89.8)	18 (30.5)
Hepatobiliary disorders		
Hepatic function abnormal	12 (10.2)	2 (3.4)
Immune system disorders		

Seasonal allergy	8 (6.8)	0 (0.0)
Infections and infestations		
Bronchitis	4 (3.4)	3 (5.1)
Cystitis	4 (3.4)	5 (8.5)
Gastroenteritis	3 (2.5)	6 (10.2)
Herpes zoster	2 (1.7)	3 (5.1)
Influenza	7 (5.9)	6 (10.2)
Nasopharyngitis	68 (57.6)	45 (76.3)
Pharyngitis	3 (2.5)	6 (10.2)
Renal cyst infection	2 (1.7)	3 (5.1)
Upper respiratory tract infection	6 (5.1)	4 (6.8)
Injury, poisoning and procedural complications		
Contusion	4 (3.4)	3 (5.1)
Investigations		
Blood creatinine increased	7 (5.9)	4 (6.8)
Weight decreased	8 (6.8)	0 (0.0)
Metabolism and nutrition disorders		
Appetite decreased	12 (10.2)	1 (1.7)
Hyperuricaemia	14 (11.9)	3 (5.1)
Musculoskeletal and connective tissue disorders		
Arthralgia	6 (5.1)	5 (8.5)
Back pain	28 (23.7)	18 (30.5)
Flank pain	0 (0.0)	3 (5.1)
Muscle spasms	2 (1.7)	4 (6.8)
Musculoskeletal pain	7 (5.9)	2 (3.4)
Myalgia	11 (9.3)	5 (8.5)
Pain in extremity	6 (5.1)	2 (3.4)
Nervous system disorders		
Dizziness	17 (14.4)	8 (13.6)
Headache	37 (31.4)	15 (25.4)
Hypoaesthesia	3 (2.5)	5 (8.5)
Psychiatric disorders		
Depression	4 (3.4)	3 (5.1)
Insomnia	10 (8.5)	2 (3.4)
Renal and urinary disorders		
Haematuria	7 (5.9)	7 (11.9)
Pollakiuria	63 (53.4)	4 (6.8)
Polyuria	40 (33.9)	5 (8.5)
Renal pain	12 (10.2)	11 (18.6)
Respiratory, thoracic and mediastinal disorders		
Cough	3 (2.5)	7 (11.9)
Oropharyngeal pain	11 (9.3)	7 (11.9)
Rhinorrhoea	6 (5.1)	2 (3.4)
Skin and subcutaneous tissue disorders		
Dermatitis contact	2 (1.7)	3 (5.1)
Dry skin	6 (5.1)	1 (1.7)
Eczema	7 (5.9)	2 (3.4)
Pruritus	8 (6.8)	1 (1.7)
Rash	11 (9.3)	4 (6.8)
Urticaria	6 (5.1)	2 (3.4)
Vascular disorders		
Hypertension	27 (22.9)	15 (25.4)

The incidences of adverse events for which a causal relationship to study drug could not be denied were 99.2% (117 of 118 subjects) in the tolvaptan group and 71.2% (42 of 59 subjects) in the placebo group, and events occurring in ≥5% of subjects in either group were palpitations (5.9% and 0%, respectively), abdominal distension (5.1% and 3.4%, respectively), abdominal pain upper (6.8% and 5.1%, respectively), constipation (9.3% and 0%, respectively), gastrooesophageal reflux disease (3.4% and 5.1%, respectively), fatigue (9.3% and 0%, respectively), malaise (6.8% and 0%, respectively), oedema peripheral (3.4% and 5.1%, respectively), thirst (89.8% and 28.8%, respectively), hepatic function abnormal (9.3% and 1.7%, respectively), blood creatinine increased (4.2% and 5.1%, respectively), weight decreased (6.8% and 0%, respectively), appetite decreased (9.3% and 0%, respectively), hyperuricaemia (11.0% and 5.1%, respectively), back pain (5.1% and 3.4%, respectively), dizziness (5.9% and 8.5%, respectively), headache (16.9% and 8.5%, respectively), insomnia (5.1% and 0%, respectively), pollakiuria (53.4% and 6.8%, respectively), polyuria (33.9% and 8.5%, respectively), renal pain (5.1% and 6.8%, respectively), and hypertension (9.3% and 6.8%, respectively).

No deaths were reported.

The incidences of serious adverse events were 19.5% (23 of 118 subjects) in the tolvaptan group and 16.9% (10 of 59 subjects) in the placebo group, and events reported by at least 2 subjects in either group were angina pectoris (2 subjects and 0 subjects, respectively), hepatic function abnormal (3 subjects and 0 subjects, respectively), renal cyst infection (2 subjects and 2 subjects, respectively), and intracranial aneurysm (2 subjects and 0 subjects, respectively).

The incidences of serious adverse events for which a causal relationship to study drug could not be denied were 7.6% (9 of 118 subjects) in the tolvaptan group and 0% (0 of 59 subjects) in the placebo group, and events reported by at least 2 subjects in the tolvaptan group were hepatic function abnormal (3 subjects, 0 subjects, respectively).

The incidences of adverse events leading to study drug discontinuation were 14.4% (17 of 118 subjects) in the tolvaptan group and 1.7% (1 of 59 subjects) in the placebo group; the events included hepatic function abnormal (6 subjects and 0 subjects, respectively), pollakiuria (5 subjects and 0 subjects, respectively), thirst (1 subject and 0 subjects, respectively), ALT increased (1 subject and 0 subjects, respectively), AST increased (1 subject and 0 subjects, respectively), appetite decreased (1 subject and 0 subjects, respectively), cerebral haemorrhage (1 subject and 0 subjects, respectively), insomnia (1 subject and 0 subjects, respectively), polyuria (1 subject and 0 subjects, respectively), and multiple endocrine neoplasia (0 subjects and 1 subject, respectively).

3.(iii).A.(4) Long-term extension studies

3.(iii).A.(4).1) Japanese TEMPO extension trial (Trial 156-[redacted]-003, Attached document 5.3.5.2-02 [started in [redacted] 20[redacted], ongoing], Data cut-off date of [redacted] [redacted], 20[redacted])

An open-label, long-term extension trial of tolvaptan orally administered BID is being conducted in

Japanese ADPKD patients who completed Trial 156-[redacted]-251 (TEMPO) at 30 sites in Japan to evaluate the long-term safety and efficacy of tolvaptan (target number of subjects, up to 150 subjects).

The trial consisted of a titration phase (3 weeks from the initiation of treatment) and a long-term treatment phase (from 3 weeks after the initiation of treatment onward). In the titration period, tolvaptan was initiated at 45 + 15 mg in a hospital and then up-titrated weekly to 60 + 30 mg and 90 + 30 mg if tolerated and the dose was down-titrated if not tolerated. Although the long-term treatment phase began at the dose tolerated at the end of titration, subjects were allowed to down-titrate/up-titrate within the above dosage range throughout the treatment period. Subjects who were unable to tolerate the 45 + 15 mg dose were to discontinue the trial.

Key inclusion criteria were as follows: among Japanese ADPKD patients who previously participated in Trial 156-[redacted]-251, (a) patients who completed 3-year treatment or patients who interrupted treatment due to pregnancy and who attended the Follow-up visit 2, (b) whose all case report forms for Trial 156-[redacted]-251 were collected, and (c) whose adverse events occurring in Trial 156-[redacted]-251 resolved or stabilized, requiring no follow-up. Key exclusion criteria were eGFR <15 mL/min/1.73 m^2.

All of 108 subjects who received study drug by the data cut-off date of [redacted], 20[redacted] were included in the safety analysis. Three subjects discontinued the trial, and the reasons for discontinuation were adverse events (1 subject), withdrawal criteria met (1 subject), and the investigator's decision (1 subject). The number of days of exposure for the entire subject population at scheduled visits closest to the data cut-off date was 113.3 ± 79.6 days and the mean daily dose was 98.5 ± 22.9 mg. During the long-term treatment period, no subjects received tolvaptan at doses higher than their starting doses for the long-term treatment phase.

Regarding safety, the incidence of adverse events was 99.1% (107 of 108 subjects), and adverse events occurring in ≥5% of subjects were thirst (75.0% [81 of 108 subjects]), pollakiuria (50.9% [55 of 108 subjects]), polyuria (41.7% [45 of 108 subjects]), nasopharyngitis (15.7% [17 of 108 subjects]), hyperuricaemia (8.3% [9 of 108 subjects]), headache (7.4% [8 of 108 subjects]), diarrhoea (6.5% [7 of 108 subjects]), and upper respiratory tract inflammation (6.5% [7 of 108 subjects]). The incidence of adverse events for which a causal relationship to study drug could not be denied was 98.1% (106 of 108 subjects), and events occurring in ≥5% of subjects were thirst (75.0% [81 of 108 subjects]), hyperuricaemia (8.3% [9 of 108 subjects]), pollakiuria (50.9% [55 of 108 subjects]), and polyuria (41.7% [45 of 108 subjects]).

No deaths were reported.

Serious adverse events occurred in 3 subjects (ligament rupture; renal pain and renal cyst haemorrhage; dizziness and hepatic cyst infection [1 subject each]), and a causal relationship to study drug could not be denied for the events of renal pain, renal cyst haemorrhage, and dizziness.

Adverse events leading to study drug discontinuation were blood creatinine increased (1 subject) and renal impairment (1 subject).

3.(iii).A.(4).2) Japanese long-term extension trial I (Trial 156-[redacted]-002, Attached document 5.3.5.2-03 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, long-term extension trial was conducted in Japanese ADPKD patients who had completed Trial 156-[redacted]-001 at 10 sites in Japan to evaluate the long-term safety and efficacy of tolvaptan (target number of subjects, up to 18 subjects). Multiple daily oral doses of 15 + 15 mg of tolvaptan were administered for 3 years.

Key inclusion criteria were: among Japanese ADPKD patients who previously participated in Trial 156-[redacted]-001, those who completed 5-day treatment and follow-up and for whom the safety of multiple doses has been confirmed based on the report from the investigator of Trial 156-[redacted]-001. Key exclusion criteria were serum creatinine ≥2.5 mg/dL.

All of 17 subjects who received study drug were included in the safety analysis. Five subjects discontinued the trial, and the reasons for discontinuation were adverse events (2 subjects), subject's request (2 subjects), and withdrawal criteria met (1 subject). The treatment duration was 872.2 ± 379.4 days and the number of days treated was 871.7 ± 380.3 days.

Regarding safety, the incidence of adverse events was 100% (17 of 17 subjects), and adverse events reported by at least 3 subjects were nasopharyngitis (13 subjects), thirst (9 subjects), contusion (6 subjects), blood antidiuretic hormone increased (5 subjects), hypertension (5 subjects), blood uric acid increased (4 subjects), headache (4 subjects), palpitations (3 subjects), vertigo (3 subjects), dental caries (3 subjects), gastritis (3 subjects), dehydration (3 subjects), and back pain (3 subjects).

The incidence of adverse events for which a causal relationship to study drug could not be denied was 100% (17 of 17 subjects), and events reported by at least 3 subjects were thirst (9 subjects), blood antidiuretic hormone increased (5 subjects), palpitations (3 subjects), blood uric acid increased (3 subjects), dehydration (3 subjects), headache (3 subjects), and hypertension (3 subjects).

One death occurred. Subarachnoid haemorrhage was a fatal adverse event, and its relationship to study drug was denied.

Serious adverse events occurred in 2 subjects (subarachnoid haemorrhage; diverticulitis [1 subject each]), and a causal relationship to study drug was denied for both cases.

Adverse events leading to study drug discontinuation occurred in 3 subjects (renal impairment; subarachnoid haemorrhage; blood creatinine increased [1 subject each]).

3.(iii).A.(4).3) Japanese long-term extension trial II (Trial 156-[redacted]-003, Attached document 5.3.5.2-04 [started in [redacted] 20[redacted], ongoing], Data cut-off date of [redacted] [redacted], 20[redacted])

An open-label, long-term extension trial is being conducted in Japanese ADPKD patients who participated in Trial 156-[redacted]-002 at 7 sites in Japan to evaluate the long-term safety and efficacy of tolvaptan (target number of subjects, up to 15 subjects). Multiple daily oral doses of 15 + 15 mg of tolvaptan are being administered.

Key inclusion criteria were: patients who previously completed 3-year treatment and follow-up or patients who discontinued treatment for reasons other than "the occurrence of adverse events (subject or physician's decision)" in Trial 156-[redacted]-002; and patients whose adverse events occurring in Trial 156-[redacted]-002 resolved or stabilized, requiring no follow-up. Key exclusion criteria were eGFR <15 mL/min/1.73 m^2.

All of 13 subjects who received study drug by the data cut-off date of [redacted] [redacted], 20[redacted] were included in the safety analysis. One subject discontinued the trial because the investigator/sub-investigator of the subject had determined that withdrawal from the trial was needed. The duration of treatment up to the data cut-off date was 205 to 724 (Min.-Max.) days. The number of days treated was 205 to 724 days, and 11 of the 13 subjects were treated for >600 days.

Regarding safety, the incidence of adverse events was 100% (13 of 13 subjects), and adverse events reported by at least 2 subjects were blood antidiuretic hormone increased (6 subjects), nasopharyngitis (5 subjects), hypertension (4 subjects), thirst (3 subjects), hyperuricaemia (3 subjects), headache (3 subjects), abdominal pain (2 subjects), hiatus hernia (2 subjects), pyrexia (2 subjects), cystitis (2 subjects), dehydration (2 subjects), renal impairment (2 subjects), polyuria (2 subjects), and pollakiuria (2 subjects). The incidence of adverse events for which a causal relationship to study drug could not be denied was 92.3% (12 of 13 subjects), and events reported by at least 2 subjects were blood antidiuretic hormone increased (6 subjects), thirst (3 subjects), hyperuricaemia (3 subjects), dehydration (2 subjects), headache (2 subjects), polyuria (2 subjects), pollakiuria (2 subjects), and hypertension (2 subjects).

No deaths were reported.

Serious adverse events occurred in 1 subject (hepatic cyst infection, abdominal pain, pyrexia), and a causal relationship to study drug was denied for all events.

There were no adverse events leading to study drug discontinuation.

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

3.(iii).B.(1) Clinical positioning of Tolvaptan

PMDA asked the applicant to explain the clinical positioning of tolvaptan for the treatment of ADPKD in

Japan, taking account of the pharmacologic effects of tolvaptan, the current situation of the treatment of ADPKD in Japan, and the results from clinical trials of tolvaptan.

The applicant responded as follows:
In cultured tubular cells derived from normal kidney and non-cystic tubular epithelial cells from ADPKD kidney, an increase in cyclic AMP (cAMP), which is a second messenger in signal transduction from the membrane receptor into the cell's interior, decreases cell proliferation. On the other hand, the proliferative activity of cells derived from cystic epithelium of ADPKD is increased when stimulated with a substance that promotes intracellular cAMP production, such as vasopressin. In addition, a chloride channel called cystic fibrosis transmembrane conductance regulator (CFTR), which is activated by cAMP, is present on the cell membrane of cyst epithelial cells, and CFTR is thought to play an important role in cyst fluid accumulation in ADPKD. Tolvaptan is an orally-available, vasopressin V_2-receptor antagonist and considered to exert its pharmacologic action, i.e. reduce cyst growth by inhibiting vasopressin-stimulated intracellular cAMP production, in ADPKD patients.

The number and size of renal and hepatic cysts continue to increase, which causes many of ADPKD symptoms. No means of sustained inhibition of cyst growth have been established and the treatment of ADPKD is generally palliative to relieve individual patients' symptoms (renal pain, abdominal distension, renal symptoms such as haematuria, hypertension, hepatic cyst, cerebral aneurysm, cyst infection, etc.). Renal cystic growth is considered to cause renal function decline leading to dialysis initiation, which significantly compromises the Quality of Life (QOL) of ADPKD patients. Currently, there are no drugs that achieve direct and sustained inhibition of renal cyst growth. In addition, renal cyst growth associated with ADPKD progression decreases renal function, and about one half of patients with ADPKD reach end-stage renal disease by 70 years of age and end up with dialysis.

The TEMPO trial was conducted in ADPKD patients with CLcr ≥60 mL/min and a rapid estimated rate of kidney volume increase as indicated by a total kidney volume of ≥750 mL by MRI. As a result, the primary endpoint of the rate of total kidney volume change (estimated slope) was 2.80%/year in the tolvaptan group, which was significantly lower than 5.51%/year in the placebo group. The analysis of the secondary composite endpoint showed that the incidence rates of four types of ADPKD clinical progression events (worsening renal function, clinically significant renal pain, new or worsening hypertension, and new or worsening albuminuria) were 43.94 events/100 subject-years of follow-up in the tolvaptan group and 50.04 events/100 subject-years of follow-up in the placebo group, and the hazard ratio for tolvaptan vs. placebo calculated using a proportional rates/means model (two-sided 95% CI for hazard ratio) was 0.865 (0.775-0.965). The estimated slope of renal function change using the reciprocal serum creatinine was -2.609 $(mg/mL)^{-1}$/year in the tolvaptan group, which was slower than -3.812 $(mg/mL)^{-1}$/year in the placebo group. The incidence rates of events of clinically significant renal pain were 4.73 events/100 subject-years of follow-up in the tolvaptan group and 7.30 events/100 subject-years of follow-up in the placebo group, and the hazard ratio (two-sided 95% CI for hazard ratio) was 0.642 (0.466-0.887). Tolvaptan compared with placebo reduced the events of urinary tract infection and haematuria based on

reports of ADPKD patients themselves.

The benefits of the treatment of ADPKD with tolvaptan include slowing of the development and progression of various ADPKD clinical symptoms such as renal function decline through blockade of vasopressin's effects on renal cystic cells and reduction of renal cyst growth. Since continuous stimulation by vasopressin increases renal cyst growth in ADPKD patients, continuous administration of tolvaptan is most important to benefit ADPKD patients. In the TEMPO trial, a reduction in the incidence rate of renal function decline by tolvaptan occurred in the early phase of treatment and this effect lasted for 3 years. Events of worsening renal function occurred from about 1 year after treatment initiation, and a reduction in the incidence of the events by tolvaptan was observed from 1.5 years after treatment initiation onward. Events of renal pain occurred frequently from immediately after treatment initiation. A reduction in the incidence by tolvaptan occurred in the early phase of treatment, and the difference between the tolvaptan and placebo groups became greater throughout the 3-year treatment period. Based on these findings, tolvaptan is expected to slow ADPKD progression over a long period of time.

As described above, tolvaptan slowed total kidney volume growth and renal function decline and reduced ADPKD clinical symptoms such as renal pain, urinary tract infection, and haematuria, showing that tolvaptan is the first drug in the world to slow the progression of ADPKD, e.g., kidney volume growth and renal function decline.

Subgroup analyses of the efficacy endpoints for the TEMPO trial were carried out by stratifying subjects according to important baseline characteristics (geographic region, age, gender, race), disease stage (total kidney volume, CLcr, the presence or absence of microalbuminuria), complications (the presence or absence of hypertension), and concomitant medications (the use or non-use of anti-hypertensive medication), which demonstrated efficacy across all subgroups. Thus, although tolvaptan may benefit late-stage ADPKD patients as well, the benefits of tolvaptan may be reduced if the time to dialysis initiation is short because the benefits to patients depend on the duration of treatment. Based on the above, when initiated early and used continuously, tolvaptan are expected to slow the progression of ADPKD, such as renal function decline, and delay the initiation of dialysis which significantly compromises the QOL of ADPKD patients.

Tolvaptan is associated with the risks of hypernatraemia and hepatic dysfunction, which can be managed by adequate guidance on fluid ingestion and periodic blood testing. In the treatment of ADPKD, the benefits of tolvaptan outweigh its risks as long as adequate information and caution are given, and tolvaptan is expected to be effective for the treatment of ADPKD.

PMDA's view on the clinical positioning of tolvaptan for the treatment of ADPKD is as follows:
The results from the TEMPO trial showed that tolvaptan reduces renal cyst growth and can slow renal function decline in ADPKD patients [see "3.(iii).B.(2) Efficacy of Tolvaptan"]. Currently, no curative therapy for ADPKD exists and existing therapies are all palliative, targeting hypertension and renal pain

etc., and ADPKD is progressive and leads to dialysis. Taking account of these points, the availability of a drug that reduces renal cyst growth and slows renal function decline as a therapeutic option is of great clinical relevance. However, since tolvaptan is associated with the risk of serious hepatic dysfunction, tolvaptan should be used under an adequate control system in which the risk of serious adverse drug reactions such as hepatic dysfunction is closely monitored and treatment with tolvaptan is promptly discontinued in the event of hepatic dysfunction [see 3.(iii).B.(5) Safety"]. In light of the above benefits and risks of tolvaptan, as long as the use of tolvaptan is limited to ADPKD patients with residual renal function in whom the condition is worsening rapidly due to particularly rapid renal cystic growth [see "3.(iii).B.(3) Intended population and indication for Tolvaptan"], it is meaningful to provide tolvaptan as a therapeutic option for ADPKD to clinical practice.

3.(iii).B.(2) Efficacy of Tolvaptan

3.(iii).B.(2).1) Efficacy endpoint

PMDA asked the applicant to provide the rationale and justification for selecting the rate of kidney volume change as the primary endpoint for the confirmatory TEMPO trial in this drug development program and explain the clinical relevance of the rate of kidney volume change, taking also account of the relationship between the rate of kidney volume change and the true endpoint for the treatment of ADPKD.

The applicant responded as follows:

In ADPKD, renal cysts grow progressively, and renal parenchymal atrophy and fibrosis lead to functioning nephron loss. GFR is normal until renal cysts become prominent because the remaining nephrons are able to compensate. When functioning nephron loss is so great that compensatory glomerular hyperfiltration of the remaining nephrons is no longer adequate, renal function begins to decline. Tolvaptan is expected to reduce renal cyst growth in ADPKD patients, resulting in a delay in renal function decline. Therefore, tolvaptan was unlikely to provide a benefit in delaying renal function decline to patients with renal impairment requiring dialysis initiation due to markedly decreased residual renal function. In order to evaluate the efficacy of tolvaptan, it was necessary to enroll patients at a relatively early stage of their disease in whom renal function is preserved to some extent. In addition, assessment of the length of time from early-stage ADPKD to dialysis initiation (end-stage renal disease), the true endpoint for the treatment of ADPKD, will require involvement of a large number of ADPKD patients treated for a long-period of time, which is not feasible as a clinical trial. At the time of initiating the TEMPO trial, no endpoint validated for assessment of treatment effect in such patients at a relatively early stage of ADPKD had been reported. However, since foreign observational studies of ADPKD patients had reported that there is an inverse correlation between kidney volume and renal function in ADPKD patients (Chapman AB et al. *Kidney Int.* 2003;64:1035-45, Fick-Brosnahan GM et al. *Am J Kidney Dis.* 2002;39:1127-34), that the total kidney volume increases also in patients in early stages of ADPKD, and that renal function declines faster in patients with greater initial total kidney volumes (Grantham JJ et al. *N Engl J Med.* 2006;354:2122-30), the rate of kidney volume change was selected as the primary endpoint.

In the TEMPO trial, tolvaptan slowed kidney volume growth in ADPKD patients and at the same time

reduced deterioration of ADPKD clinical symptoms (the secondary composite endpoint, renal function, renal pain, etc.), indicating a justification of kidney volume as a measure of treatment effect in patients at an early stage of ADPKD. Recently, a follow-up of the aforementioned foreign observational study has shown that baseline total kidney volume negatively correlates with GFR after a follow-up of 8 years (Chapman AB et al. *Clin J Am Soc Nephrol.* 2012;7:479-86) and an observational study of Japanese patients also has shown that renal function declines faster in patients with larger kidney volume (Higashihara E et al. *Clin Exp Nephrol.* 2013 Jul 18 [Epub ahead of print]). These results indicate that kidney volume is useful for predicting the degree of future deterioration of kidney function and show the possibility that early intervention to slow kidney volume growth reduces the risk of developing renal failure (the true endpoint).

Based on the above, the rate of kidney volume change is justified as a measure to assess the treatment effect of tolvaptan in patients at a relatively early stage of ADPKD and is considered a useful endpoint associated with the progression of some ADPKD clinical symptoms.

PMDA considers as follows:
The true endpoint for the treatment of ADPKD is a delay in the onset of end-stage renal disease. However, as explained by the applicant, ADPKD has a long disease course and in order to assess the length of time from early-stage ADPKD to dialysis initiation (end-stage renal disease), it will be necessary to study a large number of ADPKD patients over a very long-period of time. In addition, it is inferred that treatment with tolvaptan is effective when initiated before residual renal function is markedly decreased. Taking account of these points, it is difficult to use the true endpoint in clinical trials. Thus, in order to evaluate the efficacy of tolvaptan in clinical trials, the use of an appropriate surrogate endpoint is inevitable. The applicant's opinion that the rate of kidney volume change was chosen as the primary endpoint because it had been reported that there is an inverse correlation between kidney volume and renal function in ADPKD patients and that renal function declines faster in patients with a larger kidney volume, is acceptable. Given that ADPKD is a progressive, irreversible disease in which renal cysts grow in number and size, leading to renal function deterioration, it is pharmacologically reasonable to use tolvaptan that reduces renal cyst growth by inhibiting cyst fluid secretion etc. in patients with ADPKD, and this rationale has been supported by the results from the TEMPO trial. Clinically, the rate of kidney volume change alone is not sufficient to evaluate the efficacy of tolvaptan, but a composite of events of worsening renal function, clinically significant renal pain, new or worsening hypertension, and new or worsening albuminuria has been chosen as the secondary composite endpoint for the TEMPO trial. The efficacy of tolvaptan can be evaluated with a comprehensive and integrated assessment of the results for the secondary composite endpoint and its components as well as the primary endpoint.

Once cysts form, they do not disappear and even if cyst fluid secretion can be inhibited, morphological changes are irreversible. Considering these points, tolvaptan may not be effective in patients with a large kidney volume in whom renal cysts have expanded to a certain extent or patients in whom renal impairment progressed above a certain level, and treatment with tolvaptan is of significance when

tolvaptan is initiated at an early stage where the cysts physically compress the renal parenchyma to a lesser degree and where renal impairment is relatively mild, before numerous renal cysts form. Therefore, the stage of disease progression in patients selected for the TEMPO trial is appropriate. Taking account of the feasibility of a clinical trial, the selection of the rate of kidney volume change as the primary endpoint is justified because the outcomes will be available in several years for such patients and because the rate of kidney volume change is considered closely linked to the mechanism of action of tolvaptan.

3.(iii).B.(2).2) Consistency of efficacy of Tolvaptan between the overall trial population and Japanese subgroup in TEMPO trial

PMDA asked the applicant to examine the consistency of tolvaptan efficacy results between the overall trial population and Japanese subgroup in the TEMPO trial and then explain whether the overall trial results can be extrapolated to the Japanese population, after comparing intrinsic and extrinsic ethnic factors in the concept and treatment of ADPKD between in and outside Japan; and baseline characteristics of patients, the dose level of tolvaptan, and the results of the primary efficacy endpoint and secondary efficacy endpoints between the overall trial population and Japanese subgroup in the TEMPO trial.

The applicant responded as follows:

The consistency of efficacy results between the overall trial population and Japanese subgroup in the TEMPO trial was examined based on the results of the primary endpoint (total kidney volume), renal function, and the secondary composite endpoint and its components. The primary endpoint of the rate of increase in total kidney volume over up to 3 years of study treatment (estimated slope of change) was 2.80%/year in the tolvaptan group and 5.51%/year in the placebo group, with a treatment difference of -2.71%/year, in the overall trial population and 1.27%/year in the tolvaptan group and 5.04%/year in the placebo group, with a treatment difference of -3.77%/year, in the Japanese subgroup; tolvaptan significantly reduced the annualized rate of total kidney volume growth in both the overall trial population and Japanese subgroup ($P < 0.0001$ for both, derived from testing the treatment-by-time interaction using a linear mixed effect model). The estimated slopes of renal function change using the reciprocal serum creatinine were -2.609 $(mg/mL)^{-1}$/year in the tolvaptan group and -3.812 $(mg/mL)^{-1}$/year in the placebo group, with a treatment difference of +1.203 $(mg/mL)^{-1}$/year (95% CI, 0.622-1.783), in the overall trial population and -4.837 $(mg/mL)^{-1}$/year in the tolvaptan group and -6.279 $(mg/mL)^{-1}$/year in the placebo group, with a treatment difference of +1.442 $(mg/mL)^{-1}$/year (95% CI, 0.318-2.566), in the Japanese subgroup; tolvaptan significantly reduced the annualized rate of renal function (reciprocal serum creatinine) decline in both the overall trial population and Japanese subgroup ($P < 0.0001$ and $P = 0.0119$, respectively, derived from testing the treatment-by-time interaction using a linear mixed effect model). The incidence rates of the secondary composite events (worsening renal function, clinically significant renal pain, new or worsening hypertension, new or worsening albuminuria) were 43.94 events/100 subject-years of follow-up in the tolvaptan group and 50.04 events/100 subject-years of follow-up in the placebo group, with a hazard ratio of 0.865 (95% CI, 0.775-0.965), in the overall trial population and 40.98 events/100 subject-years of follow-up in the tolvaptan group and 51.87 events/100 subject-years of follow-up in the

placebo group, with a hazard ratio of 0.771 (95% CI, 0.552-1.078), in the Japanese subgroup; tolvaptan significantly reduced the risk of events of the secondary composite endpoint in the overall trial population (P = 0.0095, proportional rates/means model). In the Japanese subgroup, no significant difference was observed (P = 0.1281), but tolvaptan reduced the incidence of events and there was a similar trend to that found in the overall trial population. The results of between-treatment comparison of the time to multiple (recurrent) events for the components of the secondary composite endpoint in the overall trial population and Japanese subgroup were as shown in Table 9 and Table 12, respectively. Tolvaptan significantly reduced the incidences of worsening renal function events and renal pain events in the overall trial population and tended to reduce the incidences of worsening renal function events and renal pain events also in the Japanese subgroup. On the other hand, tolvaptan had no effect on the incidence of new or worsening hypertension events or new or worsening albuminuria events in the overall trial population, and a similar trend was observed also in the Japanese subgroup. Based on the above, there were no major differences in the results of any endpoint between the overall trial population and Japanese subgroup and it was considered that efficacy results were consistent between the overall trial population and Japanese subgroup.

ADPKD is a hereditary disease caused by mutations in the *PKD* genes, characterized by progressive development and growth of numerous cysts in the both kidneys. With regard to intrinsic factors, *PKD1* and *PKD2* are known as the *PKD* genes, and it has been reported that mutations in the *PKD1* or *PKD2* genes are responsible for 85% and 15% of ADPKD cases, respectively, outside Japan. According to a survey by Mizoguchi et al., 81% and 10% of Japanese patients with ADPKD had mutations in *PKD1* and *PKD2*, respectively, and these percentages were similar to those in Caucasians and the Latinos (Mizoguchi et al. *Polycystic kidney disease.* 2006;37-38). Although renal function generally declines slower in patients with mutations in *PKD2* than in patients with mutations in *PKD1*, as no reliable method for genetic diagnosis of *PKD1* and *PKD2* has been established, genetic testing for the diagnosis of ADPKD is not generally used. Based on survey reports on the numbers of Japanese and foreign ADPKD patients (Higashihara E et al. *Nephron.* 1998;80:421-7, Davies F et al. *Q J Med.* 1991;79:477-85, de Almeida E et al. *Kidney Int.* 2001;59:2374), there were no major differences in the number of ADPKD patients between in and outside Japan. According to the information published on the website of the Japanese Intractable Diseases Information Center (as of May 2013), there were no major differences between in and outside Japan also in the proportion (incidence) of end-stage renal disease patients with ADPKD in the general population. Concerning the disease conditions, the percentages of ADPKD patients with clinical symptoms or complications in Japan and overseas were 39% and 37% to 43%, respectively, for haematuria, 42% and 41%, respectively, for back pain, 64% and 52% to 70%, respectively, for hypertension, and 8% and 6% to 17%, respectively, for intracranial aneurysms; no major differences between in and outside Japan were observed for any of the clinical symptoms or complications. When the prevalence of end-stage renal disease patients on dialysis or with a renal transplant due to ADPKD was compared, 1:30000 in Wales reported by Davies et al. (Davies F et al. *Q J Med.* 1991;79:477-85) was similar to 1:27000 in Japan reported by Higashihara et al. (Higashihara E et al. *Nephron.* 1998;80:421-7)

With regard to extrinsic factors, there are no common ADPKD diagnostic criteria across countries. The ADPKD diagnostic criteria reported overseas, i.e. Ravine's criteria (Ravine D et al. *Lancet.* 1994;343:824-827) and Pei's criteria (Pei Y et al. *J Am Soc Nephrol.* 2009;20:205-212), were compared with the ADPKD diagnostic criteria established by the MHLW Research Committee for Progressive Renal Disease (2002, revised in 2010) (MHLW Research Committee for Progressive Renal Disease. *Japanese Journal of Nephrology.* 2011;53:556-83). As a result, although there is a slight difference in the number of cysts required for diagnosis among these sets of diagnostic criteria, all sets of criteria basically require the presence of multiple cysts in the kidney, and the presence of non-renal lesions such as intracranial vascular disorders and hypertension supports a diagnosis of ADPKD in both Japan and overseas. As to therapies for ADPKD, currently, there are no drugs that have effects on cyst growth in ADPKD and management focuses on treatment of abdominal pain or flank pain (renal pain) and complications such as hypertension in both Japan and overseas. For example, renal pain is treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and hypertension is treated with angiotensin II receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACE inhibitors).

The baseline characteristics were compared between Japanese and foreign subjects enrolled into the TEMPO trial. The mean age (Japan, 39.2 years [age range, 21-50 years]; overseas, 38.6 years [age range, 18-51 years]) and the male to female ratio (the percentage of male subjects) [Japan, 53.1% (94 of 177 subjects); overseas, 51.4% (652 of 1268 subjects)] were similar between Japanese and foreign subjects. The mean height was lower in Japanese subjects (Japan, 167.5 cm; overseas, 174.4 cm) and the mean body weight was also lower (Japan, 65.3 kg; overseas, 81.1 kg). In the TEMPO trial, three factors that were considered to influence efficacy (the presence or absence of hypertension, degree of renal function [CLcr, <80 mL/min or ≥80 mL/min], total kidney volume [<1000 mL or ≥1000 mL]) were used as stratification factors, and subjects were randomized with stratification in each region independently (3 regions of Japan, North and South Americas, and Europe and the rest of the world). More Japanese subjects had lower renal function (CLcr <80 mL/min) (Japan, 40.1%; oversea, 23.7%), but there were no major differences for the other 2 factors (the percentage of subjects with hypertension [Japan, 73.4%; overseas, 80.2%], the percentage of subjects with total kidney volume <1000 mL [Japan, 23.2%; overseas, 20.3%]). Renal function at baseline was lower in Japanese subjects than in foreign subjects; $eGFR_{MDRD}$ (Japan, 64.25 mL/min/1.73 m^2; overseas, 74.17 mL/min/1.73 m^2), the Cockcroft-Gault equation (Japan, 89.92 mL/min; overseas, 105.96 mL/min), and $eGFR_{CKD\text{-}EPI}$ (Japan, 71.88 mL/min/1.73 m^2; overseas, 82.97 mL/min/1.73 m^2). However, the mean $eGFR_{MDRD}$ in both Japanese and foreign subjects fell under chronic kidney disease (CKD) stage 2 (mildly reduced GFR; $eGFR_{MDRD}$, 60-89 mL/min/1.73 m^2) and it was considered that there were no major differences in the disease conditions between Japanese and foreign subjects with ADPKD. The reciprocal serum creatinine was similar (Japan, 109.78 $(mg/mL)^{-1}$; overseas, 101.99 $(mg/mL)^{-1}$). Japanese subjects had a smaller total kidney volume compared to foreign subjects (Japan, 1493.0 mL; overseas, 1720.2 mL), but the difference was smaller when adjusted for height (Japan, 888.56 mL/m; overseas, 983.39 mL/m). As differences in total kidney volume are closely associated with differences in body size, there would be no major differences in the disease conditions between Japanese and foreign subjects with ADPKD. Common initial symptoms/signs leading to a diagnosis of ADPKD were

hypertension (23.2%) and haematuria (22.0%) in Japanese subjects and hypertension (23.1%) and renal pain (15.9%) in foreign subjects. Compared with foreign subjects, Japanese subjects more frequently had the symptoms/signs of hepatic cysts (Japan, 89.3%; overseas, 55.5%) and proteinuria (Japan, 42.9%; overseas, 21.5%). Compared with Japanese subjects, foreign subjects more frequently had the symptoms/signs of urinary tract infection (Japan, 15.8%; overseas, 33.6%). The causes for these differences are unknown. In the TEMPO trial, the percentage of Japanese subjects with hypertension was 70.6%, which was slightly lower than that of foreign subjects (81.4%), which was not considered a clinically relevant difference. The percentage of Japanese subjects with renal pain was lower than that of foreign subjects (Japan, 29.9%; overseas, 53.8%). The majority of both Japanese and foreign subjects were taking anti-hypertensive medication (Japan, 66.1%; overseas, 79.0%). The percentage of Japanese subjects with albuminuria was higher than that of foreign subjects (Japan, 71.7%; overseas, 56.7%) and the percentage of Japanese subjects with overt albuminuria was also higher (Japan, 7.9%; overseas, 4.9%).

Regarding the dose of tolvaptan in Japanese subjects, subjects with a modal dose of 120 mg/day accounted for the largest proportion at Week 3 or End of Titration, being 84.5% in the tolvaptan group and 96.6% in the placebo group. The mean daily dose of tolvaptan was ≥90 mg/day at any time point during the maintenance period, and the proportions of subjects with a modal dose of 120 mg/day were about 50% in the tolvaptan group and ≥90% in the placebo group. At Month 36, the mean daily dose in the tolvaptan group was 93.09 mg/day, and the proportions of subjects with modal doses of 120 mg/day, 90 mg/day, and 60 mg/day in the tolvaptan group were 49.5% (46 of 93 subjects), 26.9% (25 of 93 subjects), and 23.7% (22 of 93 subjects), respectively. At Month 36, 78.8% of subjects in the tolvaptan group (93 of 118 subjects) and 93.2% of subjects in the placebo group (55 of 59 subjects) were receiving study drug. As for the dose of tolvaptan in foreign subjects, subjects with a modal dose of 120 mg/day accounted for the largest proportion at Week 3 or End of Titration, being 80.4% in the tolvaptan group and 93.3% in the placebo group. The mean daily dose of tolvaptan was ≥90 mg/day at any time point during the maintenance period, and the proportions of subjects with a modal dose of 120 mg/day were ≥50% in the tolvaptan group and ≥80% in the placebo group. At Month 36, the mean daily dose of tolvaptan was 96.93 mg/day and the proportions of subjects with modal doses of 120 mg/day, 90 mg/day, and 60 mg/day in the tolvaptan group were 55.2% (358 of 649 subjects), 20.3% (132 of 649 subjects), and 24.2% (157 of 649 subjects), respectively. At Month 36, 77.0% of subjects in the tolvaptan group (649 of 843 subjects) and 85.6% of subjects in the placebo group (363 of 424 subjects) were receiving study drug.

As described above, as a result of a literature review of the concept of ADPKD and ethnic factors, there were no major differences between in and outside Japan with regard to several factors such as the concept of ADPKD, the genes, the number of patients, the disease conditions, the definition and diagnosis of ADPKD, therapeutic approach, etc. Although comparison of baseline characteristics between the Japanese and non-Japanese subgroups in the TEMPO trial revealed some differences, these differences were not considered to significantly influence efficacy results. Furthermore, no major differences between the Japanese and non-Japanese subgroups were observed in the doses of tolvaptan. Based on the above, it was concluded that the overall efficacy results can be extrapolated to the Japanese population.

PMDA considers as follows:
In the TEMPO trial, the percentage of patients with lower renal function was slightly higher in the Japanese subgroup compared with the overall trial population (the foreign subgroup). Concerning the dose level of tolvaptan, outside Japan, about 55% to 66% of patients had a modal dose of 120 mg/day and only about 17% to 21% of patients had a modal dose of 90 mg/day after Month 8, while in Japan, about 48% to 53% of patients had a modal dose of 120 mg/day and about 26% to 28% of patients had a modal dose of 90 mg/day after Month 8. Compared to overseas, there was a trend towards fewer patients with a modal dose of 120 mg/day and more patients with a modal dose of 90 mg/day in Japan. As described above, there were some differences in baseline characteristics and the dose level of tolvaptan between in and outside Japan, but no major differences between in and outside Japan were observed in the disease conditions. Thus, it was considered appropriate to enroll Japanese patients with ADPKD into the TEMPO trial and to evaluate the efficacy and safety of tolvaptan.

Regarding tolvaptan efficacy results from the TEMPO trial, tolvaptan significantly reduced the annualized rate of total kidney volume growth, the primary endpoint, in both the overall trial population and Japanese subgroup; consistent results were obtained. Although a statistical analysis of the secondary composite events has a limitation due to the small number of patients in the Japanese subgroup, tolvaptan compared to placebo tended to reduce the risk of the events in the Japanese subgroup as in the overall trial population. Analyses of the components of the secondary composite endpoint showed that tolvaptan significantly reduced the incidence rates of worsening renal function events and renal pain events but had no effect on the incidence rate of new or worsening hypertension events or that of new or worsening albuminuria events in the overall trial population. In addition, tolvaptan tended to reduce the incidence rates of worsening renal function events and renal pain events also in the Japanese subgroup but there was no clear treatment effect on the incidence rate of new or worsening hypertension events or new or worsening albuminuria events in the Japanese subgroup. Thus, similar results were obtained for the overall trial population and Japanese subgroup. Although there were no treatment effects on the incidence rate of new or worsening hypertension events or new or worsening albuminuria events, factors other than kidney volume growth, such as the activation of the renin-angiotensin system, are also presumed to be closely relevant to new or worsening hypertension. Additionally, factors other than kidney volume, such as hypertension, are presumed to be closely relevant also to new or worsening albuminuria. Therefore, there is a possibility that tolvaptan may have shown no apparent improvement because of these factors. However, tolvaptan showed no trend towards worsening of the condition for either of the above two components.

Based on the above, the results of the primary and secondary efficacy endpoints were consistent between the Japanese subgroup and the overall trial population in the TEMPO trial. Thus, the overall efficacy results from the TEMPO trial can be extrapolated to the Japanese population and the efficacy of tolvaptan as demonstrated by the entire TEMPO trial can be expected also in Japanese patients with ADPKD.

3.(iii).B.(2).3) Clinical relevance of primary and secondary endpoints in clinical trial and the efficacy

of tolvaptan

PMDA asked the applicant to explain the clinical relevance of the differences between the tolvaptan and placebo groups in the results of the primary endpoint and the secondary composite endpoint observed in the TEMPO trial.

The applicant responded as follows:

Renal cyst formation is the first detectable symptom in ADPKD patients, which always precedes clinical symptoms of ADPKD (e.g., renal pain, hypertension, haematuria, renal stone, kidney infection, renal function decline). The rate of increase in kidney volume varies among individuals, and many papers have reported that there is inverse correlation between kidney volume and renal function (Fick-Brosnahan GM et al. *Am J Kidney Dis.* 2002;39:1127-34, Chapman AB et al. *Kidney Int.* 2003;64:1035-45, Grantham JJ et al. *N Engl J Med.* 2006;354:2122-30, etc.). Other renal complications are associated with increased kidney volume (Grantham JJ et al. *Clin J Am Soc Nephrol.* 2006;1:148-57), and it has also been reported that baseline total kidney volume negatively correlates with GFR at 8 years after baseline. (Chapman AB et al. *Clin J Am Soc Nephrol.* 2012;7:479-86). Namely, kidney volume is the most important predictor of loss of kidney function and renal complications.

With respect to the primary endpoint for the TEMPO trial, tolvaptan slowed kidney volume growth due to renal cyst growth. The rate of increase in total kidney volume over up to 3 years of study treatment (estimated slope of change) was 2.80%/year in the tolvaptan group, which was significantly lower than 5.51%/year in the placebo group. The treatment difference was -2.71%/year, which represented a 49.2% decrease in kidney volume growth. As the results of a subgroup analysis of the slope of change in total kidney volume showed no differences in efficacy between patients with baseline total kidney volume ≥1000 mL and <1000 mL, tolvaptan is expected to slow kidney volume growth, regardless of kidney volume at the start of treatment. Using 3-year data from the TEMPO trial, the effects of tolvaptan beyond 3 years of administration were predicted. As a result, it is predicted that treatment effects (a reduction of about 2%/year in the growth rate) will continue, and taking account of increased incidences of chronic pain and complications and increased risk of renal function deterioration associated with kidney volume growth as previously mentioned, the clinical relevance of the effect of tolvaptan in slowing total kidney volume growth should be great.

Based on the results of the secondary composite endpoint for the TEMPO trial, the incidence of clinical symptoms of ADPKD is expected to decrease as tolvaptan slows kidney volume growth. A combined analysis of the four clinical events (worsening renal function, renal pain, new or worsening hypertension, new or worsening albuminuria) associated with the progress of ADPKD showed that tolvaptan significantly reduced the risk of composite events (about a 13.5% reduction). An analysis of events contributing this difference between the tolvaptan and placebo groups revealed that tolvaptan reduced the risk of worsening renal function by 61.4% and the risk of renal pain by 35.8%, among the four types of clinical events. Worsening renal function events appeared at around Month 12 (Day 360) in both the tolvaptan and placebo groups, and the efficacy of tolvaptan compared to placebo became evident at around

Month 18 (Day 500). Tolvaptan showed an effect on renal pain events early following treatment initiation, and the difference between the tolvaptan and placebo groups became larger during a 3-year treatment period. The reduction in the risk of worsening renal function by Tolvaptan was confirmed also by a significant reduction in the estimated slope of $eGFR_{CKD-EPI}$ change in the Tolvaptan group (-2.723 mL/min/1.73 m2/year) compared to the placebo group (-3.700 mL/min/1.73 m2/year): a treatment effect of 0.977 mL/min/1.73 m2/year. It is known that reductions in GFR become greater with the progression of the disease in ADPKD patients. The results of a subgroup analysis of the TEMPO trial also showed that renal function tended to decline faster in patients with lower levels of renal function ($eGFR_{CKD-EPI}$) at baseline in the placebo group, whereas the reduction in the rate of renal function decline by tolvaptan was almost constant, regardless of the patient's eGFR [see Table 14]. Although tolvaptan has never been used in ADPKD patients with markedly decreased renal function requiring dialysis initiation and no efficacy data from these patients have been obtained, tolvaptan is considered to reduce the rate of GFR decrease to about two-thirds and is expected to prolong the time to renal function decline to a given level by about 1.5 times, at least in patients with CKD stages 1 to 3 (GFR ≥30 mL/min/1.73 m^2). The effect of tolvaptan in reducing the rate of GFR decline (about 1 mL/min/1.73 m^2/year) was similar to the effect of losartan in reducing the rate of progression to end-stage renal disease in the RENAAL study in diabetic nephropathy (Brenner BM et al. *N Engl J Med* 2001, 345:861-9), i.e. 0.8 mL/min/1.73 m^2/year (losartan, -4.4 mL/min/1.73 m^2/year; placebo, -5.2 mL/min/1.73 m^2/year).

Table 14. Renal function at baseline and change in renal function slope (Adapted from submitted data)

$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	N		Slope		Treatment effect	Relative Effect Size
	Tolvaptan	Placebo	Tolvaptan	Placebo		
≥90	330	173	-1.926	-2.860	0.935	33%
≥60 and <90	465	224	-2.640	-3.850	1.209	31%
≥30 and <60	163	84	-3.582	-5.315	1.733	33%

With respect to tolvaptan's reduction in the risk of renal pain, the proportion of patients who were hospitalized for renal pain was significantly lower in the tolvaptan group than in the placebo group (0.94% [9 of 961 subjects] in the tolvaptan group, 3.93% [19 of 484 subjects] in the placebo group). Based on the above, when initiated at earlier stages of the disease and administered continuously in ADPKD patients, tolvaptan is expected to delay dialysis initiation by slowing renal function decline and reduce renal pain events from the early phase of treatment and throughout the treatment period. Clinical symptoms associated with the progression of ADPKD significantly impair the QOL of ADPKD patients and therefore the clinical relevance of the effects of tolvaptan in reducing these should be great.

PMDA considers as follows:

Concerning the effect of tolvaptan on the efficacy endpoint of the rate of increase in total kidney volume, as explained by the applicant, clinically relevant efficacy was shown for up to 3 years of study treatment in the TEMPO trial. Meanwhile, ADPKD has a very long disease course and whether the efficacy of tolvaptan is maintained beyond 3 years of treatment is unknown. Thus, the applicant's discussion has a limitation. Although the applicant explained the clinical relevance by predicting long-term efficacy from

efficacy results of study treatment for up to 3 years in the TEMPO trial, whether tolvaptan continues to provide the same level of efficacy from the early phase of treatment until several years later (a more advanced stage of disease) is unknown, and there is no evidence that a reduction of about 2%/year in the rate of growth is still maintained well beyond 3 years of treatment. However, ADPKD is a progressive, irreversible disease and no curative therapies exist. Moreover, tolvaptan produced a clinically relevant effect in slowing the progression of ADPKD at least within the duration of evaluation in the TEMPO trial, and the progression of ADPKD varies among individuals. Taking account of these points, as long as tolvaptan is used selectively in patients with a rapidly increasing kidney volume deemed to be at high risk for rapidly progressing disease [see "3.(iii).B.(3) Intended population and indication for Tolvaptan"] and periodic liver function tests etc. are performed to carefully watch for serious adverse drug reactions such as hepatic dysfunction [see "3.(iii).B.(5) Safety"], providing tolvaptan to clinical practice is of significance. However, since both of the long-term efficacy and safety of tolvaptan when administered beyond several years are unknown, it will be essential to collect post-approval information on these issues if tolvaptan is approved.

Among the secondary endpoints, worsening renal function is the most important finding in the disease. It is not necessarily appropriate to discuss the effect of tolvaptan on the rate of renal function decline based on comparison with the results from a study in diabetic nephropathy, which has a different pathology and course from ADPKD. Meanwhile, under the current situation where there are no other therapeutic drugs, the possibility that tolvaptan may slow renal function decline even slightly has been suggested, which is considered of clinical relevance. Currently, NSAIDs etc. are also available as therapeutic options to manage renal pain. Thus, the effect of tolvaptan in reducing renal pain events itself is not necessarily of great clinical relevance. However, this finding indirectly indicates that tolvaptan slows renal cyst growth, and therefore a reduction in renal pain events together with a reduction of the rate of kidney volume increase (the primary endpoint) and a reduction in the rate of renal function decline (one of the secondary endpoints) are all important findings supporting the clinically relevant efficacy of tolvaptan.

3.(iii).B.(2).4) Assurance of blinding of TEMPO trial

The incidences of thirst, polyuria, nocturia, pollakiuria, polydipsia, constipation, and appetite decreased etc. were clearly higher in the tolvaptan group than in the placebo group in the TEMPO trial. PMDA asked the applicant to explain whether the blinding in the trial was maintained.

The applicant responded as follows:

As patients who participated in the TEMPO trial had never received tolvaptan, they did not know the degree of diuretic effect of tolvaptan. In the TEMPO trial, subjects were instructed to actively ingest fluid in response to thirst to prevent dehydration, as required by the protocol: "The standard way of fluid intake recommends subjects to ingest fluid actively to prevent excessive thirst throughout the daytime period. Additionally, subjects are instructed to intake an additional 1-2 cups of water before bedtime and replenishment with each episode of nocturia to prevent dehydration" etc. As a result, patients randomized to the placebo group also became more polyuric than usual and moreover, patients were more likely to

experience thirst due to persistent polyuria driven by increased water intake. Therefore, it was difficult for individual patients to know their treatment assignment from experience of thirst or polyuria etc. In addition, compared with healthy adults, ADPKD patients tend to have higher urine output due to decreased ability to concentrate urine. Namely, for the above-mentioned reasons, it is difficult to classify thirst, polyuria, nocturia, pollakiuria, and polydipsia as adverse events specific to tolvaptan-treated patients, and constipation and appetite decreased are also unlikely to be events specific to tolvaptan. Therefore, it was difficult for the investigators to become aware of the treatment assignments from the occurrence of these adverse events.

Based on the extent of exposure to study drug (tolvaptan and placebo) in the TEMPO trial, the proportion of patients exposed to the high doses was higher in the placebo group than in the tolvaptan group throughout the entire treatment period. However, also in the placebo group as in the tolvaptan group, the dose received was shown to shift from 120 mg/day to 90 mg/day (13.0% [23 of 177 subjects] at ≥36 months of treatment) and to 60 mg/day (7.3% [13 of 177 subjects] at ≥36 months of treatment) over time; patients were down-titrated based on tolerability. The results for the individual components of the secondary composite endpoint, "renal pain," "worsening renal function," "new or worsening hypertension," and "new or worsening albuminuria," were compared between the groups of subjects with and without aquaretic adverse events (thirst, polyuria, nocturia, pollakiuria, polydipsia, dry mouth) in the TEMPO trial, and there were no major differences between the two groups for any component. The results for either "renal pain," which depends on the subject's subjective point of view and the investigator's assessment, or "worsening renal function," which is an objective endpoint, were not affected by the occurrence of aquaretic adverse events associated with tolvaptan. Therefore, the applicant considers that the blinding of the TEMPO trial was maintained.

PMDA considers as follows:
While the potent diuretic effects of tolvaptan were known from the previous clinical trials etc., the TEMPO trial showed clear between-treatment differences in the incidence of aquaretic adverse events and adverse events leading to treatment discontinuation, which cannot be disregarded. It is necessary to carefully determine whether the blinding in the TEMPO trial was maintained adequately. According to the applicant's explanation, it was not suggested that efficacy assessment etc. were clearly affected by the occurrence of aquaretic adverse events in the TEMPO trial. Additionally, all subjects were instructed to maintain adequate fluid ingestion in the TEMPO trial and as a result, some subjects were down-titrated from 120 mg/day to 90 mg/day or 60 mg/day based on tolerability even in the placebo group, though such subjects were fewer than in the tolvaptan group. Based on this explanation, it is inferred that there were no serious breaks of the blinding for subjects or physicians that would overturn the interpretation of the results of between-treatment comparison in the TEMPO trial. Given that the results for total kidney volume and multiple renal function-related endpoints, which are considered objective endpoints, all supported the efficacy of tolvaptan, the efficacy of tolvaptan can be evaluated based on the results of between-treatment comparison in the TEMPO trial.

3.(iii).B.(2).5) Long-term persistence of effectiveness

The applicant explained that the between-treatment difference of urine osmolality was smaller at Month 36 (approximately 190 mOsm/kg) compared to Week 3 (approximately 250 mOsm/kg) in the TEMPO trial because "more subjects were receiving 45 + 15 mg or 60 + 30 mg of tolvaptan at Month 36 compared with Week 3 or End of Titration." PMDA asked the applicant to present urine osmolality at each time point by treatment group and then explain the possibility that resistance to tolvaptan developed with prolonged use.

The applicant responded as follows:

The between-treatment difference in urine osmolality reduction by modal dose was largest at a dose of 120 mg/day at all time points from Week 3 or End of Titration to Month 36. When looking at the time course of the between-treatment difference in urine osmolality reduction by modal dose, the treatment difference was slightly decreased from Week 3 or End of Titration at Months 12 to 36 at modal doses of 60 mg/day and 90 mg/day and at Months 24 to 36 at a modal dose of 120 mg/day. The proportion of subjects with a modal dose of 120 mg/day decreased from Week 3 or End of Titration over time (84% at Week 3 or End of Titration, 55% at Month 36). This decrease in the proportion of subjects with a modal dose of 120 mg/day was considered one of the causes for the decrease in the difference in urine osmolality reduction between the entire tolvaptan group and the placebo group. However, analysis by modal dose also showed that the treatment difference in urine osmolality reduction tended to decrease over time, possibly because excessive water ingestion in response to thirst related to the potent aquaretic effects of tolvaptan, from immediately after the start of treatment, was adjusted to the appropriate water intake over time. Although it cannot be ruled out that resistance to tolvaptan's effects may have developed, the applicant considers that no relevant resistance to tolvaptan developed even after 3 years of treatment as urine osmolality suppressed by tolvaptan kept lower than plasma osmolality even at Month 36.

PMDA concluded as follows:

The pharmacological action of tolvaptan expected for the treatment of ADPKD is to inhibit cAMP. Urine osmolality maintained below plasma osmolality (approximately 280 mOsm/kg) indirectly indicates that V_2-receptor blockade is kept. Tolvaptan continuously inhibited cAMP (the pharmacological action required), at least during the TEMPO trial and no clinically relevant resistance to tolvaptan developed.

3.(iii).B.(3) Intended population and indication for Tolvaptan

3.(iii).B.(3).1) Population studied in TEMPO trial

PMDA asked the applicant to provide the rationale for the inclusion criteria for the TEMPO trial: "patients with a rapid estimated rate of kidney volume increase defined by a total kidney volume ≥750 mL (excluding those meeting volumetric criteria solely due to six or fewer predominant cysts)" and then describe the characteristics of an ADPKD patient population meeting the inclusion criteria.

The applicant explained the rationale for the inclusion criteria as to kidney volume for the TEMPO trial as follows:

ADPKD patients with a rapid estimated rate of kidney volume increase are considered to represent the

patient population most in need of therapeutic drugs. Tolvaptan has a mechanism of action of slowing renal cyst growth by inhibiting cAMP production in renal cyst cells. Thus, with a view to establishing the inclusion criteria as to kidney volume for the TEMPO trial, patients in which kidney volume growth was expected within the treatment period needed to be studied in order to evaluate the efficacy of tolvaptan. At the time of designing the TEMPO trial, it had been reported that the annual growth rate of kidney volume (mL/year) is higher in ADPKD patients with a total kidney volume ≥750 mL than in those with a total kidney volume <750 mL, and the ADPKD diagnostic criteria by the MHLW Research Committee for Progressive Renal Disease (developed in 2002) had specified the minimum number of cysts in both kidneys. Based on these, the inclusion criteria for the TEMPO trial were established. Recently, in an observational study of Japanese patients with ADPKD, the analyses of kidney volumes and renal function in a broad range of ADPKD patients with CKD stages 1 to 5 revealed that patients with a total kidney volume ≥750 mL can be in any stage of CKD (stages 1-5) (Higashihara E et al. *Clin Exp Nephrol.* 2013, Jul 18 [Epub ahead of print]). Based on the above, it was considered that an ADPKD patient population meeting the inclusion criteria for the TEMPO trial, i.e. "patients with a rapid estimated rate of kidney volume increase as indicated by a total kidney volume ≥750 mL," represents most ADPKD patients with CKD stages 1 to 5.

PMDA considers as follows:
It is understandable that patients in which kidney volume growth was expected within the treatment period needed to be studied in order to evaluate the efficacy of tolvaptan, and it was appropriate to select patients with a certain degree of kidney enlargement, i.e. a total kidney volume ≥750 mL, for the TEMPO trial. Taking also account of the applicant's explanation that a patient population meeting the inclusion criteria for the TEMPO trial represents most ADPKD patients in terms of renal function, the inclusion criteria as to kidney volume for the trial were appropriate. Based on these views, the TEMPO trial enrolled ADPKD patients with a rapid estimated rate of kidney volume increase in whom the benefits of tolvaptan would outweigh the risks [see "3.(iii).B.(3).2) Intended population and indication for tolvaptan"].

3.(iii).B.(3).2) Intended population and indication for Tolvaptan
PMDA asked the applicant to explain the levels of renal function in ADPKD patients at which tolvaptan is expected to be effective, taking account of the range of renal function in which kidney volume growth is correlated with renal function decline and the expected effects of tolvaptan in the treatment of ADPKD.

The applicant responded as follows:
A number of reports have shown that there is a correlation between kidney volume and renal function in ADPKD patients. For example, renal function declined faster in patients with a larger kidney volume for both 229 American patients and 73 Japanese patients (Fick-Brosnahan GM et al. *Am J Kidney Dis.* 2002;39:1127-34, Tokiwa S et al. *Clin Exp Nephrol.* 2011;15:539-45). An exploratory retrospective analysis of the TEMPO trial was performed to examine the relationship between the percent changes of last visit total kidney volume and last visit renal function in all subjects, which demonstrated a weak correlation (Correlation coefficient, -0.28675 to -0.23006, $P < 0.0001$ for all). However, there are no

reports or data that clearly define the levels of renal function that correlate with kidney volume.

When focusing on the rate of kidney volume increase and the rate of renal function decline, some papers on Japanese and American patients have shown that the rate of renal function decline is higher in patients with a rapid rate of kidney volume increase and also that renal function deterioration tends to progress in patients with a larger kidney volume (Chapman AB et al. *Clin J Am Soc Nephrol.* 2012;7:479-86). The results of the TEMPO trial also demonstrated a weak correlation between the percent changes of kidney volume and renal function; similar results of analyses were obtained for all subjects, the tolvaptan group, and the placebo group. However, there are no reports or data that clearly define the range of renal function over which the rate of kidney volume increase is correlated with the rate of renal function decline.

With regard to the levels of renal function in ADPKD patients at which tolvaptan is expected to be effective, as CLcr was ≥60 mL/min in patients included in the TEMPO trial, there are no data on the efficacy of tolvaptan initiated in patients with CLcr <60 mL/min. However, analyses of the correlation between kidney volume and renal function in ADPKD patients demonstrated a correlation of a wide range of renal function with kidney volume, indicating the possibility that slowing of kidney volume growth results in slowing of renal function decline in patients with a wide range of renal function.

GFR is generally used for evaluation of renal function in ADPKD patients. Since blood creatinine is secreted by the tubules as well as being filtered by the glomerulus, it is known that CLcr values are higher (by 20%-30%) than GFR values. Recently, the CKD-EPI equation has been developed overseas to estimate GFR using serum creatinine concentrations etc., and it has been used as an equation that can estimate a wide range of GFR values. GFR values in patients enrolled into the TEMPO trial were estimated using this CKD-EPI equation and it was inferred that about 17% to 18% of the patients had GFR <60 mL/min/1.73 m^2 at the time of treatment initiation. Based on these $eGFR_{CKD\text{-}EPI}$ values, subgroup analyses of the slopes of changes in total kidney volume and renal function ($eGFR_{CKD\text{-}EPI}$) were performed. As a result, regarding the efficacy of tolvaptan, the percent reduction in kidney volume growth in patients with $eGFR_{CKD\text{-}EPI}$ <60 mL/min/1.73 m^2 (CKD stage 3) was slightly lower than that in patients with $eGFR_{CKD\text{-}EPI}$ ≥60 and <90 mL/min/1.73 m^2 (CKD stage 2), but was comparable to that in patients with $eGFR_{CKD\text{-}EPI}$ ≥90 mL/min/1.73 m^2 (CKD stage 1). The percent reduction in renal function decline by tolvaptan was almost constant, regardless of $eGFR_{CKD\text{-}EPI}$ ($eGFR_{CKD\text{-}EPI}$ ≥90 mL/min/1.73 m^2, 33%; ≥60 and <90 mL/min/1.73 m^2, 31%; ≥30 and <60 mL/min/1.73 m^2, 33%). Thus, the TEMPO trial demonstrated the efficacy of tolvaptan in ADPKD patients with a wide range of renal function (CKD stages 1-3). As only 1 patient in the placebo group had an even lower level of renal function at the time of treatment initiation (CKD stages 4-5, $eGFR_{CKD\text{-}EPI}$ <30 mL/min/1.73 m^2), no data on the efficacy of tolvaptan in such patients were obtained. The results of the TEMPO trial demonstrated the efficacy of tolvaptan in patients with CKD stages 1 to 3 and the effect of tolvaptan in slowing renal function decline was consistent in CKD stages 1 to 3. Additionally, a wide range of renal function correlated with kidney volume in ADPKD patients. Therefore, tolvaptan may slow renal function decline even in patients with CKD stage 4 or higher.

Also in ADPKD patients with markedly decreased residual renal function who are unlikely to benefit from tolvaptan in delaying further renal function decline, tolvaptan potentially inhibits further renal cyst growth. Thus, tolvaptan is expected to be effective against abdominal pain caused by stretching of the renal capsule or traction of blood vessels in the renal hilum due to renal enlargement and chronic pain caused by increased burden on the spine or psoas/back muscles due to increased kidney weight, via inhibition of renal cyst growth. Therefore, the efficacy of tolvaptan is expected in ADPKD patients with an increased kidney volume, regardless of the level of renal function.

PMDA asked the applicant to explain the appropriateness of the use of tolvaptan in patients with CLcr <60 mL/min from an efficacy and safety point of view, taking account of the rationale for the inclusion criteria as to renal function and kidney volume etc. for the TEMPO trial.

The applicant responded as follows:
Patients with CLcr <60 mL/min were excluded from the TEMPO trial in accordance with the inclusion criteria. However, ongoing extension trials of the TEMPO trial, Trial 156-[redacted]-271 and Trial 156-[redacted]-003 include patients with CLcr <60 mL/min at the start of the trial. Thus, using pooled data from Trial 156-[redacted]-271 and Trial 156-[redacted]-003, the efficacy and safety of tolvaptan in patients with CLcr <60 mL/min were evaluated. Although subjects moved from trials other than the TEMPO trial are also included in Trial 156-[redacted]-271, patients from the TEMPO trial only were assessed. In order to evaluate the efficacy of tolvaptan initiated in patients with CLcr <60 mL/min, patients who had been assigned to the placebo group in the TEMPO trial (patients who received tolvaptan for the first time in the extension trial) for both Trial 156-[redacted]-271 and Trial 156-[redacted]-003 were included in the analyses. At the start of treatment in these trials, the number of patients with CLcr was <60 mL/min was 52 and those with CLcr ≥60 mL/min was 228.

Regarding the efficacy of tolvaptan, the time courses of renal function (reciprocal serum creatinine and $eGFR_{CKD\text{-}EPI}$) in Trial 156-[redacted]-271 and Trial 156-[redacted]-003 were as shown in Tables 15 and 16, respectively.

Table 15. Time course of renal function (Reciprocal serum creatinine) (Adapted from submitted data)

Visit	CLcr (mL/min) at baseline	N	Renal function ($(mg/dL)^{-1}$)	Change from baseline		
				Mean ± SD	Least-squares mean	Standard error (SE)
Baseline	<60	52	58.04 ± 19.96	—	—	—
	≥60	228	98.11 ± 27.76	—	—	—
Month 6	<60	43	57.72 ± 19.64	-3.43 ± 8.33	-5.64	1.65
	≥60	209	93.66 ± 28.13	-3.79 ± 10.55	-3.40	0.69
Month 12	<60	27	53.88 ± 18.66	-4.05 ± 6.71	-6.53	1.91
	≥60	169	92.99 ± 29.28	-5.80 ± 9.80	-6.08	0.74
Month 18	<60	9	54.03 ± 21.61	-5.79 ± 11.04	-4.35	3.48
	≥60	52	97.01 ± 35.76	-4.31 ± 11.73	-5.62	1.40

Table 16. Time course of $eGFR_{CKD-EPI}$ (Adapted from submitted data)

Visit	CLcr (mL/min) at baseline	N	$eGFR_{CKD-EPI}$ (mL/min/1.73m^2)	Change from baseline		
				Mean ± SD	Least-squares mean	SE
Baseline	<60	52	37.64 ± 13.69	—	—	—
	≥60	228	76.05 ± 20.73	—	—	—
Month 6	<60	43	37.25 ± 13.94	-2.67 ± 6.50	-3.67	1.41
	≥60	209	72.06 ± 21.79	-3.31 ± 8.59	-3.04	0.58
Month 12	<60	27	34.54 ± 13.30	-3.30 ± 5.06	-5.48	1.54
	≥60	169	69.92 ± 20.35	-5.80 ± 7.71	-5.80	0.59
Month 18	<60	9	33.12 ± 14.19	-4.63 ± 7.96	-4.84	2.72
	≥60	52	70.24 ± 19.99	-5.71 ± 8.47	-5.88	1.03

Based on the above results from the extension trials, there were no major differences in the degree of renal function decline after treatment initiation between patients with CLcr <60 mL/min and those with CLcr ≥60 mL/min; the degree of renal function decline at ≥1 year of treatment (Month 12, Month 18) was comparable or slightly smaller in patients with CLcr <60 mL/min.

Safety analysis included both patients in the tolvaptan and those in placebo group in the TEMPO trial. At the start of treatment in Trial 156-[redacted]-271 and Trial 156-[redacted]-003, CLcr was <60 mL/min in 108 patients and CLcr was ≥60 mL/min in 567 patients. The incidences of adverse events in patients with CLcr <60 mL/min and patients with CLcr ≥60 mL/min were 79.6% and 77.2%, respectively; the incidences of serious adverse events were 5.6% and 4.2%, respectively; and the incidences of adverse events rated as severe were 6.5% and 6.9%, respectively. With respect to the occurrence of overall adverse events, there were no clinically relevant differences between patients with CLcr <60 mL/min and patients with CLcr ≥60 mL/min. Adverse events with a ≥2% higher incidence in patients with CLcr <60 mL/min than in patients with CLcr ≥60 mL/min were dizziness (the incidences in patients with CLcr <60 mL/min and those with CLcr ≥60 mL/min were 5.6% and 2.3%, respectively), nocturia (20.4% and 18.3%, respectively), renal impairment (2.8% and 0.0%, respectively), and oropharyngeal pain (2.8% and 0.5%, respectively). The incidences of polyuria and pollakiuria were higher in patients with CLcr ≥60 mL/min. As described above, the results of the analysis of safety data from the extension trials of the TEMPO trial (Trial 156-[redacted]-271 and Trial 156-[redacted]-003) raised no safety concerns for patients with CLcr <60 mL/min at the start of the trial compared to patients with CLcr ≥60 mL/min.

The results of clinical studies in subjects with varying degrees of renal impairment (Trial 156-[redacted]-282, Trial 156-[redacted]-260, Trial 156-[redacted]-284) identified no risk specific to tolvaptan in subjects with impaired renal function.

Based on these findings, the use of tolvaptan in patients with CLcr <60 mL/min is considered appropriate. Data on the efficacy and long-term safety of tolvaptan in ADPKD patients with CLcr <60 mL/min will be collected via post-marketing drug use-results survey and the need for adding a new precaution for use in these patients will be examined.

PMDA asked the applicant to explain the appropriateness of the use of tolvaptan in patients with earlier (milder) ADPKD than the study population of the TEMPO trial from an efficacy and safety point of view.

The applicant responded as follows:
The TEMPO trial enrolled patients with a clinical diagnosis of ADPKD, relatively preserved renal function (CLcr ≥60 mL/min), and increased total kidney volume (total kidney volume ≥750 mL). The renal function ($eGFR_{CKD\text{-}EPI}$) of enrolled patients was 81.61 ± 21.6 mL/min/1.73 m^2, ranging widely from a minimum of 26.4 mL/min/1.73 m^2 to a maximum of 186.7 mL/min/1.73 m^2, and the percentages of patients with GFR stage G1 (≥90 mL/min/1.73 m^2) were 34.45% in the tolvaptan group and 35.89% in the placebo group, indicating that mild patients in terms of renal function were also included. The results of subgroup analyses showed that tolvaptan slows kidney volume growth and renal function decline also in patients with stage G1.

Regarding kidney volume, patients with a total kidney volume <750 mL were not enrolled into the TEMPO trial and there are no data on the efficacy of tolvaptan in patients with a smaller kidney volume. However, "total kidney volume ≥750 mL" was selected as inclusion criteria for the TEMPO trial, not because the efficacy of tolvaptan in patients with a total kidney volume <750 mL was denied. According to a report of Fick-Brosnahan et al. (Fick-Brosnahan GM et al. *Kidney Int.* 2001;59:1654-62), cysts start to develop before the age of 20 years and increase exponentially. Renal growth is highly variable and some ADPKD patients have a single kidney volume >350 mL before 20 years of age. Once kidney volume growth begins, it continues to progress and the growth rate increases at an accelerated rate. Given these facts, treatment should be initiated in patients whose kidney volume increases even if the total kidney volume is <750 mL. Subgroup analyses of the TEMPO trial showed that tolvaptan significantly slowed kidney volume growth in all subgroups of total kidney volume ≥1500 mL, <1500 mL, <1000 mL, and ≥1000 mL.

Although the efficacy of tolvaptan in ADPKD patients with a total kidney volume <750 mL has not been confirmed, in light of the mechanism of action, tolvaptan is expected to slow kidney volume growth in these patients as well. Thus, ADPKD patients with a total kidney volume <750 mL should not be excluded uniformly from treatment with tolvaptan. Regarding safety, patients with earlier (milder) ADPKD than the study population of the TEMPO trial have a smaller kidney volume and preserved renal function, and they are considered to be closer to healthy adults. The TEMPO trial enrolling patients with normal GFR as well has confirmed the safety of tolvaptan in these patients. No safety issues were identified also for healthy adult subjects treated with multiple doses of 120 mg/day. Therefore, the risks associated with the use of tolvaptan in patients with earlier (milder) ADPKD than the population of the TEMPO trial can be managed with precautionary statements in the package insert based on safety information obtained from the TEMPO trial.

Based on the above, the applicant considers that the use of tolvaptan should not be uniformly limited to patients with a total kidney volume ≥750 mL and that tolvaptan should be used, monitoring the patient's

condition and paying attention to safety.

PMDA's view on the eligible patient population for tolvaptan is as follows:
The expected efficacy of tolvaptan is prevention or delay in progression to end-stage renal disease, and tolvaptan needs to achieve slowing of renal function decline. The levels of renal function or kidney volume at which tolvaptan slows renal function decline are undefined at present. However, previous reports have shown that the rate of renal function decline is higher in ADPKD patients with a rapid rate of kidney volume increase and that renal function deterioration tends to progress in patients with a larger kidney volume. Also in the TEMPO trial, tolvaptan reduced the rate of kidney volume change (the primary endpoint) and worsening renal function (a component of the secondary composite endpoint) and there was a weak correlation between the percent changes of kidney volume and renal function, suggesting the possibility that tolvaptan slows kidney volume growth, resulting in slowing of renal function decline. Therefore, basically, tolvaptan is expected to slow renal function decline by slowing kidney volume growth as long as administration is initiated before renal function is markedly decreased to a level at which further delay in renal function decline with tolvaptan is considered difficult.

PMDA's view on the appropriateness of the use of tolvaptan in patients with more advanced renal impairment (CLcr <60 mL/min), who were excluded from the TEMPO trial, is as follows:
Although the efficacy of tolvaptan in patients with CLcr <60 mL/min is unknown, as the TEMPO trial enrolled ADPKD patients with a wide range of renal function (CKD stages 1-3) based on $eGFR_{CKD\text{-}EPI}$, the efficacy of tolvaptan in patients with CKD stages 1 to 3 has been demonstrated. However, no information on patients with even lower levels of renal function (CKD stages 4-5; $eGFR_{CKD\text{-}EPI}$ <30 mL/min/1.73 m^2) has been obtained.

In analyses of the data from extension trials of the TEMPO trial, Trial 156-[redacted]-271 and Trial 156-[redacted]-003, the number of patients with CLcr <60 mL/min was as small as 52 patients even at baseline and the number of these patients observed continuously until Month 18 was only 9 patients. Since these analyses were pooled subgroup analyses of the two trials and since these trials were not designed to compare the efficacy and safety of tolvaptan between patients with CLcr <60 mL/min and patients with CLcr ≥60 mL/min, there is a limitation on evaluation of the efficacy and safety of tolvaptan in patients with CLcr <60 mL/min based on the results of these analyses. Though the above-mentioned limitation exists, the results of the pooled analyses suggested similar efficacy of tolvaptan in slowing renal function decline between patients with CLcr <60 mL/min and patients with CLcr ≥60 mL/min, and there was also no major differences in safety. Furthermore, previous clinical studies in subjects with varying degrees of renal impairment (Trial 156-[redacted]-282, Trial 156-[redacted]-260, Trial 156-[redacted]-284) also showed no major different trends in safety between subjects with CLcr <60 mL/min and subjects with CLcr ≥60 mL/min. Based on the above, given the current situation where no other alternative therapies for ADPKD have been established, in clinical practice, providing an opportunity to receive tolvaptan also to patients with lower levels of renal function than the population studied in the TEMPO trial is appropriate as long as patients whose renal function has not decreased to a level at which it is considered difficult to benefit from tolvaptan in delaying further renal

function decline are selected and closely monitored [see "3.(iii).B.(5) Safety"]. If tolvaptan is approved, it will be essential to collect post-approval information on the efficacy and safety of tolvaptan in patients with more advanced renal impairment such as patients with CLcr <60 mL/min.

However, tolvaptan should not be indicated for ADPKD patients with markedly decreased residual renal function who are unlikely to benefit from tolvaptan in delaying further renal function decline, given that the expected effect of tolvaptan is slowing of renal function decline, that other measures such as analgesics are available for pain due to kidney volume growth, and that tolvaptan is associated with the risk of hepatic dysfunction [see "3.(iii).B.(5).1) Risk of hepatic dysfunction"]. The use of tolvaptan in patients with serious renal impairment requiring dialysis or renal transplant will be discussed in "3.(iii).B.(3).3) Use of tolvaptan in dialysis patients and patients with significantly advanced renal impairment."

The efficacy of tolvaptan in patients with earlier (milder) ADPKD than the study population of the TEMPO trial is unknown. Also, given that tolvaptan is associated with the risk of serious hepatic dysfunction as described later [see "3.(iii).B.(5).1) Risk of hepatic dysfunction"], the use of tolvaptan is not necessarily considered appropriate in patients for whom the benefits of tolvaptan are not great, i.e. patients with milder disease in whom the rate of progression to end-stage renal disease is not considered rapid, when balancing the risks and benefits. Theoretically, when initiated in patients with a smaller kidney volume where renal cysts are relatively small and renal function is less adversely affected, tolvaptan inhibits renal cyst growth and slows renal function decline, which is of significance. This view is understandable and the benefits of initiating tolvaptan in patients at an earlier stage of ADPKD are not denied. However, since ADPKD is a progressive, irreversible disease, the earlier patients start treatment with tolvaptan, the longer they will need to take tolvaptan. Moreover, ADPKD has a very long disease course and it is expected that the time to end-stage renal disease is long even without treatment with tolvaptan. It is inferred that the benefits of tolvaptan outweigh the risks for ADPKD patients with a rapid estimated rate of kidney volume increase like those enrolled into the TEMPO trial, whereas the risks of serious hepatic dysfunction etc. may outweigh the benefits for patients in whom ADPKD progresses slowly and who will not develop renal failure during their lifetime even without treatment with tolvaptan. Moreover, when patients are at an early stage of disease (with milder symptoms), it is difficult to determine whether the disease will progress slowly or rapidly with a rapid growth of renal cysts. Thus, based on the submitted data etc., it is not appropriate to allow the use of tolvaptan in patients with a smaller kidney volume at an earlier stage of their disease than the population studied in the TEMPO trial. At present, it would be appropriate to limit the use of tolvaptan to patients who clearly benefit from tolvaptan, i.e. patients deemed to be at high risk for rapidly progressing disease, like patients enrolled into the TEMPO trial.

Although the above patient selection should be stipulated in the "Precautions for Indications" section etc., based on the submitted results from clinical trials and their clinical relevance, the appropriate indication for tolvaptan should be "slowing of the progression of autosomal dominant polycystic kidney disease".

The eligible patient population for tolvaptan, including the appropriateness of the use of tolvaptan in

patients with more advanced renal impairment (CLcr <60 mL/min etc.), the details of post-approval information collection, and the appropriateness of the use of tolvaptan in ADPKD patients with a smaller kidney volume at an earlier stage of their disease than the study population of the TEMPO trial, will be finalized, taking also account of comments from the Expert Discussion.

3.(iii).B.(3).3) Use of Tolvaptan in dialysis patients and patients with significantly advanced renal impairment

PMDA asked the applicant to explain the risk of further deterioration of renal function associated with tolvaptan in patients with renal impairment, taking account of the mechanism of action of tolvaptan and the results from clinical studies etc., and then explain the need for a precautionary statement regarding use in patients with renal impairment.

The applicant responded as follows:

As safety evaluation studies in the ADPKD development program, 3 short-term studies in subjects with renal impairment were conducted (Trial 156-[redacted]-282, Trial 156-[redacted]-260, Trial 156-[redacted]-284). In Trial 156-[redacted]-282 (single-dose administration) in non-ADPKD subjects with renal impairment, the incidence of adverse events was as high as 84.6% in subjects with $eGFR_{CKD\text{-}EPI}$ <30 mL/min/1.73 m^2. The incidences of adverse events were 63.6% in subjects with $eGFR_{CKD\text{-}EPI}$ of ≥30 and ≤60 mL/min/1.73 m^2 and 61.5% in subjects with $eGFR_{CKD\text{-}EPI}$ >60 mL/min/1.73 m^2. Adverse events reported frequently in Trial 156-[redacted]-282 (≥10% in any group) were thirst, dry mouth, pollakiuria, diarrhoea, and hyperglycaemia. Adverse events occurring in subjects with $eGFR_{CKD\text{-}EPI}$ <30 mL/min/1.73 m^2 were dry eye, abdominal discomfort, diarrhoea, chills, infusion site extravasation, hyperkalaemia, hyperglycaemia, dizziness, and presyncope. The incidences of thirst and pollakiuria decreased with decreasing renal function. No adverse events related to renal function deterioration were observed in any group. Also in Trial 156-[redacted]-284 (21-day multiple-dose administration) and Trial 156-[redacted]-260 (8-day multiple-dose administration), there were no clinically noteworthy safety issues related to differences in $eGFR_{CKD\text{-}EPI}$. There were no major differences in safety between subjects with decreased renal function and those with preserved renal function enrolled in Trial 156-[redacted]-284 and Trial 156-[redacted]-260, but the incidences of aquaretic adverse events were lower in subjects with decreased renal function.

In the TEMPO trial, the incidence of blood creatinine increased was higher in subjects with decreased renal function ($eGFR_{CKD\text{-}EPI}$ 30-60 mL/min/1.73 m^2) compared with subjects with preserved renal function ($eGFR_{CKD\text{-}EPI}$ >60 mL/min/1.73 m^2) in both of the tolvaptan and placebo groups, but the incidence was lower in the tolvaptan group than in the placebo group. Adverse events reported at a ≥5% higher incidence in subjects with decreased renal function than in subjects with preserved renal function in the tolvaptan group were oedema peripheral and dizziness. As in Trial 156-[redacted]-282, there were no major differences in the incidence of adverse events between subjects with decreased renal function and subjects with preserved renal function in the TEMPO trial, but the incidences of thirst and polyuria were lower in subjects with decreased renal function. Subjects with decreased renal function enrolled into the TEMPO trial had no particular adverse events from a safety point of view. The incidences of adverse events related to the

aquaretic effects of tolvaptan (thirst, pollakiuria, etc.) were lower in subjects with decreased renal function compared with subjects with normal or preserved renal function, probably because in subjects with decreased renal function, the number of functioning nephrons is decreased, GFR is low, and dilute urine is not produced due to the inhibition of the formation of hypoosmotic urine in the thick ascending limb of Henle's loop, resulting in a reduction in the aquaretic effects of a V_2-receptor antagonist and a smaller increase in urine volume from baseline.

As shown above, no risks specific to tolvaptan were identified in patients with decreased renal function in previous clinical studies. However, 3 studies of Trial 156-[redacted]-282, Trial 156-[redacted]-260, and Trial 156-[redacted]-284 were of short treatment duration (up to 21 days) and there were no patients with CKD stage 4 or higher (eGFR <30 mL/min/1.73 m^2) in the tolvaptan group in the confirmatory TEMPO trial. Thus, no data on the long-term safety of tolvaptan in patients with decreased renal function have been available. Based on the above, the following precautionary statement regarding use in patients with renal impairment has been included in the "Precautions for Indications" section of the proposed package insert: "No clinical studies in patients with serious renal impairment (GFR <15mL/min/1.73 m^2) have been conducted. The use of tolvaptan in patients requiring dialysis or renal transplant should be determined after carefully balancing the expected therapeutic benefits with the possible risks." In addition, patients with serious renal impairment have been listed in the "Careful Administration" section, and blood uric acid increased, hyperkalaemia, blood creatinine increased, haematuria, renal pain, urinary tract infection, oliguria, urinary retention, renal stone, renal impairment and other events have been listed in the "Other Adverse Reactions" section. Therefore, no additional precautionary statement regarding use in the intended patient population is needed.

PMDA asked the applicant to explain whether tolvaptan is expected to be effective also in patients with very advanced ADPKD, such as dialysis patients.

The applicant responded as follows:
Tolvaptan has never been used in ADPKD patients on dialysis. Tolvaptan is expected to inhibit renal cyst growth in ADPKD patients, resulting in a delay in renal function decline. Therefore, patients with markedly decreased renal function requiring dialysis initiation are unlikely to benefit from tolvaptan in delaying further renal function decline. However, also in such patients who have already developed end-stage renal disease, tolvaptan is expected to potentially inhibit further renal cyst growth and to be effective against abdominal pain caused by stretching of the renal capsule or traction of blood vessels in the renal hilum due to renal enlargement and chronic pain caused by increased burden on the spine or psoas/back muscles due to increased kidney weight. Although the kidney volume is often reduced in ADPKD patients on dialysis, it has been reported that kidney volume growth continues to progress in some of these patients and the efficacy of tolvaptan is expected in such patients.

Based on the above response, PMDA asked the applicant to consider the need for an additional precautionary statement or a contraindication etc. regarding use in dialysis patients and patients with

significantly advanced renal impairment.

The applicant responded as follows:
As described above, there is little evidence for the efficacy and long-term safety of tolvaptan in ADPKD patients with significantly advanced renal impairment. However, as tolvaptan is expected to inhibit renal cyst growth by reducing cAMP levels in renal cyst cells, regardless of the level of renal function in patients, it was considered appropriate to include the following statement in the "Precautions for Indications" section of the draft package insert: "No clinical studies in patients with serious renal impairment (GFR < 15 mL/min/1.73 m^2) have been conducted. The use of tolvaptan in patients requiring dialysis or renal transplant should be determined after carefully balancing the expected therapeutic benefits with the possible risks." As the efficacy of tolvaptan in ADPKD patients (inhibition of renal cyst growth) is not related to its aquaretic effects, even in anuric patients with ADPKD, it cannot necessarily be concluded that no benefit of tolvaptan in slowing kidney volume growth etc. can be expected. Thus, for the indication of ADPKD, tolvaptan is not contraindicated in anuric patients. Since the ability to concentrate urine diminishes in ADPKD patients due to decreased renal function, urine output is maintained even with decreased renal function. Therefore, ADPKD patients rarely become anuric. Data on the efficacy and long-term safety of tolvaptan in ADPKD patients with significantly advanced renal impairment will be collected via drug use-results survey and the need for a new precautionary statement regarding use in these patients will be considered.

PMDA considers as follows:
Since ADPKD is an irreversible disease and no curative therapies exist at present, it is not preferable to deprive patients for whom tolvaptan with potential to slow renal function decline is recommended, of the opportunity of treatment. However, the expected effect of tolvaptan is slowing of renal function decline and in patients with markedly decreased residual renal function who are unlikely to benefit from tolvaptan in delaying further renal function decline, the effects of tolvaptan on renal function cannot be expected from an efficacy point of view. In addition, considering the risk of hepatic dysfunction associated with tolvaptan, the expected benefits are not considered to outweigh the risks in such patients. Therefore, the use of tolvaptan should be avoided in patients with markedly decreased residual renal function who are unlikely to benefit from tolvaptan in delaying further renal function decline, e.g. patients requiring dialysis or renal transplant, and tolvaptan should be contraindicated depending on the degree of renal impairment. Concerning the effects of tolvaptan on abdominal pain and chronic pain as explained by the applicant, since there are other treatments to manage these symptoms, chronic use of drugs associated with a high safety risk like tolvaptan for the purpose of relieving pain is not appropriate.

Though not observed in clinical studies of tolvaptan, it also cannot be ruled out that renal function is further decreased due to decreased renal blood flow associated with the aquaretic effects of tolvaptan in patients with decreased renal function. Therefore, the use of tolvaptan in patients who have not developed end-stage renal disease but have particularly advanced renal impairment should be determined carefully, and the package insert should advise that the use of tolvaptan should be determined, after balancing the

risks and benefits. Handling of dialysis patients, determination of the indication of tolvaptan in patients with significantly advanced renal impairment, and the details of a precautionary statement regarding use in these patients will be finalized, taking also account of comments from the Expert Discussion.

3.(iii).B.(3).4) Details of regulatory review in the US

The applicant explained the circumstances behind FDA's decision not to approve tolvaptan for ADPKD as follows. The pivotal trial for the applications for ADPKD in Japan and overseas, a multinational phase III trial (TEMPO trial) was conducted under an agreement with FDA. The content of discussions with FDA prior to the start of the trial and while the trial was in progress and the reasons for FDA's decision not to approve tolvaptan for ADPKD (the content of a complete response letter from FDA as of [redacted], 20[redacted]) etc. are shown below.

[redacted]

The reasons for not approving tolvaptan for ADPKD were explained as follows. [redacted]

i) [redacted]

ii) [redacted]

[redacted]

iii) [redacted]

In addition, FDA presented the following two points as other important views.

i) [redacted]

ii) [redacted]

PMDA considers as follows:

With regard to the endpoint for the TEMPO trial, as described in "3.(iii).B.(2).1) Efficacy endpoint," the true endpoint for the treatment of ADPKD is a delay in the onset of end-stage renal disease. However, in view of the features of ADPKD that has a very long disease course, it is difficult to evaluate the true endpoint in a clinical trial and the use of a surrogate endpoint is inevitable. As it has been reported that there is an inverse correlation between kidney volume and renal function in ADPKD patients and that renal function declines faster in patients with a larger kidney volume etc., selection of the rate of change in kidney volume as the primary endpoint is acceptable. Although the rate of change in kidney volume alone is not sufficient to assess the clinical relevance of the efficacy of tolvaptan, the efficacy of tolvaptan can be evaluated with a comprehensive and integrated assessment of the results for the secondary composite endpoint (a composite of worsening renal function, clinical significant renal pain, new or worsening hypertension, and new or worsening albuminuria) and its components and other renal function-related endpoints as well as the primary endpoint.

In connection with assessment of the primary endpoint and the secondary composite endpoint, missing data

were more common in the tolvaptan group than in the placebo group, which is a serious issue relevant to the integrity of the results. Meanwhile, more patients in the tolvaptan group could not continue treatment due to tolerability issues because of the aquaretic effects of tolvaptan, which seemed unavoidable. Because of a concern that a high discontinuation rate in the tolvaptan group may have influenced efficacy assessment, in addition to the results of analyses prospectively planned for the secondary composite endpoint, the results of multiple sensitivity analyses performed additionally after unblinding, including analyses where placebo data were supplemented with missing data, were also assessed. Since all the analyses results supported the efficacy of tolvaptan, PMDA concluded that the efficacy of tolvaptan on the primary endpoint and the secondary composite endpoint has been demonstrated.

Given that only the limited population was studied in the TEMPO trial, it is difficult to say that the results from the TEMPO trial clearly showed the magnitude of the effect of tolvaptan in slowing renal function decline and the long-term efficacy of tolvaptan beyond the duration of the TEMPO trial is unknown because of lack of information at present. Meanwhile, considering that ADPKD is a progressive disease leading to end-stage renal disease and that there are currently no curative drugs that slow renal function decline via inhibiting cyst growth, the clinical relevance of tolvaptan has been shown.

Concerning the adequacy of blinding in the TEMPO trial, as previously mentioned [see "3.(iii).B.(2).4) Assurance of blinding of TEMPO trial"], it is inferred from the applicant's explanation that there were no serious breaks of the blinding that would overturn the interpretation of the results of between-treatment comparison in the TEMPO trial. Since the data on total kidney volume and multiple renal function-related endpoints, which are considered important objective endpoints, all supported the efficacy of tolvaptan, it was concluded that the efficacy of tolvaptan can be evaluated based on the results of between-treatment comparison in the TEMPO trial. Accordingly, evaluation was possible to a certain extent for the endpoints based on subjective symptoms of subjects, such as the onset of renal pain.

As previously mentioned, suppression of urine osmolality was maintained during the TEMPO trial and it was unlikely that resistance to tolvaptan developed [see "3.(iii).B.(2).5) Long-term persistence of effectiveness"]. With regard to the rate of change in kidney volume, tolvaptan continuously reduced the rate of kidney volume increase, at least during the TEMPO trial. PMDA concluded that meaningful efficacy was maintained during the TEMPO trial, even though the effect of tolvaptan in slowing kidney volume growth might tend to be attenuated with prolonged use.

Based on the above, PMDA concluded that the results from the TEMPO trial demonstrated the efficacy of tolvaptan in ADPKD.

Although tolvaptan is associated with the risk of serious hepatic dysfunction and it would be difficult to completely eradicate the risk of serious hepatic dysfunction by any measure, the risk of hepatic dysfunction can be reduced in Japan by risk management, including selection of eligible patients and administration under the proper control, as described later [see "3.(iii).B.(5).1) Risk of hepatic dysfunction"]. While

tolvaptan is associated with the risk of serious hepatic dysfunction, theoretically, tolvaptan is expected to be effective to a greater or lesser degree in all ADPKD patients, based on its mechanism of action of inhibiting renal cyst growth in ADPKD. Taking account of these points, as long as the use of tolvaptan is limited to patients with rapidly progressing disease at high risk of progression to renal failure, tolvaptan can offer a good risk-benefit balance. Therefore, provided that tolvaptan is indicated for patients deemed to be at high risk for rapidly progressing disease and that an environment to reduce the risk of hepatic dysfunction is created, making tolvaptan available in clinical practice is of significant.

Since the long-term efficacy and safety of tolvaptan and the efficacy and safety of tolvaptan in patients with more advanced ADPKD than the population studied in the TEMPO trial are unknown, sufficient information should be collected if tolvaptan is approved. Especially, information on the safety centering on hepatic dysfunction should be analyzed over time and appropriate action should be taken promptly.

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

3.(iii).B.(4).1) Recommended dose

The applicant explained the rationale for the proposed dosing regimen of tolvaptan as follows:

The dosing regimen of tolvaptan for ADPKD patients was established based on the results from a Japanese clinical pharmacology study (Trial 156-[redacted]-001), an US clinical pharmacology study (Trial 156-[redacted]-249), an US long-term extension trial (Trial 156-[redacted]-250), and the multinational TEMPO trial (Trial 156-[redacted]-251). The optimal dose of tolvaptan was determined using urine osmolality as a surrogate marker of V_2-receptor inhibition. Normally, urine osmolality is above plasma osmolality (approximately 280 mOsm/kg) only when vasopressin is acting on the kidney's distal collecting ducts. Thus, a trough (prior to the morning dose) spot urine osmolality <300 mOsm/L can be taken as evidence of constant and effective inhibition of the V_2-receptor. A clinical pharmacology study of tolvaptan administered at 30 mg/day for 5 days in 18 Japanese patients with ADPKD (Trial 156-[redacted]-001) indicated that a split-dose regimen (BID) inhibits vasopressin binding to V_2-receptors longer than a once-daily regimen. Similar results were obtained also from the US clinical pharmacology study (Trial 156-[redacted]-249). During the titration period in the US long-term extension trial in 46 patients with ADPKD (Trial 156-[redacted]-250), subjects received split doses of 15 + 15, 30 + 15, 45 + 15, 60 + 30, and 90 + 30 mg of tolvaptan and spot urine osmolality was measured prior to the morning dose, prior to the evening dose, and prior to bedtime. As a result, greater reductions in urine osmolality prior to the evening dose and prior to bedtime were shown at a higher dose of tolvaptan. The 45 + 15 mg dose was the lowest dose at which >90% of subjects had urine osmolality values ≤300 mOsm/kg for both the prior to the evening dose and prior to bedtime samples, indicating that urine osmolality would be suppressed for at least 16 hours per day in a large majority of subjects at doses ≥45 + 15 mg, but there were subjects with urine osmolality values >300 mOsm/kg at all dose levels. The percentage of subjects who tolerated the 90 + 30 mg dose was 46%. Based on these results, it was considered necessary to administer the highest tolerated dose of tolvaptan that can be chronically used while checking the tolerability in individual subjects in order to achieve higher efficacy in more patients. Based on the above, the optimal dosing regimen is as follows: tolvaptan should be initiated at 45 + 15 mg/day, which is a relatively lower effective dose and then titrated, based on patient tolerability, to higher

doses (60 + 30 mg, 90 + 30 mg).

In the TEMPO trial in ADPKD patients (Trial 156-[redacted]-251), tolvaptan was administered for up to 3 years using this dosing regimen. As a result, tolvaptan was well tolerated, and 77.0% of subjects in the tolvaptan group were treated for 3 years and completed the trial (placebo group, 86.2%). Tolvaptan exhibited significantly superior efficacy to placebo for the rate of change in total kidney volume, the time to multiple ADPKD clinical progression events, and the slope of renal function (reciprocal serum creatinine) decline. These results show the usefulness of tolvaptan in the treatment of ADPKD. Dose changes based on tolerability were allowed also during the long-term treatment period, and the dose was changed in many subjects, mainly for tolerability reasons.

While the titration scheme employed in the TEMPO trial precluded direct between-dose comparison, the rate of total kidney volume change from baseline was analyzed by modal dose over the period from the previous visit to each time point of evaluation and its relationship with the dose was investigated. As a result, the effect of tolvaptan was greater in subjects with a higher modal dose, which was consistent with slower total kidney volume growth in the high dose group (60 + 30 mg) in the fixed-dose period of Trial 156-[redacted]-250. According to PPK/pharmacodynamic analysis, the $C_{min,ss}$ of tolvaptan that produces 50% of maximal suppression of urine osmolality is 43 ng/mL, which is close to the $C_{min,ss}$ at 45 + 15 mg (geometric mean, 38 ng/mL). The geometric mean of the $C_{min,ss}$ at 90 + 30 mg is 81 ng/mL, and this concentration produces 70.9% of maximal suppression of urine osmolality. The AUC_{ss} of tolvaptan that produces 50% of maximal suppression of urine osmolality is between the AUC_{ss} at 45 + 15 mg (geometric mean, 3.7 μg·h/mL) and the AUC_{ss} at 60 + 30 mg (geometric mean, 5.5 μg·h/mL). The AUC_{ss} at 90 + 30 mg (geometric mean, 7.5 μg·h/mL) produces 88% of maximal suppression of urine osmolality. Based on these findings, it is inferred that the optimal therapeutic effect was achieved in subjects treated with 90 + 30 mg. These results justify the dosing regimen used for the TEMPO trial in which tolvaptan was titrated upward to a maximum dose of 90 + 30 mg, based on the individual's tolerability, and subjects were maintained on their highest tolerated dose.

Based on the above, a dosing regimen of tolvaptan for ADPKD patients proposed in the application has been established in accordance with the dosing regimen used in the TEMPO trial.

PMDA asked the applicant to present the results regarding the primary efficacy endpoint, the secondary composite endpoint and its components, and the rate of change in renal function by modal dose of tolvaptan (the most frequent dose that each subject took up to each evaluation point) in the overall trial population and Japanese subgroup of the TEMPO trial and then explain the significance of increasing the dose of tolvaptan within the proposed dosing regimen.

The applicant responded as follows:
All modal doses of tolvaptan demonstrated efficacy in the primary endpoint for the TEMPO trial, total kidney volume, compared to placebo, in the overall trial population, and the effect was greater at a higher

dose of tolvaptan (between-treatment difference at Month 36 [95% CI], 60 mg, -7.56% [-9.97 to -5.16]; 90 mg, -9.36% [-11.9 to -6.84]; 120 mg, -9.75% [-11.8 to -7.65]). Also in the Japanese subgroup, all doses of tolvaptan demonstrated efficacy for total kidney volume compared to placebo (between-treatment difference at Month 36 [95% CI], 60 mg, -8.17% [-15.6 to -0.70]; 90 mg, -15.3% [-21.0 to -9.63]; 120 mg, -9.73% [-15.5 to -3.99]). For the secondary composite endpoint, 90 mg and 120 mg of tolvaptan demonstrated a favorable treatment effect in the overall trial population (Hazard ratio [95% CI], 60 mg, 0.991 [0.849-1.158]; 90 mg, 0.773 [0.641-0.933]; 120 mg, 0.849 [0.748-0.963]) and a similar trend was observed also in the Japanese subgroup (Hazard ratio [95% CI], 60 mg, 0.896 [0.540-1.487]; 90 mg, 0.789 [0.495-1.256]; 120 mg, 0.711 [0.476-1.061]).

All modal doses of tolvaptan had no effects on new or worsening hypertension events or new or worsening albuminuria events in the overall trial population, and similar results were obtained also for the Japanese subgroup. Analysis of clinically significant renal pain events showed that 90 mg and 120 mg of tolvaptan demonstrated a favorable treatment effect in the overall trial population (Hazard ratio [95% CI], 60 mg, 0.980 [0.579-1.658]; 90 mg, 0.435 [0.253-0.747]; 120 mg, 0.589 [0.413-0.839]), and a similar trend was observed also in the Japanese subgroup (Hazard ratio [95% CI], 60 mg, 1.571 [0.306-8.074]; 90 mg, 0.788 [0.163-3.801]; 120 mg, 0.428 [0.088-2.085]). Analysis of worsening renal function events showed that all modal doses of tolvaptan demonstrated a favorable treatment effect in the overall trial population (Hazard ratio [95% CI], 60 mg, 0.301 [0.140-0.648]; 90 mg, 0.221 [0.090-0.540]; 120 mg, 0.469 [0.306-0.719]), and a similar trend was observed also in the Japanese subgroup (Hazard ratio [95% CI], 120 mg, 0.327 [0.113-0.943]; no events occurred at 60 mg or 90 mg). Analysis of change from Week 3 or End of Titration in renal function (reciprocal serum creatinine) showed that all modal doses of tolvaptan demonstrated a favorable treatment effect in the overall trial population (between-treatment difference at Month 36 [95% CI], 60 mg, 4.16 [1.97-6.34] $(mg/mL)^{-1}$; 90 mg, 4.05 [2.06-6.03] $(mg/mL)^{-1}$; 120 mg, 4.02 [2.35-5.69] $(mg/mL)^{-1}$) and a similar treatment effect was demonstrated also in the Japanese subjects (treatment difference at Month 36 [95% CI], 60 mg, 6.52 [0.55-12.49] $(mg/mL)^{-1}$; 90 mg, 5.74 [0.08-11.40] $(mg/mL)^{-1}$; 120 mg, 6.65 [2.49-10.81] $(mg/mL)^{-1}$).

Based on the above analyses results, a treatment effect in favor of all modal doses of 60 mg/day to 120 mg/day of tolvaptan was demonstrated for “the primary endpoint,” “worsening renal function events” as a component of the secondary composite endpoint, and “change from Week 3 or End of Titration in renal function (reciprocal serum creatinine),” and the effect increased with increasing dose for “the primary endpoint.” In contrast, no favorable treatment effect was demonstrated at any dose level for “new or worsening hypertension events” or “new or worsening albuminuria events” as components of the secondary composite endpoint. In the overall trial population, enhanced efficacy was observed when the dose was increased from 60 mg/day to 90 mg/day, for “the primary endpoint,” “the secondary composite endpoint,” and “clinically significant renal pain events” as a component of the secondary composite endpoint, and enhanced efficacy was also observed for “the primary endpoint” when the dose was increased from 90 mg/day to 120 mg/day. These results indicate that increasing the dose of tolvaptan from 60 mg/day to 90 mg/day and further to 120 mg/day is of significance for obtaining a stronger inhibitory

effect on total kidney volume growth in ADPKD patients. On the other hand, as tolerability decreases with increasing dose due to the aquaretic effects of tolvaptan, it is considered necessary to administer, based on tolerability, the highest tolerated dose that individual subjects can use chronically in order to achieve higher efficacy in more patients.

PMDA considers as follows:
No Japanese or foreign parallel-group study assessed the dose-response relationship of 60 mg/day to 120 mg/day of tolvaptan for efficacy, and the effect of dose increase has not been demonstrated rigorously. However, in the TEMPO trial, tolvaptan demonstrated efficacy at all doses of 60 mg/day to 120 mg/day and there was a trend towards increasing effect with increasing dose for the primary efficacy endpoint, the rate of change in total kidney volume. Also, there was a trend towards enhanced efficacy with a dose increase from 60 mg/day to 90 mg/day for the secondary composite endpoint. Moreover, there was a trend towards enhanced efficacy with a dose increase from 60 mg/day to 90 mg/day for "clinically significant renal pain events" as a component of the secondary composite endpoint. Thus, it is concluded from overall findings that the significance of the initial dose of 60 mg/day with titration up to 120 mg/day has been demonstrated. The results in the Japanese subgroup were also consistent with the results in the overall trial population, and therefore it is concluded that the significance of increasing the dose of tolvaptan over the range of 60 mg/day to 120 mg/day has been suggested in the Japanese subgroup as in the overall trial population.

Based on the above, taking account of the efficacy and safety results in the overall trial population of the TEMPO trial and the actual doses administered to the Japanese subgroup in the TEMPO trial, tolvaptan should be initiated at 45 mg (morning)/15 mg (evening) and titrated upward to 60 mg (morning)/30 mg (evening) and then to a maximum of 90 mg (morning)/30 mg (evening) if tolerated. As implemented in the TEMPO trial, tolvaptan should be administered at the same inital dose for at least 1 week, and the dose should be up-titrated in a stepwise manner only if considered appropriate. The dose may be adjusted based on patient tolerability, as appropriate.

3.(iii).B.(4).2) Appropriateness of the dosing regimen in Japanese patients
PMDA asked the applicant to explain the occurrence of hepatic dysfunction-related adverse events including ALT increased and AST increased, renal impairment-related adverse events including blood creatinine increased, aquaretic adverse events including thirst, polyuria, pollakiuria, and dehydration, hypernatraemia, and study drug discontinuation by dose level of tolvaptan in the overall trial population and Japanese subgroup of the TEMPO trial and to investigate whether there was a particular trend between the incidence of these events and the dose of tolvaptan, taking also account of the severity of adverse events and the number of subjects and duration of treatment for each dose.

The applicant responded as follows:
In the TEMPO trial, the modal doses of tolvaptan were 60 mg/day in 247 of 961 subjects (25.7%), 90 mg/day in 184 of 961 subjects (19.1%), and 120 mg/day in 530 of 961 subjects (55.2%) in the overall trial

population. In the Japanese subgroup, the modal doses were 60 mg/day in 27 of 118 subjects (22.9%), 90 mg/day in 32 of 118 subjects (27.1%), and 120 mg/day in 59 of 118 subjects (50.0%). According to analyses of adverse events by modal dose, hepatic dysfunction-related adverse events tended to occur earlier (within 3 months of therapy) in subjects with higher modal doses (90 mg/day, 120 mg/day) and slightly later (during the 3- to 9-month period after treatment initiation) in subjects with a lower modal dose (60 mg/day) in the overall trial population and Japanese subgroup [see "3.(iii).B.(5).1) Risk of hepatic dysfunction"]. There was no particular trend between the incidence of renal impairment-related adverse events and the dose of tolvaptan in the overall trial population. In the Japanese subgroup, higher modal doses were associated with a higher incidence of blood creatinine increased (120 mg/day, 10.2% [6 of 59 subjects]; 90 mg/day, 3.1% [1 of 32 subjects]; 60 mg/day, 0.0% [0 of 27 subjects]), but blood creatinine increased was reported at a similar incidence also in the placebo group (6.8% [4 of 59 subjects]); it could not be concluded that there was a particular trend between the dose of tolvaptan and the incidence of blood creatinine increased. Analysis by dose at the time of event onset showed that the incidence of aquaretic adverse events was high in subjects receiving 60 mg/day in the overall trial population and Japanese subgroup, which was considered attributable to the fact that aquaretic adverse events often occurred early before upward titration. Analysis by modal dose showed that all modal doses were associated with a high incidence of aquaretic adverse events; there was no particular trend between the incidence of events and the dose of tolvaptan. There was no particular trend between the incidence of hypernatraemia and the dose of tolvaptan in the overall trial population, and no adverse events related to increased blood sodium concentration were reported in the Japanese subgroup. Analysis by dose at the time of event onset showed that the incidence of adverse events leading to study drug discontinuation was high in subjects receiving 60 mg/day in the overall trial population and Japanese subgroup, which was considered due to treatment discontinuation after dose reduction in many subjects. Analysis by modal dose also showed that the incidence was highest in subjects with a modal dose of 60 mg/day, which was presumably attributable to the fact that many subjects receiving the lowest dose in the titration phase due to tolerability discontinued the study drug in the long-term treatment phase for tolerability.

PMDA asked the applicant to present the reasons for dose reduction, the relationship between up-titration and adverse events, and the transition of dose over time in Japanese patients with ADPKD in the TEMPO trial and then provide a justification for the dosage and administration proposed in the application.

The applicant responded as follows:

In the TEMPO trial, if the status of study drug administration was changed during the trial period, the reason for change was to be selected from the 4 items (Adverse Events, Per Protocol, Dose missed, and Other). The common reason for dose reduction in Japanese subjects was "Adverse Events." In the TEMPO trial, the incidences of adverse events leading to dose reduction were 38.5% (370 of 961 subjects) in the tolvaptan group and 16.8% (81 of 483 subjects) in the placebo group. Among which, thirst (7.8% [75 of 961 subjects]) and polyuria (8.9% [86 of 961 subjects]) were reported by ≥5% of subjects in the tolvaptan group, and the incidences of these events were ≥2-fold higher than those in the placebo group. Among events rated as severe in the tolvaptan group, polyuria had the highest incidence (1.4% [13 of 961

subjects]) and no other events were reported at an incidence of ≥1%. Among events rated as severe in the placebo group, thirst had the highest incidence (0.6% [3 of 483 subjects]). In the Japanese subgroup, the incidences of adverse events leading to dose reduction were 41.5% (49 of 118 subjects) in the tolvaptan group and 5.1% (3 of 59 subjects) in the placebo group. Among which, thirst (18.6% [22 of 118 subjects]), pollakiuria (16.9% [20 of 118 subjects]), and polyuria (8.5% [10 of 118 subjects]) were reported by ≥5% of subjects in the tolvaptan group and the incidences of these events were all ≥2-fold higher than those in the placebo group. Events rated as severe in the tolvaptan group were pollakiuria only (1.7% [2 of 118 subjects]).

In the TEMPO trial, 936 of 961 subjects in the tolvaptan group and 482 of 483 subjects in the placebo group had their dose up-titrated at least once during the study treatment period. The incidences of adverse events occurring after up-titration (the day of up-titration and the following day) were 35.9% (336 of 936 subjects) in the tolvaptan group and 24.1% (116 of 482 subjects) in the placebo group. Among which, thirst (9.6% [90 of 936 subjects]) and polyuria (5.8% [54 of 936 subjects]) were reported by ≥5% of subjects in the tolvaptan group, and events with an incidence of ≥5% in the tolvaptan group and ≥2-fold that of the placebo group were also thirst and polyuria. Among 11 events rated as severe in the tolvaptan group (abdominal pain, dry mouth, dyspepsia, fatigue, feeling cold, thirst, polydipsia, insomnia, nocturia, pollakiuria, polyuria), polyuria had the highest incidence (1.1% [10 of 936 subjects]).

In the Japanese subgroup, 117 of 118 subjects in the tolvaptan group and 59 of 59 subjects in the placebo group had their dose up-titrated at least once during the study treatment period. In the Japanese subgroup, the incidences of adverse events occurring after up-titration (the day of up-titration and the following day) were 49.6% (58 of 117 subjects) in the tolvaptan group and 20.3% (12 of 59 subjects) in the placebo group. Among which, thirst (22.2% [26 of 117 subjects]) and polyuria (12.0% [14 of 117 subjects]) were reported by ≥5% of subjects in the tolvaptan group, and events with an incidence of ≥5% in the tolvaptan group and ≥2-fold that of the placebo group were also thirst and polyuria. An event rated as severe in the tolvaptan group was pollakiuria (0.9% [1 of 117 subjects]).

With regard to the transition of dose over time in the Japanese subgroup, 111 of 117 subjects (94.9%) were receiving 90 mg/day at Week 2 and 98 of 116 subjects (84.5%) were receiving 120 mg/day at Week 3 in the titration period. The proportion of subjects receiving 120 mg/day was highest in the tolvaptan group during the maintenance period; 49% to 52% of subjects were receiving 120 mg/day, 27% to 28% of subjects were receiving 90 mg/day, and 20% to 24% of subjects were receiving 60 mg/day between Month 12 and Month 36.

As described above, in the Japanese subgroup of the TEMPO trial, adverse events related to the aquaretic effects of tolvaptan occurred after up-titration and these events often led to dose reduction. This is probably because the study protocol specified a criterion for dose reduction that dose was to be reduced in the case of intolerance, and the events fell under this criterion. Adverse events leading to dose reduction and rated as severe in the Japanese subgroup were pollakiuria only (1.7% [2 of 118 subjects]). Beyond 1 year of

therapy, there were no major changes in the proportion of subjects by dose, indicating that subjects were maintained on the highest tolerable doses that could be used chronically in individuals. Based on these findings, the proposed dosing regimen, i.e. tolvaptan should be initiated at 60 mg/day and up-titrated to higher doses (a maximum of 120 mg/day) according to tolerability and the highest tolerable dose that can be used chronically in individuals should be maintained, is justified.

PMDA considers as follows:
Given the incidence of adverse events by dose of tolvaptan in the TEMPO trial, from a safety point of view, it should be noted that the incidence of hepatic dysfunction was higher, especially at the high dose of 120 mg/day compared to other doses in Japanese patients [see "3.(iii).B.(5).1) Risk of hepatic dysfunction"]. The incidences of adverse events other than hepatic dysfunction did not tend to increase dose-proportionally in the overall trial population or Japanese subgroup. Thus, regarding the safety of 60 to 120 mg/day of tolvaptan, there should be no risks specific to Japanese patients.

In the TEMPO trial in which dose reduction was specified based on intolerance, the proportion of subjects receiving 120 mg/day was highest throughout the trial period following the end of the titration phase in the Japanese subgroup as in the overall trial population. This finding also justifies a maximum dose of 120 mg/day from a safety point of view. However, since the proportion of subjects chronically treated with 120 mg/day was lower and the proportion of subjects treated with 90 mg/day or 60 mg/day was higher in the Japanese subgroup than in the overall trial population of the TEMPO trial, more patients will be treated with 90 mg/day or 60 mg/day rather than 120 mg/day also in clinical practice in Japan. As the common reason for dose reduction was the occurrence of adverse events related to the aquaretic effects of tolvaptan such as thirst, pollakiuria, and polyuria, and these adverse events occurred commonly after up-titration (the day of up-titration and the following day), attention should be paid to the possible occurrence of adverse events related to the aquaretic effects of tolvaptan during treatment and especially, immediately after up-titration. Provided that an adequate precautionary statement concerning this issue is included in the package insert, the following dosing regimen is considered appropriate for use in Japan: tolvaptan should be initiated at 60 mg/day and titrated upward to 60 mg (morning)/30 mg (evening) and then to a maximum of 90 mg (morning)/30 mg (evening) with at least weekly intervals between titrations only when considered appropriate after checking tolerability etc., as implemented in the TEMPO trial, and thereafter the dose should be adjusted based on tolerability.

Specific rules, including dosage increments and timing of up-titration, as well as the maximum dose and dose adjustment will be further reviewed, taking also account of comments from the Expert Discussion.

3.(iii).B.(5) Safety

3.(iii).B.(5).1) Risk of hepatic dysfunction

PMDA asked the applicant to explain the incidence of hepatic dysfunction by dose of tolvaptan in the overall trial population and Japanese subgroup of the TEMPO trial and then examine the relationship

between the occurrence of these events and the given dose of tolvaptan.

The applicant responded as follows:
In the TEMPO trial, the modal doses of tolvaptan were 60 mg/day in 247 of 961 subjects (25.7%), 90 mg/day in 184 of 961 subjects (19.1%), and 120 mg/day in 530 of 961 subjects (55.2%) in the overall trial population, and 60 mg/day in 27 of 118 subjects (22.9%), 90 mg/day in 32 of 118 subjects (27.1%), and 120 mg/day in 59 of 118 subjects (50.0%) in the Japanese subgroup. According to analysis of adverse events by modal dose, in the overall trial population of the TEMPO trial, the incidence of hepatic dysfunction-related adverse events in the liver-related investigations, signs and symptoms standardized MedDRA queries (SMQ) was highest in the modal dose 60 mg/day group (14.2%, 35 of 247 subjects), followed by the modal dose 90 mg/day group (12.5%, 23 of 184 subjects) and then the modal dose 120 mg/day group (10.8%, 57 of 530 subjects). In the Japanese subgroup, the incidence of hepatic dysfunction-related adverse events in the liver-related investigations, signs and symptoms SMQ was highest in the modal dose 120 mg/day group (20.3%, 12 of 59 subjects), followed by the modal dose 60 mg/day group (11.1%, 3 of 27 subjects) and then the modal dose 90 mg/day group (9.4%, 3 of 32 subjects). According to analysis of adverse events by modal dose and time of occurrence, in the overall trial population of the TEMPO trial, the incidence of liver function-related adverse events was highest in the first 3 months of study treatment in the modal dose 90 mg/day and 120 mg/day groups (4.9% [9 of 184 subjects] in the 90 mg/day group, 2.8% [15 of 530 subjects] in the 120 mg/day group) and in the 6- to 9-month period in the modal dose 60 mg/day group (4.4% [8 of 182 subjects]). In the Japanese subgroup, the incidence of liver function-related adverse events was highest in the first 3 months of study treatment in the modal dose 90 mg/day and 120 mg/day groups (6.3% [2 of 32 subjects] in the 90 mg/day group, 11.9% [7 of 59 subjects] in the 120 mg/day group) and in the 3- to 6-month period in the modal dose 60 mg/day group (8.3% [2 of 24 subjects]). As described above, in the overall trial population and Japanese subgroup, adverse events tended to occur earlier (within 3 months of therapy) in subjects with higher modal doses (90 mg/day, 120 mg/day) and slightly later (3-9 months) in subjects with a lower modal dose (60 mg/day).

The applicant explained the risk of hepatic dysfunction associated with tolvaptan as follows:
The TEMPO trial was monitored by an Independent Data Monitoring Committee and the sponsor (the applicant) according to FDA's guidance on drug-induced liver injury (DILI) (the final version as of July 2009), which revealed a higher proportion of subjects on tolvaptan with elevated transaminases compared to subjects on placebo. No signal for DILI was observed in clinical trials of tolvaptan in patients with heart failure or hyponatraemia, and no signal for DILI was detected in the post-marketing data. Therefore, an Independent Hepatic Adverse Event Adjudication Committee (Adjudication Committee) consisting of hepatic experts, was formed to evaluate safety data on liver function obtained from safety evaluation studies in the ADPKD development program[10] (the final data cut-off date of [redacted], 20[redacted]; [redacted], 20[redacted] in Japan only), the data from clinical trials in other indications, and post-marketing data and to determine

[10] Studies in ADPKD patients (TEMPO trial, Trial 156-[redacted]-250, Trial 156-[redacted]-002, Trial 156-[redacted]-271, Trial 156-[redacted]-003, Trial 156-[redacted]-003, Trial 156-[redacted]-001, Trial 156-[redacted]-248, Trial 156-[redacted]-249, Trial 156-[redacted]-285, Trial 156-[redacted]-290), studies in subjects with renal impairment (Trial 156-[redacted]-260, Trial 156-[redacted]-282, Trial 156-[redacted]-284), and studies in healthy adult subjects (Trial 156-[redacted]-295, Trial 156-KOA-0801, Trial 156-[redacted]-262)

liver function safety. Using some criteria (>3 times the upper limit of normal [ULN], >5 times ULN, etc.), elevated transaminases were evaluated. As a result, in the TEMPO trial, the proportion of subjects with ALT and AST elevations was higher in the tolvaptan group than in the placebo group. In the tolvaptan group, transaminase elevations occurred during the 3- to 14-month period. Based on the evaluation of central and local laboratory data from safety evaluation studies in the ADPKD development program, 3 tolvaptan-treated subjects met the laboratory criteria (elevated ALT or AST of >3 times ULN accompanies by an increase in total bilirubin >2 times ULN within 30 days) of Hy's Law (FDA Guidance: Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation) (2 subjects from the TEMPO trial [including 1 Japanese subject], 1 subject from Trial 156-[redacted]-271). As a result of a blinded independent review and medical differential diagnosis by hepatic experts, these 3 subjects were adjudicated as Hy's Law cases.

Adverse events in any of the 5 hepatic SMQs (liver-related investigations, signs and symptoms SMQ; cholestasis and jaundice of hepatic origin SMQ; hepatitis, non-infectious SMQ; hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ; liver-related coagulation and bleeding disturbances SMQ) in the TEMPO trial were assessed. As a result, the incidence of those events classified as serious was higher in the tolvaptan group than in the placebo group (2.3% [22 of 961 subjects] in the tolvaptan group, 1.0% [5 of 483 subjects] in the placebo group).

In order to identify subjects potentially at risk of clinically significant liver disorder in safety evaluation studies in the ADPKD development program, the Adjudication Committee defined criteria for hepatocellular disturbances regarding reported adverse events and clinical laboratory data (central and local laboratory data) and evaluated data for subjects meeting one or more of the followings:

i) An adverse event leading to discontinuation of study drug or any serious adverse event falling within any of the 5 hepatic SMQs listed above,
ii) ALT >3 times ULN and total bilirubin >2 times ULN,
iii) AST >3 times ULN and total bilirubin >2 times ULN,
iv) AST or ALT >5 times ULN,
v) Total bilirubin >2 times ULN.

Based on the above evaluation, 59 subjects were identified as meeting the criteria: 46 of 1444 subjects in the TEMPO trial, 9 of 904 subjects in Trial 156-[redacted]-271, 2 of 108 subjects in Trial 156-[redacted]-003 (excluding a subject counted in the TEMPO trial), and 2 of 18 subjects in Trial 156-[redacted]-290.

In the TEMPO trial, 46 subjects who met the criteria for hepatocellular disturbances included 35 of 961 subjects in the tolvaptan group and 11 of 483 subjects in the placebo group. With regard to the time to first increase in ALT of >3 times ULN in subjects with ALT elevations in the TEMPO trial, there were no differences in the proportion of subjects with ALT elevations between the tolvaptan and placebo groups in the first 3 months of treatment, but the proportion was higher in the tolvaptan group between 3 and 14 months of treatment. The time to resolution to ≤3 times ULN in subjects with elevations in ALT >3 times

ULN was examined. Of the 35 subjects in the tolvaptan group, 21 continued treatment after peak ALT was reached (subjects who continued treatment). Resolution to ≤3 times ULN occurred within 4 months after peaking for approximately 80% of the subjects. Of the 35 subjects in the tolvaptan group, 14 discontinued tolvaptan before peak ALT was reached or within 2 days of reaching peak ALT (subjects who discontinued treatment). Resolution to ≤3 times ULN occurred within 40 days after peaking for approximately 80% of the subjects. The longest time to resolution to ≤3 times ULN was approximately 15.5 months for subjects who continued treatment and was approximately 19 months for subjects who discontinued treatment. ALT resolved to ≤ULN within 17 months after peak in approximately 80% of subjects who continued treatment. Resolution of ALT elevations to ≤ULN was faster in subjects who discontinued treatment, and ALT decreased within 3.5 months in 71.4% of subjects (10 of the 14 subjects). Resolution of ALT elevations to ≤ULN was not confirmed at the time of the final test in 5 subjects. Total bilirubin was elevated above the normal range in 9 subjects in the tolvaptan group and 3 subjects in the placebo group. In the tolvaptan group, total bilirubin returned to normal within 3 months after peak in 6 of the 9 subjects (within 50 days for subjects who continued treatment; within 3 months for subjects who discontinued treatment) and resolution to ≤ULN was not confirmed at the time of the final test in 3 of the 9 subjects.

The association between dose/AUC and transaminase elevations was analyzed. Modal doses were not disproportionately high in subjects who met the criteria, and the AUC values in all subjects were distributed around the median AUC calculated in PPK analysis. These findings indicated that transaminase elevations are not associated with the modal dose or AUC of tolvaptan.

With respect to baseline characteristics, in the tolvaptan group, subjects who met the criteria for hepatocellular disturbances were older (a mean of 40.3 years in subjects who met the criteria and a mean of 38.5 years in subjects who unmet the criteria), more likely to be female (51.4% [18 of 35 subjects] and 48.4% [448 of 926 subjects], respectively), and more likely to be Asian (25.7% [9 of 35 subjects] and 12.1% [112 of 926 subjects], respectively) than subjects who unmet the criteria. The percentages of Japanese subjects were 25.7% (9 of 35 subjects) and 11.8% (109 of 926 subjects), respectively. In the tolvaptan group, subjects who met the criteria for hepatocellular disturbances had lower renal function than subjects who unmet the criteria ($eGFR_{CKD\text{-}EPI}$, 75.5 ± 19.1 mL/min/1.73 m^2 and 81.6 ± 21.1 mL/min/1.73 m^2, respectively).

Concerning concomitant medications, subjects who met the criteria for hepatocellular disturbances used vitamin D more frequently in both the tolvaptan and placebo groups (8.6% [3 of 35 subjects] and 6.9% [64 of 926 subjects], respectively, in the tolvaptan group, 18.2% [2 of 11 subjects] and 5.9% [28 of 473 subjects], respectively, in the placebo group). In the tolvaptan group, subjects who met the criteria used statins (17.1% [6 of 35 subjects] and 12.9% [119 of 926 subjects], respectively) and allopurinol (8.6% [3 of 35 subjects] and 6.7% [62 of 926 subjects], respectively) more frequently.

The data from Japanese extension trials (the cut-off date of [redacted], 20[redacted]) were reviewed for hepatocellular disturbances. As a result, 3 of 108 subjects from Trial 156-[redacted]-003 were identified as meeting one or more

of the criteria for hepatocellular disturbances. One of the 3 subjects was also included in the TEMPO trial (Trial 156-[redacted]-251). Another subject discontinued treatment due to drug-induced liver injury after the data cut-off date of [redacted], 20[redacted]. In 2 subjects other than the subject included in the TEMPO trial, ALT was elevated to >5 times ULN and the time to first elevation in ALT of >3 times ULN was at 3 months of treatment. For 1 of the 2 subjects, no decrease in ALT was confirmed as of the data cut-off date of [redacted], 20[redacted] but resolution to ≤3 times ULN was confirmed by [redacted], 20[redacted]. For the other subject, ALT decreased 3 months after discontinuation of tolvaptan.

Trial 156-[redacted]-003 and Trial 156-[redacted]-003 were ongoing in Japan at the time of submission of the application for the additional indication of ADPKD, and the data through [redacted], 20[redacted] after the data cut-off date of [redacted], 20[redacted] were reviewed for liver function safety. As a result, 1 subject in Trial 156-[redacted]-003 and 4 subjects in Trial 156-[redacted]-003 were identified as meeting the criteria for hepatocellular disturbances. After the data cut-off date, 4 of 108 subjects (3.7%) in Trial 156-[redacted]-003 had ALT ≥5 times ULN [1 of 67 subjects who completed the TEMPO trial in the tolvaptan group (TLV FROM 251) (1.5%); 3 of 41 subjects who completed the TEMPO trial in the placebo group (PLC FROM 251) (7.3%)]. All of the 4 subjects from Trial 156-[redacted]-003 had elevated ALT >5 times ULN. For these 4 subjects, the time to first elevation in ALT of >3 times ULN was 5 to 9 months. One of the 4 subjects had ALT >3 times ULN at screening and ALT decreased to ≤3 times ULN at 2 weeks of treatment, but rose again at 9 months of treatment. Among the 4 subjects with elevated ALT >5 times ULN, 1 subject discontinued treatment (for reasons other than adverse events) and 3 subjects continued treatment. In the 1 subject who discontinued treatment, ALT decreased to ≤3 times ULN 2 months after peak. In the 3 subjects who continued treatment, ALT decreased 20 days to 3 months after peak.

PMDA considered as follows:
With regard to hepatic dysfunction associated with tolvaptan in ADPKD patients, it has been suggested that tolvaptan has the potential to cause serious hepatic dysfunction at a high incidence, and furthermore, the incidence of hepatic dysfunction tended to be high especially in Japanese patients. Thus, this is the most critical issue for the safety of tolvaptan. If tolvaptan is approved for the treatment of ADPKD, the package insert should provide adequate warning and include provisions for liver function monitoring so that hepatic dysfunction is detected in clinical practice as early as possible and that tolvaptan is discontinued immediately in the event of hepatic dysfunction.

Concerning the risk of hepatic dysfunction associated with tolvaptan, PMDA asked the applicant to explain the reason for a higher incidence of hepatic function abnormal in the Japanese subgroup than in the overall trial population in the TEMPO trial, taking also account of differences in the pathology of ADPKD and baseline characteristics such as concomitant medications between the Japanese subgroup and overall trial population.

The applicant responded as follows:
Hepatic function abnormal occurred in 1.2% of subjects (12 of 961 subjects) in the tolvaptan group in the

overall trial population of the TEMPO trial, but all of them were Japanese patients and the incidence in the tolvaptan group in the Japanese subgroup was 10.2% (12 of 118 subjects). However, as raised liver function tests (LFTs), ALT increased (4.1% [39 of 961 subjects]), AST increased (3.7% [36 of 961 subjects]), hepatic enzyme increased (1.8% [17 of 961 subjects]), liver function test abnormal (0.6% [6 of 961 subjects]), and transaminases increased (1.1% [11 of 961 subjects]) were reported in the tolvaptan group in the overall trial population, while the incidences of raised LFTs in the tolvaptan group in the Japanese subgroup were as follows: 2.5% (3 of 118 subjects) for ALT increased, 2.5% (3 of 118 subjects) for AST increased, and 2.5% (3 of 118 subjects) for transaminases increased.

In order to identify factors associated with the occurrence of hepatic function abnormal, the baseline characteristics of patients with hepatic dysfunction-related adverse events (HEPATIC) were compared with those of patients without hepatic dysfunction-related adverse events (NON-HEPATIC) in the overall trial population and Japanese subgroup of the TEMPO trial. As a result, no major differences were observed.

It was inferred that the incidence of hepatic function abnormal was higher in the Japanese subgroup due mainly to differences in the choice of terms among the countries where trials were conducted. Namely, instead of the term “hepatic function abnormal,” the terms related to raised LFTs (ALT increased, AST increased, etc.) were chosen overseas, leading to a higher incidence of hepatic function abnormal in the Japanese subgroup than in the overall trial population. However, even when comparison was made based on “liver-related investigations, signs and symptoms SMQ” that includes these events, the incidence was slightly higher in the Japanese subgroup (12.0% [115 of 961 subjects] in the overall trial population, 15.3% [18 of 118 subjects] in the Japanese subgroup). Therefore, it cannot be ruled out that the risk of hepatic dysfunction may be higher in Japanese subjects compared with foreign subjects. Although no major differences in the baseline characteristics between HEPATIC and NON-HEPATIC were observed in the overall trial population or Japanese subgroup, HEPATIC in the tolvaptan group had a slightly lower GFR in both the overall trial population and Japanese subgroup. As the mean GFR (72.74 mL/min/1.73 m^2) at the start of the trial in the tolvaptan group in the Japanese subgroup was lower than the mean value in the overall trial population (81.35 mL/min/1.73 m^2), this difference in renal function at the start of the trial might have been associated with a slightly higher incidence of hepatic dysfunction in Japanese patients compared with foreign patients. However, since the difference in GFR between HEPATIC and NON-HEPATIC was not very large in either the overall trial population or Japanese subgroup (3.9 mL/min/1.73 m^2 and 3.4 mL/min/1.73 m^2, respectively) and since patients included in the TEMPO trial had preserved renal function (CLcr >60 mL/min), this difference in renal function at the start of the trial was unlikely to be the main cause for a slightly higher incidence of hepatic dysfunction in the Japanese subgroup. Based on these, after all, the main reason for a higher incidence of hepatic function abnormal in the Japanese subgroup than in the overall trial population was considered to be differences in the choice of terms among the countries, but this is a matter of speculation.

Regarding liver function monitoring during treatment with tolvaptan, the draft package insert states, “Serum transaminase and total bilirubin should be measured monthly for about 1 year and 6 months after

the initiation of treatment with tolvaptan and at regular intervals thereafter." PMDA asked the applicant to explain the basis for the above monitoring requirements.

The applicant responded as follows:
As previously mentioned, since the proportion of subjects with serum transaminase (AST, ALT) elevations was higher in the tolvaptan group than in the placebo group in the TEMPO trial (the proportion of subjects with serum transaminase of >3 times ULN, 4.6% in the tolvaptan group, 1.7% in the placebo group), an Adjudication Committee was formed to review the data on subjects with adverse events related to hepatic function abnormal. As a result, signs of tolvaptan-induced liver injury were detected in a few subjects. The incidence of transaminase elevations was higher in the tolvaptan group than in the placebo group between 3 and 14 months of treatment but there were no differences in the incidence between the tolvaptan and placebo groups beyond 14 months of treatment [see Figure 6].

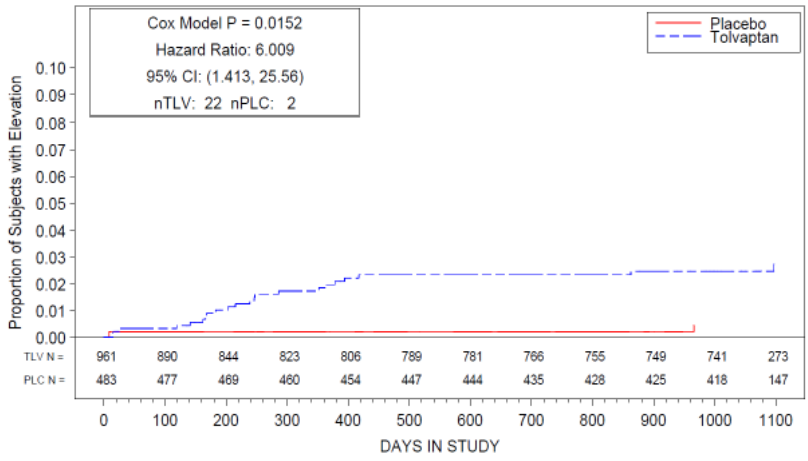

Figure 6. Time to first elevation in ALT or AST of >5 times ULN

Based on the above, it was thought that the risk of liver injury in ADPKD patients can be mitigated by frequent (monthly) blood testing during the initial phase of long-term treatment (for 1 year and 6 months after treatment initiation) and prompt discontinuation of tolvaptan in the event of signs of transaminase elevations. As sings of tolvaptan-induced liver injury were scarcely observed beyond 1 year and 6 months of treatment, it was considered unnecessary to continue such frequent testing. However, as the possibility that tolvaptan-induced liver injury occurs beyond 1 year and 6 months of treatment cannot be excluded, monitoring at regular intervals thereafter is also considered necessary. Therefore, the draft package insert should advise caution that "serum transaminases and total bilirubin should be measured monthly for about 1 year and 6 months after the initiation of treatment with tolvaptan and at regular intervals thereafter."

PMDA asked the applicant to explain the need for a precautionary statement for patients with underlying liver disease such as hepatic cirrhosis as underlying condition, based on the data from clinical trials etc.

The applicant responded as follows:
In the TEMPO trial, 35 of 961 subjects in the tolvaptan group and 20 of 483 subjects in the placebo group

had underlying liver disease such as hepatic cirrhosis (hepatitis, non-infectious SMQ; cholestasis and jaundice of hepatic origin SMQ; liver-related investigations, signs and symptoms SMQ; liver-related coagulation and bleeding disturbances SMQ; hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ). The incidences of adverse events in any of the 5 hepatic SMQs were 22.9% (8 of 35 subjects) in HEPATIC and 13.0% (120 of 926 subjects) in NON-HEPATIC of the tolvaptan group and 25.0% (5 of 20 subjects) in HEPATIC and 7.8% (36 of 463 subjects) in NON-HEPATIC of the placebo group. No individual events were reported by ≥3 HEPATIC subjects in the tolvaptan group, and therefore it was difficult to compare individual events between HEPATIC and NONHEPATIC. Events reported by HEPATIC were all mild or moderate in severity. Based on the above, in the TEMPO trial, the incidence of hepatic dysfunction-related adverse events was higher in subjects with underlying liver disease such as hepatic cirrhosis, but a similar trend was observed also in the placebo group. Thus, tolvaptan is unlikely to increase the risk of these events. No specific events occurred more frequently, and all events were mild or moderate in severity. Based on the above, the applicant considers that there is no need for including a precautionary statement for patients with underlying liver disease such as hepatic cirrhosis as underlying condition in the draft package insert etc.

PMDA considers as follows:
It is evident from the results of the TEMPO trial etc. that tolvaptan is associated with the risk of hepatocellular disturbances. Moreover, 3 Hy's law cases were identified, which also predicts that tolvaptan will have the potential to cause serious hepatic dysfunction. Since the incidence of hepatic dysfunction was higher in Japanese subjects than in foreign subjects in a clinical trial and since one of three subjects with serious hepatic dysfunction meeting Hy's Law criteria was Japanese, it cannot be ruled out that the risk of hepatic dysfunction associated with tolvaptan may be high, especially in Japanese patients, though the cause is unknown. Furthermore, it should be noted that the incidence of hepatic dysfunction was particularly high in the high dose (120 mg/day) group in the Japanese subgroup.

However, discontinuation of tolvaptan led to improvement in hepatic dysfunction in most cases. Among subjects who experienced hepatic dysfunction in the TEMPO trial, 5 subjects failed to show resolution of ALT elevations to ≤ULN at the time of the final test, but these subjects had no subsequent data or had resolution to about 1.2 to 2.8 times ULN, etc. Resolution of total bilirubin elevations to ≤ULN was not confirmed in 3 subjects (one of them was the aforementioned subject who did not have resolution of ALT values): 1 subject showed recovery from hepatitis 7 months later; 1 subject with the peak total bilirubin value of 1.1 times ULN, whose concurrently-evaluated ALT and AST values also returned to about the baseline level; and 1 (Japanese) subject with total bilirubin values of 2.2 to 2.6 times ULN who showed no ALT elevation. Based on the above, it is evident that tolvaptan is associated with the risk of serious hepatic dysfunction and the possibility that irreversible hepatic dysfunction persists even after discontinuation of tolvaptan cannot be excluded. However, the results of clinical trials showed that liver function tended to recover over time after discontinuation of tolvaptan in many subjects with hepatic dysfunction. In addition, resolution tended to be faster in subjects who discontinued tolvaptan early after the onset of hepatic dysfunction than in subjects who continued treatment even after the onset of hepatic dysfunction.

Therefore, tolvaptan can be made available in clinical practice under the following conditions: treatment should be started on eligible patients selected by performing liver function tests prior to the initiation of treatment with tolvaptan and by excluding patients with co-morbidities related to hepatic impairment; blood testing for liver function should be performed at regular intervals during treatment with tolvaptan; and if blood testing results suggest hepatic dysfunction, treatment should be discontinued immediately.

In the TEMPO trial, clinical laboratory tests (blood and urine collection) were to be performed on Day 1, titration Week 1, Week 2, and Week 3 or End of Titration, and Month 4 and every 4 months thereafter. In Japan, subjects were required to visit the medical institution every month (± 2 weeks) for clinical examination, safety assessments based on laboratory data, and measurement of vital signs (heart rate, blood pressure, body weight). Although tolvaptan is associated with the risk of serious hepatic dysfunction, given that hepatic dysfunction occurring in Japanese patients did not lead to a serious outcome under such conditions, liver function tests including serum transaminases and total bilirubin should be monitored at intervals in accordance with the requirements of the TEMPO trial in Japan, and liver function tests should be performed after each up-titration and monthly thereafter during treatment with tolvaptan. Based on the findings from the TEMPO trial (the incidence of transaminase elevations was higher in the tolvaptan group than in the placebo group between 3 and 14 months of treatment but there were no differences in the incidence between the tolvaptan and placebo groups beyond 14 months of treatment), the applicant recommends that serum transaminases and total bilirubin should be measured monthly for about 1 year and 6 months after the initiation of treatment with tolvaptan and at regular intervals thereafter without specifying the frequency of testing. In clinical practice relative to the TEMPO trial, a broader range of patients with various co-morbidities will receive tolvaptan continuously over a longer period of time. As the incidence of hepatic dysfunction etc. beyond 14 months of treatment cannot be determined, a time point beyond which monthly monitoring is no longer necessary cannot be established. In light of the seriousness of hepatic dysfunction-related adverse reactions to tolvaptan, liver function tests should be continued at least monthly during treatment with tolvaptan.

Due to the very limited number of patients with underlying liver disorder such as hepatic cirrhosis in the TEMPO trial, no sufficient information has been obtained to assess the safety of tolvaptan in ADPKD patients with liver disease. However, as it seems evident that tolvaptan has hepatocellular toxicity, the use of tolvaptan in ADPKD patients with liver disorder should basically be avoided unless at least the mechanism of tolvaptan-induced liver injury has been elucidated and tolvaptan has been proven not to adversely affect pre-existing liver disorder.

Tolvaptan is associated with the risk of serious hepatic dysfunction and the possibility that the risk may be high especially in Japanese patients cannot be ruled out. However, ADPKD is a progressive, irreversible disease that could lead to end-stage renal disease and in a situation where no curative alternative therapies exist, tolvaptan is expected to slow renal cyst growth and renal function decline. Thus, making tolvaptan available as a therapeutic option in clinical practice is of significant as long as liver function monitoring prior to initiation and during treatment with tolvaptan is mandated as described above and the package

insert includes a strict warning about the risk of hepatic dysfunction associated with tolvaptan. However, measures against the risk of hepatic dysfunction are particularly important and considering the incidence of hepatic dysfunction associated with tolvaptan and the seriousness of potential hepatic dysfunction, physicians who are familiar with the safety and efficacy profiles of tolvaptan should administer tolvaptan to ADPKD patients. It is also important that patients to be treated with tolvaptan are fully informed of the possible occurrence of adverse drug reactions including hepatic dysfunction that can lead to a serious outcome during long-term treatment with tolvaptan, the need for appropriate fluid ingestion and periodic monitoring by blood testing, and other information, and that informed consent is obtained from the patients. The use of tolvaptan should be limited to such cases [see "3.(iii).B.(6) Post-marketing investigations"].

Whether the balance between the risk of hepatic dysfunction and the efficacy of tolvaptan is acceptable for ADPKD patients and if acceptable, the requirements of hepatic laboratory monitoring prior to initiation and during treatment with tolvaptan, the details of warnings and precautions in the package insert, and the details of a precautionary statement regarding use in patients with liver disorder will be further reviewed, taking also account of comments from the Expert Discussion.

3.(iii).B.(5).2) Risk associated with an increase in serum sodium levels

PMDA asked the applicant to explain the risk of hypernatraemia associated with tolvaptan, based on the results from the overall trial population and Japanese subgroup in the TEMPO trial and the results from other clinical trials etc.

The applicant responded as follows:

Although the incidence of adverse events in the hypernatraemia Customized MedDRA Queries (CMQ) was higher in the tolvaptan group than in the placebo group in the TEMPO trial (5.2% [50 of 961 subjects] in the tolvaptan group, 1.4% [7 of 483 subjects] in the placebo group), most events were mild in severity and none was classified as serious or led to treatment discontinuation. Among adverse events in the hypernatraemia CMQ, hypernatraemia had the highest incidence in the tolvaptan group (2.8% [27 of 961 subjects]) (1.0% [5 of 483 subjects] in the placebo group). In the Japanese subgroup, as an adverse event in the hypernatraemia CMQ, urine osmolality increased occurred in 1 subject only. In the TEMPO trial, the incidence of increased sodium as clinically significant laboratory changes was higher in the tolvaptan group than in the placebo group (4.0% [38 of 960 subjects] in the tolvaptan group, 1.4% [7 of 483 subjects] in the placebo group). In the initial 3-week titration period, the changes from baseline to Week 3 in serum sodium concentrations were 2.24 ± 2.71 mEq/L in the tolvaptan group and 0.02 ± 2.45 mEq/L in the placebo group. In the Japanese subgroup, no subjects had increased sodium as clinically significant laboratory changes.

Based on the data from supportive studies (long-term extension trials that enrolled subjects who completed the TEMPO trial, Trial 156-[redacted]-271 and Trial 156-[redacted]-003; a long-term treatment study positioned as a dose-finding study, Trial 156-[redacted]-250), no adverse events in the hypernatraemia CMQ were reported in Trial 156-[redacted]-003 and during the extension phase of Trial 156-[redacted]-250. In Trial 156-[redacted]-271, the incidences

of adverse events in the hypernatraemia CMQ were 0.9% (5 of 530 subjects) in the TLV FROM 251 group and 2.4% (7 of 293 subjects) in the PLC FROM 251 group. The incidences of hypernatraemia were 0.4% (2 of 530 subjects) and 1.7% (5 of 293 subjects), respectively. In Trial 156-[redacted]-271, no events were rated as severe, classified as serious, or led to treatment discontinuation. During the fixed-dose phase of Trial 156-[redacted]-250, 1 subject in the tolvaptan 45 + 15 mg group had hypernatraemia (mild). In Trial 156-[redacted]-271, the incidences of increased sodium as clinically significant laboratory changes were 1.0% (5 of 496 subjects) in the TLV FROM 251 group and 2.1% (6 of 280 subjects) in the PLC FROM 251 group. During either the fixed-dose or extension phase of Trial 156-[redacted]-250, no subjects had increased sodium as clinically significant laboratory changes. The data from Trial 156-[redacted]-003 were not analyzed because clinically significant laboratory changes had not been defined at the time of preparing an interim report.

As described above, hypernatraemia occurred in the TEMPO trial and Trial 156-[redacted]-271 and during the fixed-dose phase of Trial 156-[redacted]-250, but the incidence was around 2% and none of the events was rated as severe, classified as serious, or led to treatment discontinuation. No marked changes in serum sodium concentrations were observed in any study. Therefore, the risk of hypernatraemia associated with tolvaptan in ADPKD patients is considered low.

PMDA asked the applicant to explain time when hypernatraemia associated with tolvaptan occurs more commonly and what the risk factors for it are.

The applicant responded as follows:
Adverse events in the hypernatraemia CMQ occurred in the early phase of treatment. In supportive studies, the incidences of adverse events in the hypernatraemia CMQ were low, and therefore when hypernatraemia occurred more commonly was not identified.

In order to identify risk factors for hypernatraemia associated with tolvaptan, the baseline characteristics of subjects with adverse events in the hypernatraemia CMQ (HYPERNATREMIA) were compared with those of subjects without adverse events in the hypernatraemia CMQ (NON-HYPERNATREMIA) in the TEMPO trial. In the tolvaptan group in the TEMPO trial, HYPERNATREMIA was older and had a lower $eGFR_{CKD\text{-}EPI}$ than NON-HYPERNATREMIA. HYPERNATREMIA were more likely to be white, black, and Hispanic and were more likely to use ACE inhibitors or ARBs, HMG-CoA reductase inhibitors, or vitamin D preparations. Comparison of HYPERNATREMIA and NON-HYPERNATREMIA in the placebo group showed the same trend as in the tolvaptan group, for age, race (whites only), and the use of ACE inhibitors or ARBs, HMG-CoA reductase inhibitors, or vitamin D preparations. In the Japanese subgroup, only 1 subject had adverse events in the hypernatraemia CMQ and the trend was not clear. In supportive studies, it was difficult to predict risk factors due to the limited number of subjects with adverse events in the hypernatraemia CMQ. Based on the above, renal function decline was predicted to be a risk factor for adverse events in the hypernatraemia CMQ associated with tolvaptan, but there were no marked differences in the mean age between HYPERNATREMIA and NON-HYPERNATREMIA. In the TEMPO trial, the mean $eGFR_{CKD\text{-}EPI}$ in HYPERNATREMIA of the tolvaptan group was 77.0 mL/min/1.73 m^2,

indicating preserved renal function. Therefore, risk factors for hypernatraemia associated with tolvaptan in ADPKD patients could not be identified. It was suggested that regardless of the use of tolvaptan, subjects on ACE inhibitors or ARBs, HMG-CoA reductase inhibitors, or vitamin D preparations are potentially at risk of developing hypernatraemia.

Given the pharmacological effects of tolvaptan, PMDA considers that there is a major concern with concluding, based on the results from limited clinical trials and in accordance with the applicant's claim, that the risk of hypernatraemia associated with tolvaptan is low across all ADPKD patients. Thus, PMDA asked the applicant to explain the appropriateness of the serum sodium monitoring requirements in the draft package insert.

The applicant responded as follows:
For precautions before use, the draft package insert lists "patients who cannot sense thirst or who have difficulty in ingestion of fluid" (who are considered to be at increased risk of hypernatraemia), and "patients with hypernatraemia" (in whom an increase in serum sodium concentrations can cause further serious symptoms) in the "CONTRAINDICATIONS" section and states that "patients should be advised, prior to treatment initiation, about the need for appropriate hydration" in the "WARNINGS" section and that "serum sodium should be measured prior to treatment initiation and if hyponatraemia is detected, serum sodium should be corrected prior to treatment initiation because rapid increases in serum sodium may cause central pontine myelinolysis" in the "Important Precautions" section, in order to prevent hypernatraemia and associated serious disorders immediately after treatment initiation. The package insert also prescribes dosing instructions as follows: "During the initial dose titration phase, tolvaptan should be initiated at the lowest dose of 60 mg/day and if tolerated, the dose should be titrated upward to 90 mg/day and then to 120 mg/day in a step-wise manner with at least weekly intervals between titrations. Serum sodium should be measured at each up-titration visit and thereafter monitored at regular intervals to watch the change in serum sodium over time." Based on change in serum sodium concentrations over time in the Japanese subgroup in the TEMPO trial, the mean increase in serum sodium on the day following treatment initiation was 3.5 mEq/L (the maximum concentration was 150 mEq/L), but the mean increase from the day of up-titration in the next week to the following day was <1 mEq/L (the maximum concentration was 149 mEq/L) and there were no major changes in serum sodium during the subsequent maintenance phase. These findings indicate that the risk of hypernatraemia can be reduced by ensuring that patients are advised, prior to treatment initiation, to maintain hydration etc. and that the risk of hypernatraemia can be managed by serum sodium monitoring as specified in the draft package insert.

For patients with serum sodium <125 mEq/L, since the cause for hyponatraemia in ADPKD patients is mostly water intake and this can be corrected by appropriate guidance regarding water intake, the following statement is included in the "Important Precautions" section to caution against initiating tolvaptan in patients with hyponatraemia: "serum sodium should be measured prior to treatment initiation and if hyponatraemia is detected, serum sodium should be corrected because rapid increases in serum sodium can cause central pontine myelinolysis." If "patients with serum sodium <125 mEq/L" are listed in

the “Careful Administration” section as for the approved indications, it might be interpreted that tolvaptan may be initiated carefully in patients with serum sodium <125 mEq/L. Thus, “patients with serum sodium <125 mEq/L” should not be listed in the “Careful Administration” section and only the “Important Precautions” section should provide the caution. Materials such as an information leaflet on proper use will recommend that “serum sodium should be measured prior to treatment initiation and if hyponatraemia is detected, serum sodium should be corrected before initiating treatment” to ensure safety measures.

PMDA considers as follows:
Although neither serious hypernatraemia nor hypernatraemia leading to treatment discontinuation was observed in ADPKD patients on tolvaptan in the TEMPO trial and supportive studies, the incidence of hypernatraemia was higher in the tolvaptan group than in the placebo group in all studies and increases in serum sodium levels were observed in the tolvaptan group during the initial 3-week titration period in the TEMPO trial. These findings suggest that tolvaptan is associated with the risk of hypernatraemia in ADPKD patients, and therefore, adequate attention needs to be paid to the possible occurrence of hypernatraemia during treatment with tolvaptan. The applicant’s explanation about the “WARNINGS” section that includes the need for hydration, the “CONTRAINDICATIONS” section that includes patients who cannot sense thirst or who have difficulty in ingestion of fluid and patients with hypernatraemia, and cautions about appropriate hydration and dehydration in the “Important Precautions” section is largely acceptable.

On the other hand, PMDA’s view on the serum sodium monitoring requirements is as follows:
Since risk factors for hypernatraemia could not be identified from the results from the TEMPO trial and supportive studies, serum sodium monitoring during treatment is required for all ADPKD patients for whom tolvaptan is indicated, and if an increase in serum sodium levels is detected, appropriate measures should be taken. Especially, hypernatraemia frequently occurred in the early phase of treatment with tolvaptan. Thus, attention needs to be paid to the possible occurrence of hypernatraemia or an increase in serum sodium levels, especially immediately after the initiation of tolvaptan treatment and immediately after up-titration of tolvaptan. Given that subjects were required to visit the medical institution every month (± 2 weeks) for clinical examination, safety assessments based on laboratory data, and measurement of vital signs (heart rate, blood pressure, body weight) in the TEMPO trial in Japan, in light of the risk of hypernatraemia associated with tolvaptan, serum sodium also should be monitored at intervals in accordance with the requirements of the TEMPO trial in Japan and especially, measurement of serum sodium after up-titration is essential. If tolvaptan is approved, it will be essential to collect post-approval information on the occurrence of hypernatraemia-related adverse events.

Hyponatraemia occurs mostly due to the pathology of the underlying disease or concomitant medications in patients with fluid retention resulting from heart failure or hepatic cirrhosis (the previously approved indications for tolvaptan), whereas hyponatraemia normally occurs in ADPKD patients when they have other co-morbidities, etc. Therefore, the risk of central pontine myelinolysis due to rapid increases in serum sodium following treatment with tolvaptan should be lower in ADPKD patients compared with patients

with fluid retention resulting from heart failure or hepatic cirrhosis. However, if hyponatraemia is detected in a patient with ADPKD prior to treatment initiation etc., it is necessary to correct serum sodium while identifying the cause, and to carefully determine whether tolvaptan should be indicated to the patient. Once treatment with tolvaptan is initiated, the patient should be more closely monitored, including measurement of serum sodium.

The details of a warning/precaution about the risk of hypernatraemia in the package insert and the details of the requirements for serum sodium monitoring during treatment with tolvaptan will be further reviewed, taking also account of comments from the Expert Discussion.

3.(iii).B.(5).3) Risk associated with the aquaretic effects of tolvaptan

PMDA asked the applicant to explain the risk of adverse events related to the aquaretic effects of tolvaptan (dehydration, thrombosis, dizziness, syncope, etc.), based on the results in the overall trial population and Japanese subgroup from the TEMPO trial and the results from other clinical trials etc.

The applicant responded as follows:

In the TEMPO trial, the incidences of aquaretic adverse events were 14.3% (137 of 961 subjects) in the tolvaptan group and 11.0% (53 of 483 subjects) in the placebo group. Dehydration (0.3% [3 of 961 subjects]) and dizziness (0.1% [1 of 961 subjects]) in the tolvaptan group and dehydration (0.4% [2 of 483 subjects]) and dizziness (0.2% [1 of 483 subjects]) in the placebo group were rated as severe. Dehydration (0.3% [3 of 961 subjects]), dizziness (0.1% [1 of 961 subjects]), and syncope (0.1% [1 of 961 subjects]) in the tolvaptan group and dehydration (0.4% [2 of 483 subjects]) in the placebo group were classified as serious. No events leading to treatment discontinuation were reported in either group. In the Japanese subgroup, the incidences of aquaretic adverse events were 16.1% (19 of 118 subjects) in the tolvaptan group and 15.3% (9 of 59 subjects) in the placebo group, and dehydration was rated as severe in both the tolvaptan and placebo groups; the incidences were 0.8% (1 of 118 subjects) and 1.7% (1 of 59 subjects), respectively. Dehydration (0.8% [1 of 118 subjects]) in the tolvaptan group was classified as serious.

Based on the data from supportive studies (Trial 156-[redacted]-003, Trial 156-[redacted]-271, Trial 156-[redacted]-250), the incidences of aquaretic adverse events were 4.5% (3 of 67 subjects) in the TLV FROM 251 group and 7.3% (3 of 41 subjects) in the PLC FROM 251 group in Trial 156-[redacted]-003. None of the events was rated as severe. Dizziness (2.4% [1 of 41 subjects]) in the PLC FROM 251 group was classified as serious. In Trial 156-[redacted]-271, the incidences of aquaretic adverse events were 1.7% (9 of 530 subjects) in the TLV FROM 251 group and 7.5% (22 of 293 subjects) in the PLC FROM 251 group. None of the events was rated as severe. During the fixed-dose phase of Trial 156-[redacted]-250, the incidences of aquaretic adverse events were 36.4% (8 of 22 subjects) in the tolvaptan 45 + 15 mg group and 29.2% (7 of 24 subjects) in the tolvaptan 60 + 30 mg group. None of the events was rated as severe. During the extension phase of Trial 156-[redacted]-250, only dizziness (23.5% [4 of 17 subjects]) occurred as aquaretic adverse events in the tolvaptan 45 + 15 mg group and all events were mild in severity. The risk of adverse events related to the aquaretic effects of tolvaptan is high, which poses no serious safety risk.

PMDA asked the applicant to explain time when adverse events related to the aquaretic effects of tolvaptan occur more commonly and what the risk factors are and then explain the appropriateness of warnings/precautions for adverse events related to the aquaretic effects of tolvaptan (dehydration, thrombosis, dizziness, syncope, etc.) in the draft package insert.

The applicant responded as follows:
In the TEMPO trial, aquaretic adverse events occurred in the early phase of treatment. Similarly, these adverse events occurred more commonly in the early phase of treatment in Trial 156-[redacted]-271 and the fixed-dose phase of Trial 156-[redacted]-250 among supportive studies. Although potential risk factors for adverse events related to the aquaretic effects of tolvaptan were assessed, the TEMPO trial and the supportive studies showed different trends and risk factors could not be identified. It was suggested that regardless of the use of tolvaptan, subjects on ACE inhibitors or ARBs are potentially at increased risk of aquaretic adverse events.

For precautions before use, the draft package insert states “patients who cannot sense thirst or who have difficulty in ingestion of fluid” (who are considered to be at increased risk of hypernatraemia) in the “CONTRAINDICATIONS” section, a warning about the need for appropriate hydration in the “WARNINGS” section, and precautions for dehydration and syncope, loss of consciousness, dizziness, etc. in the “Important Precautions” section, in order to prevent aquaretic adverse events and associated serious disorders immediately after treatment initiation. The package insert also prescribes dosing instructions as follows: “During the initial dose titration phase, tolvaptan should be initiated at the lowest dose of 60 mg/day and if tolerated, the dose should be titrated upward to 90 mg/day and then to 120 mg/day in a step-wise manner with at least weekly intervals between titrations.” In addition, a precautionary statement regarding use in patients who are unable to maintain adequate hydration due to decreased ability to drink or restricted access to water and a precaution for symptoms such as thirst and dehydration immediately after up-titration are added to the “Important Precautions” section.

As described above, the risk of aquaretic adverse events can be reduced by ensuring that patients are given guidance on water intake prior to the initiation of tolvaptan treatment and cautioned after treatment initiation. Therefore, the above warning/precautions in the draft package insert are appropriate.

PMDA considers as follows:
In the TEMPO trial and the supportive studies, the incidence of aquaretic adverse events such as dehydration, dizziness, and syncope was higher in the tolvaptan group than in the placebo group and the incidence itself in the tolvaptan group was as high as 14.3% in the overall trial population and 16.1% in the Japanese subgroup. Furthermore, the incidences of serious or severe adverse events were also higher in the tolvaptan group. Therefore, adequate attention needs be paid to the possible occurrence of aquaretic adverse events during treatment with tolvaptan. Especially, aquaretic adverse events tended to frequently occur in the early phase of treatment. Thus, attention needs to be paid particularly to the possible

occurrence of these adverse events immediately after treatment initiation and immediately after up-titration. The principles of warnings/precautions for possible adverse events related to the aquaretic effects of tolvaptan in the "CONTRAINDICATIONS" section, the "WARNINGS" section, and the "Important Precautions" section of the draft package insert presented by the applicant, are largely acceptable. Measures against the risk of adverse events related to the aquaretic effects of tolvaptan, including warnings/precautions in the package insert, will be further reviewed, taking also account of comments from the Expert Discussion.

3.(iii).B.(5).4) Risk of hyperkalaemia

PMDA asked the applicant to explain the risk of hyperkalaemia associated with tolvaptan, based on the results on the overall trial population and Japanese subgroup from the TEMPO trial and the results from other clinical trials. PMDA also asked the applicant to explain when hyperkalaemia occurs more commonly and what the risk factors for hyperkalaemia are and then explain the appropriateness of the serum potassium monitoring requirements in the draft package insert, based on these findings.

The applicant responded as follows:

In the TEMPO trial, the incidence of adverse events in the hyperkalaemia CMQ was comparable between the tolvaptan and placebo groups (5.8% [56 of 961 subjects] in the tolvaptan group, 5.0% [24 of 483 subjects] in the placebo group). The incidences of hyperkalaemia were 0.7% (7 of 961 subjects) in the tolvaptan group and 0.6% (3 of 483 subjects) in the placebo group, and these events were mild or moderate in severity. None of the events was classified as serious or led to treatment discontinuation. Among the adverse events in the hyperkalaemia CMQ, muscle spasms occurred with the highest incidence in the tolvaptan group (3.6% [35 of 961 subjects]) and the incidence was similar to that in the placebo groups (3.5% [17 of 483 subjects]). In the Japanese subgroup, as adverse events in the hyperkalaemia CMQ, muscle spasms only occurred and the incidence was lower in the tolvaptan group than in the placebo group. The incidence of increased potassium as clinically significant laboratory changes was comparable between the tolvaptan and placebo groups (3.1% [30 of 960 subjects] and 3.7% [18 of 483 subjects], respectively). Serum potassium concentrations remained almost unchanged from treatment initiation. In the Japanese subgroup, no subjects in the tolvaptan group had increased potassium as clinically significant laboratory changes.

Based on the data from supportive studies (Trial 156-[redacted]-003, Trial 156-[redacted]-271, Trial 156-[redacted]-250), no adverse events in the hyperkalaemia CMQ were reported during the extension phase of Trial 156-[redacted]-250. In Trial 156-[redacted]-003, the incidences of adverse events in the hyperkalaemia CMQ were 3.0% (2 of 67 subjects) in the TLV FROM 251 group and 2.4% (1 of 41 subjects) in the PLC FROM 251 group, and these events were all mild in severity. Hyperkalaemia did not occur. In Trial 156-[redacted]-271, the incidences of adverse events in the hyperkalaemia CMQ were 1.1% (6 of 530 subjects) in the TLV FROM 251 group and 2.7% (8 of 293 subjects) in the PLC FROM 251 group. Hyperkalaemia occurred in 1 subject in the PLC FROM 251 group, and the event was mild in severity. During the fixed-dose phase of Trial 156-[redacted]-250, the incidences of adverse events in the hyperkalaemia CMQ were 4.5% (1 of 22 subjects) in the tolvaptan 45 +

15 mg group and 16.7% (4 of 24 subjects) in the tolvaptan 60 + 30 mg group, and these events were mild or moderate in severity. Hyperkalaemia did not occur. In all studies, none of the adverse events in the hyperkalaemia CMQ was classified as serious or led to treatment discontinuation. In Trial 156-[redacted]-271, the incidences of increased potassium as clinically significant laboratory changes were 1.4% (7 of 496 subjects) in the TLV FROM 251 group and 2.5% (7 of 280 subjects) in the PLC FROM 251 group. In Trial 156-[redacted]-250, increased potassium occurred in the tolvaptan 45 + 15 mg group only with an incidence of 9.1% (2 of 22 subjects) during the fixed-dose phase and 5.9% (1 of 17 subjects) during the extension phase. In all studies, potassium concentrations remained almost unchanged from baseline. Based on the above, tolvaptan is unlikely to cause hyperkalaemia in ADPKD patients.

Concerning the most common timing of occurrence of hyperkalaemia, adverse events in the hyperkalaemia CMQ occurred in the early phase of treatment in the TEMPO trial. In the supportive studies, the incidence of adverse events in the hyperkalaemia CMQ was low, and therefore it was difficult to predict when hyperkalaemia will occur more commonly. Subjects with adverse events in the hyperkalaemia CMQ were more likely to be white and female in the TEMPO trial, which was not consistent with the findings from the supportive studies, and these could not be determined to be risk factors. It was suggested that regardless of the use of tolvaptan, subjects on ACE inhibitors or ARBs or vitamin D preparations are potentially at increased risk of adverse events in the hyperkalaemia CMQ.

In the draft package insert, the “Careful Administration” section includes “Patients with hyperkalaemia [The aquaretic effects of tolvaptan may exacerbate hyperkalaemia.],” and the “Interactions (precautions for concomitant use)” section states that “Drug Names etc.: potassium preparations, potassium-sparing diuretics (spironolactone, triamterene, etc.), aldosterone antagonists (eplerenone etc.), angiotensin-converting enzyme inhibitors (enalapril maleate etc.), angiotensin II receptor blockers (losartan potassium etc.), renin inhibitors (aliskiren fumarate etc.); Clinical Symptoms and Measures: Serum potassium concentrations may be increased when tolvaptan is used concomitantly with these drugs; Mechanism and Risk Factors: The aquaretic effects of tolvaptan reduce circulating plasma volume, which may result in a relative increase in serum potassium.” In addition, the “Important Precautions” section states that “Serum potassium should be measured during treatment with tolvaptan since the aquaretic effects of tolvaptan reduce circulating plasma volume, which may result in an increase in serum potassium concentrations.” The frequency of serum potassium monitoring etc. has not been specified. However, since the results from previous clinical trials in ADPKD patients indicate that the risk of hyperkalaemia associated with tolvaptan in ADPKD patients is very low and since serum potassium is included in routine clinical laboratory testing, the risk of hyperkalaemia can be managed by the above requirements in the draft package insert, also in ADPKD patients chronically treated with tolvaptan.

PMDA considers as follows:
The results from clinical trials of tolvaptan in ADPKD patients showed no obvious trend towards an increased risk for hyperkalaemia in the tolvaptan group compared to the placebo group. However, the aquaretic effects of tolvaptan can cause hyperkalaemia and especially in clinical practice, antihypertensives

that may cause hyperkalaemia, such as ACE inhibitors and ARBs, will be commonly used with tolvaptan for the treatment of hypertension associated with ADPKD. Thus, adequate attention should be paid to the risk of hyperkalaemia. It should also be noted that especially, the risk of hyperkalaemia related to renal impairment is further increased along with the progression of ADPKD. Therefore, the package insert should caution about these issues relating to the risk of hyperkalaemia. The details of precautions in the package insert, including the serum potassium monitoring requirements, will be finalized, taking also account of comments from the Expert Discussion.

3.(iii).B.(5).5) Risk of gout/hyperuricaemia

PMDA asked the applicant to explain the risk of gout/hyperuricaemia associated with tolvaptan, time when gout/hyperuricaemia occurs more commonly, and the risk factors for gout/hyperuricaemia, based on the results on the overall trial population and Japanese subgroup from the TEMPO trial and the results from other clinical trials, and then explain the need for a caution about gout/hyperuricaemia in the package insert.

The applicant responded as follows:

In the TEMPO trial, the incidences of gout/hyperuricaemia were 6.7% (64 of 961 subjects) in the tolvaptan group and 2.9% (14 of 483 subjects) in the placebo group. None of the events was rated as severe, classified as serious, or led to treatment discontinuation. In the Japanese subgroup, the incidences of gout/hyperuricaemia were 12.7% (15 of 118 subjects) in the tolvaptan group and 8.5% (5 of 59 subjects) in the placebo group. The incidences of increased uric acid as clinically significant laboratory changes were 6.2% (59 of 953 subjects) in the tolvaptan group and 1.7% (8 of 481 subjects) in the placebo group. Blood uric acid concentrations increased after treatment initiation and the changes in blood uric acid concentration were higher in the tolvaptan group than in the placebo group during the treatment period, but blood uric acid concentrations were similar between the tolvaptan and placebo groups at Follow-up Visit 2. In the Japanese subgroup, increased uric acid was observed in 2.5% of subjects in the tolvaptan group (3 of 118 subjects), but none in the placebo group. Based on the data from supportive studies (Trial 156-[redacted]-003, Trial 156-[redacted]-271, Trial 156-[redacted]-250), the incidences of gout/hyperuricaemia were 9.0% (6 of 67 subjects) in the TLV FROM 251 group and 12.2% (5 of 41 subjects) in the PLC FROM 251 group in Trial 156-[redacted]-003, and these events were mild in severity. In Trial 156-[redacted]-271, the incidences of gout/hyperuricaemia were 1.7% (9 of 530 subjects) in the TLV FROM 251 group and 1.4% (4 of 293 subjects) in the PLC FROM 251 group, and the events were mild or moderate in severity. In Trial 156-[redacted]-250, the incidences of gout/hyperuricaemia were 8.3% (2 of 24 subjects) in the tolvaptan 60 + 30 mg group during the fixed-dose phase and 5.9% (1 of 17 subjects) in the tolvaptan 45 + 15 mg group during the extension phase, and the events were mild or moderate in severity. The incidences of increased uric acid as clinically significant laboratory changes were 4.8% (24 of 496 subjects) in the TLV FROM 251 group and 3.6% (10 of 280 subjects) in the PLC FROM 251 group in Trial 156-[redacted]-271. In Trial 156-[redacted]-250, the incidences of increased uric acid were 13.6% (3 of 22 subjects) in the tolvaptan 45 + 15 mg group and 8.3% (2 of 24 subjects) in the tolvaptan 60 + 30 mg group during the fixed-dose phase and 11.8% (2 of 17 subjects) in the tolvaptan 45 + 15 mg group and 5.6% (1 of 18 subjects) in the tolvaptan 60

+ 30 mg group during the extension phase. In all studies, uric acid concentrations increased during the treatment period.

Based on the results from previous studies in patients with heart failure or hyponatraemia, an effect of tolvaptan on uric acid has been anticipated from the pharmacological activity of tolvaptan. In all of the TEMPO trial and the supportive studies, uric acid concentrations increased following treatment. In the TEMPO trial, the incidence of hyperuricaemia was higher in the tolvaptan group. However, the incidence of symptomatic gout was comparable between the tolvaptan and placebo groups, and none of the events was serious or led to treatment discontinuation. Based on the above, although the risk of hyperuricaemia resulting from increased uric acid is high, clinically serious risks such as gout are unlikely to occur as long as uric acid is measured prior to the initiation of tolvaptan treatment and attention is paid to increases in uric acid also during treatment.

Analyses were performed to identify time when gout/hyperuricaemia associated with tolvaptan occurs more commonly and the risk factors for gout/hyperuricaemia. As a result, time when gout/hyperuricaemia occurred more commonly in the TEMPO trial was not identified. Subjects with gout/hyperuricaemia were more likely to use vitamin D preparations in the TEMPO trial, which was not consistent with the findings from the supportive studies, and this could not be determined to be a risk factor. It was suggested that regardless of the use of tolvaptan, subjects on ACE inhibitors or ARBs or HMG-CoA reductase inhibitors are potentially at increased risk of gout/hyperuricaemia.

The draft package insert includes the statement that “Blood uric acid concentration may be increased due to decreased uric acid clearance by the kidney following tolvaptan treatment. Attention should be paid to blood uric acid concentrations during treatment with tolvaptan” in the “Important Precautions” section, and “blood uric acid increased (≥5%)” and “gout (<1%-5%)” are listed in the “Other Adverse Reactions” section to draw attention. Therefore, given the extent of the risk of increased blood uric acid and hyperuricaemia observed in clinical trials in ADPKD patients, an additional caution about gout/hyperuricaemia is unnecessary.

PMDA considers as follows:
The TEMPO trial and the supportive studies clearly indicate the risk of gout/hyperuricaemia associated with tolvaptan. Compared with patients treated with tolvaptan under the approved indications who have already been considered to be at risk of increased blood uric acid, ADPKD patients are treated with tolvaptan at very high doses and special caution is needed for ADPKD patients during treatment with tolvaptan and monitoring by blood testing is necessary. Therefore, the package insert should caution about the risk of gout/hyperuricaemia and advise monitoring by blood testing. If tolvaptan is approved, it will be necessary to collect post-approval information on the occurrence of gout/hyperuricaemia. A caution about the risk of gout/hyperuricaemia and the details of the blood testing requirements in the package insert and the details of information collection via post-marketing surveillance will be further reviewed, taking also account of comments from the Expert Discussion.

3.(iii).B.(5).6) Need for patient management in a hospital for administration of Tolvaptan

In Japan, subjects were required to stay overnight in a hospital on Day 1 of study treatment and the day of up-titration (at Weeks 1 and 2) for monitoring in the TEMPO trial. PMDA asked the applicant to explain the occurrence of adverse events, treatment discontinuation, and dose change during hospitalization (from the day of study treatment initiation until the following day, from the day of up-titration until the following day) and its details and reasons and then explain the need for hospitalized management for the initiation and up-titration of tolvaptan.

The applicant responded as follows:

In the Japanese subgroup of the TEMPO trial, the incidences of adverse events from the day of study treatment initiation until the following day (DAY 1), from the day of up-titration at Week 1 until the following day (WEEK 1), and from the day of up-titration at Week 2 until the following day (WEEK 2) were 72.9% (86 of 118 subjects), 13.7% (16 of 117 subjects), and 4.9% (5 of 103 subjects), respectively, in the tolvaptan group and 32.2% (19 of 59 subjects), 10.2% (6 of 59 subjects), and 1.7% (1 of 59 subjects), respectively, in the placebo group. Adverse events occurring in ≥10% of subjects in the tolvaptan group were thirst (55.9% [66 of 118 subjects]), pollakiuria (38.1% [45 of 118 subjects]), and polyuria (26.3% [31 of 118 subjects]) for DAY 1 and thirst (17.1% [20 of 117 subjects]) for WEEK 1. Events occurring in ≥5% and <10% of subjects were headache (5.1% [6 of 118 subjects]) for DAY 1 and pollakiuria (9.4% [11 of 117 subjects]) for WEEK 1. There were no events occurring in ≥5% of subjects in the tolvaptan group for WEEK 2. For all of the events occurring in ≥5% of subjects in the tolvaptan group for DAY 1 and WEEK 1, the incidence in the tolvaptan group was 2 times higher than that in the placebo group. Events rated as severe during hospitalization were pollakiuria (2.5% [3 of 118 subjects]) and polyuria (0.8% [1 of 118 subjects]) in the tolvaptan group and polyuria (1.7% [1 of 59 subjects]) in the placebo group.

In the Japanese subgroup of the TEMPO trial, subjects who discontinued treatment on Day 1 or the following day or the day of up-titration (at Weeks 1 and 2) or the following day were: One subject in the tolvaptan group (118 subjects), who discontinued treatment due to an adverse event on Day 2. The prescribed dose at the time of discontinuation was 45 + 15 mg/day. The adverse event leading to discontinuation was polyuria, which was rated as severe and classified as non-serious.

In the Japanese subgroup of the TEMPO trial, the dose was reduced in 9 subjects in the tolvaptan group (118 subjects) and 1 subject in the placebo group (59 subjects) on Day 1 or the following day or the day of up-titration (at Weeks 1 and 2) or the following day. The prescribed doses at the time of dose reduction were 60 + 30 mg in 4 subjects and 90 + 30 mg in 5 subjects in the tolvaptan group and 90 + 30 mg in 1 subject in the placebo group. The reasons for dose reduction were “adverse events” in 8 subjects and “as per protocol” in 1 subject in the tolvaptan group and “adverse events” in 1 subject in the placebo group. The subject for whom the reason was “as per protocol” was asked a question to assess the tolerability of tolvaptan, “Could you tolerate taking this dose of study drug for the rest of your life?” and answered “no.” Commonly reported adverse events in the 9 subjects in the tolvaptan group at the time of dose reduction

were thirst (8 subjects), pollakiuria (5 subjects), and polyuria (4 subjects).

In the tolvaptan group in the Japanese subgroup of the TEMPO trial, the most common reason for trial discontinuation or dose reduction during hospitalization was the occurrence of adverse events related to the aquaretic effects of tolvaptan (thirst, pollakiuria, and polyuria). The protocol for the TEMPO trial stated, "Subjects are recommended to ingest fluid actively to prevent excessive thirst throughout the daytime period" and "subjects are instructed to intake an additional 1-2 cups of water before bedtime and replenishment with each episode of nocturia to prevent dehydration." It seems that since subjects complied with the protocol, not dehydration and hypernatraemia that may be caused by the aquaretic effects of tolvaptan, but polyuria and pollakiuria led to discontinuation or dose reduction. Two of the adverse events leading to discontinuation or dose reduction during hospitalization (polyuria and pollakiuria) were rated as severe, but these adverse events of thirst and polyuria/pollakiuria can be self-managed and do not necessarily require hospitalized management. In order to prevent dehydration and hypernatraemia related to the aquaretic effects of tolvaptan, high-risk patients should be excluded from treatment with tolvaptan and measures should be taken to ensure that subjects themselves understand the risk and manage fluid balance. Since a majority of ADPKD patients for whom tolvaptan is indicated will be in their thirties or forties, in order also to minimize the impact on their lifestyle, it is preferable that patients will be educated to manage fluid balance for themselves and managed in an ambulatory setting, instead of a hospital setting, for administration of tolvaptan including the initiation and up-titration of tolvaptan.

PMDA considers as follows:
For the approved indications of treatment of fluid retention in patients with heart failure or hepatic cirrhosis, tolvaptan must be initiated and re-initiated in a hospital. Compared with patients treated with tolvaptan under the approved indications, ADPKD patients are treated with tolvaptan at very high doses. Therefore, with a view to ensuring safety, subjects in the TEMPO trial in Japan were required to be in a hospital for the initiation and up-titration of tolvaptan and monitored in a hospital immediately after the initiation and up-titration of tolvaptan. As a result, the TEMPO trial clearly showed that adverse events frequently occurred immediately after treatment initiation and after up-titration. However, the reported adverse events were all subjective symptoms perceived by subjects, e.g. thirst, polyuria, and pollakiuria. As long as (1) guidance on the possible occurrence of thirst, polyuria, and pollakiuria associated with tolvaptan and on the need for appropriate hydration is provided for patients prior to treatment initiation, (2) the patients and their families clearly understand its content, and (3) these subjective symptoms are considered able to be appropriately managed; the initiation and up-titration of tolvaptan in a hospital are not essential to secure safety. Therefore, as long as the package insert advises that patients who cannot sense thirst or who have difficulty in ingestion of fluid should be excluded and that tolvaptan should appropriately be prescribed only to patients considered to be able to maintain appropriate hydration and clearly states that patients should be educated adequately prior to treatment initiation, it is unnecessary to require ADPKD patients to be in a hospital for administration of tolvaptan including the initiation and up-titration of tolvaptan. The need for hospitalized management and the details of warnings/precautions for the initiation and up-titration of tolvaptan will be further reviewed, taking also account of comments from

the Expert Discussion.

3.(iii).B.(5).7) Risk associated with long-term treatment with tolvaptan

PMDA asked the applicant to explain any risk associated with V_2-receptor antagonism that may occur more frequently with prolonged treatment with tolvaptan.

The applicant responded as follows:

Common effects of tolvaptan via V_2-receptor antagonism are aquaretic adverse events that occur relatively early (thirst/dry mouth, pollakiuria/polyuria/nocturia, dehydration, events related to an increase in serum sodium levels, etc.). On the other hand, V_2-receptor blockade in organs other than the kidneys reduces the levels of von Willebrand factor and factor VIII activity, which may lead to an increased incidence of increased bleeding-related adverse events including gastrointestinal haemorrhage in ADPKD patients. Thus, increased bleeding-related adverse events associated with tolvaptan including gastrointestinal haemorrhage in ADPKD patients were analyzed to examine the possibility that the incidence of these events increases with prolonged treatment with tolvaptan. Aquaretic adverse events were as described in "3.(iii).B.(5).2) Risk associated with an increase in serum sodium levels." In the TEMPO trial (up to 36 months of treatment with tolvaptan), increased bleeding-related adverse events were analyzed using haemorrhage terms (excl laboratory terms) SMQ, gastrointestinal haemorrhage SMQ, and haemorrhage laboratory terms SMQ. The incidence of adverse events in the haemorrhage terms (excl laboratory terms) SMQ in the tolvaptan group was similar to or lower than that in the placebo group. The incidence of haematuria was also lower in the tolvaptan group (7.8% in the tolvaptan group and 14.1% in the placebo group). The incidence of adverse events in the gastrointestinal haemorrhage SMQ was similar between the tolvaptan and placebo groups (1.0% and 1.4%, respectively). No noteworthy effects were observed also for adverse events in the haemorrhage laboratory terms SMQ. Based on these results, the applicant considered that tolvaptan does not increase the risk of hemostatic disorder- or increased bleeding-related adverse events and that there is no risk associated with V_2-receptor antagonism.

PMDA considers as follows:

Regarding the long-term safety of tolvaptan, only the information on the safety of up to 3 years of treatment with tolvaptan was obtained in the clinical development program including the TEMPO trial. Thus, the long-term safety of tolvaptan beyond 3 years is unknown, and if tolvaptan is approved, it will be essential to collect post-approval information on this issue. As safety issues related to V_2-receptor antagonism by tolvaptan, haemorrhagic adverse events as well as aquaretic events may be increased. Although the TEMPO trial showed no obvious trend towards an increased incidence of haemorrhagic adverse events in the tolvaptan group, it will be necessary to collect post-approval information on this issue as well if tolvaptan is approved, as the possibility that haemorrhagic adverse events become unacceptable risk beyond 3 years of treatment cannot be ruled out. Safety measures including collection of post-approval information on the long-term safety of tolvaptan beyond 3 years will be further reviewed, taking also account of comments from the Expert Discussion.

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

The applicant explained post-marketing surveillance as follows:

A drug use-results survey of patients treated with tolvaptan to slow the progression of ADPKD will be conducted to confirm the safety and efficacy of tolvaptan in routine clinical settings. The survey plans to collect infromtion from [redacted] patients for [redacted] years (information will be collected form ≥[redacted] patients observed for ≥[redacted] years) via central registration system (registration period, [redacted] years; observation period, [redacted] years). The departments of internal medicine, nephrology, and urology, etc. will primarily be involved. As a rule, each patient will be observed for [redacted] years. After patient registration, survey forms will be collected every [redacted] years. For patients who have completed or discontinued treatment, information up to that point will be collected. The information to be collected includes patient characteristics, the status of administration of tolvaptan and other therapeutic drugs, safety information including adverse events and laboratory data, and the symptoms and findings of ADPKD over time (such as renal function and renal pain), etc. The safety analysis items include the occurrence of adverse drug reactions/infections by patient characteristics, the risk factors for serious adverse drug reactions etc., and adverse events of special interest, and the efficacy analysis items include efficacy by patient characteristics and the time course of observations. A planned sample size of [redacted] patients has been chosen, which provides a ≥95% probability of detecting unknown adverse drug reactions with an incidence of 0.5%. As tolvaptan is expected to be chronically used in ADPKD patients, each patient will be observed for [redacted] years.

For efficacy evaluation in a drug use-results survey, the long-term efficacy of tolvaptan will be investigated. This is because, despite the fact that tolvaptan is intended for chronic use for ADPKD, no subjects were treated with tolvaptan continuously for >3 years during development and no information on the long-term efficacy of tolvaptan in Japan has been obtained. The primary efficacy endpoint for trials before approval was “kidney volume,” which is rarely measured in clinical practice. Thus, efficacy observations will be focused on subjective and objective findings such as renal function over time and the presence or absence of renal pain. Regarding safety, efforts will be made to collect missing information and risk factor analysis will be performed.

For safety evaluation in a drug use-results survey, the priority items will be hepatic dysfunction, transaminase (ALT or AST) increased, total bilirubin increased, thirst, hypernatraemia, blood sodium increased, dehydration, gout, hyperuricaemia, dizziness, and drug-drug interactions (concomitant use with CYP3A4 inhibitors). In addition, the occurrence of thrombosis/thromboembolism, renal failure/renal impairment, central pontine myelinolysis, teratogenicity, excretion into milk, hyperkalaemia, diabetes mellitus/hyperglycaemia, glaucoma/intraocular pressure increased, syncope/loss of consciousness, skin neoplasms (basal cell carcinoma, malignant melanoma), etc. will also be investigated. An interim analysis will be performed after submission of periodic safety update reports on information collected from up to about [redacted] patients. The risk management plan will be reviewed when a new risk has been identified and after each data lock point for the submission of a periodic safety update report, and whether or not the package insert and materials should be revised will be discussed if the most common timing of occurrence or risk factors are identified for important identified risks, important potential risks, and important missing

information etc.

PMDA considers as follows:
If tolvaptan is approved, measures against the risk of hepatic dysfunction are particularly important. Considering the incidence of hepatic dysfunction associated with tolvaptan and the seriousness of potential hepatic dysfunction, limiting the use of tolvaptan for ADPKD to physicians who are familiar with the safety and efficacy profiles of tolvaptan should be considered. It is important to ensure that patients to be treated with tolvaptan and their families are fully informed of the need for chronic use of tolvaptan, the possible occurrence of adverse drug reactions including serious hepatic dysfunction during chronic use, and the need for appropriate hydration and periodic monitoring by blood testing etc. and that informed consent is obtained from such patients. The use of tolvaptan should be limited to cases where these conditions are met.

It is evident that tolvaptan is associated with the risk of serious hepatic dysfunction and the long-term efficacy and safety of tolvaptan have not been evaluated adequately, and therefore it is necessary to continue to evaluate them carefully and collect data as early as possible. Thus, if tolvaptan is approved, a post-marketing surveillance study covering all patients treated with tolvaptan should be conducted to collect safety and efficacy information in routine clinical settings. With respect to hepatic dysfunction, it is necessary to collect information on the occurrence of serious hepatic dysfunction and perform analysis to identify the characteristics of patients susceptible to hepatic dysfunction. It is necessary to consider conducting interim assessments after the accumulation of a certain volume of information, e.g. yearly or every 2 years, before the final outcomes are available, and feedbacking the results to clinical practice and taking appropriate actions. It is essential to investigate the risk of hepatic dysfunction beyond 3 years of treatment, etc. without limiting the observation period to 4 years, modify the pharmacovigilance plan, as appropriate, based on the obtained information, and provide information to clinical practice and revise the package insert, etc. It is also necessary to collect information on thirst, hypernatraemia, dehydration, gout, hyperuricaemia, dizziness, and drug-drug interactions (concomitant use with CYP3A4 inhibitors). Furthermore, it is necessary to collect information on syncope/loss of consciousness, hyperkalaemia, and central pontine myelinolysis. Information on diabetes mellitus and hyperglycaemia should be collected, taking also account of the following points: as discussed by the applicant, it has been suggested that tolvaptan-induced increase in blood vasopressin may stimulate hepatic glucose production via the gluconeogenetic/glycogenolytic pathway; and in the TEMPO trial, the incidence of clinically significant increases in blood glucose was lower in the tolvaptan group (5.5%) than in the placebo group (6.8%), but diabetes mellitus reported as adverse events occurred in the tolvaptan group only (0.7% [7 of 961 subjects]). It is also necessary to collect information on events associated with V_2-receptor antagonism by tolvaptan. Information on glaucoma and intraocular pressure increased needs to be collected, taking account of the following points: as discussed by the applicant, there are some reports on the association between vasopressin receptor inhibition and intraocular pressure; the effects of tolvaptan on intraocular pressure are unclear; and the incidence of glaucoma-related adverse events was higher in the tolvaptan group (0.7% [7 of 961 subjects]) than in the placebo group (0.4% [2 of 483 subjects]) in the TEMPO trial.

Information on skin neoplasms (basal cell carcinoma, malignant melanoma) should be collected, taking account of the following points: previous non-clinical data, the data from clinical trials in non-ADPKD patients, and publications showed no association between tolvaptan and malignant tumors, but the incidences were higher in the tolvaptan group than in the placebo group in the TEMPO trial (basal cell carcinoma, 0.8% [8 of 961 subjects] in the tolvaptan group, 0.2% [1 of 483 subjects] in the placebo group; malignant melanoma, 0.2% [2 of 961 subjects] in the tolvaptan group, 0% [0 of 483 subjects] in the placebo group). It is also essential to collect information on the safety of tolvaptan in patients with lower levels of renal function, who were not included in the population of the TEMPO trial. As antihypertensives for ADPKD patients on tolvaptan, diuretics to control underlying hypertension are not recommended and diuretics can be used only when other types of antihypertensives (more than one antihypertensive) cannot lower blood pressure adequately. If such cases are reported after approval, information should be collected to evaluate safety.

Regarding efficacy, it is essential to investigate the long-term efficacy of tolvaptan beyond the duration of the TEMPO trial via post-marketing surveillance. It is also essential to collect information on the efficacy of tolvaptan in patients with lower levels of renal function, who were not included in the population of the TEMPO trial. The use of tolvaptan is not recommended in patients with earlier-stage ADPKD than the population of the TEMPO trial, but if such patients are treated with tolvaptan after approval, efficacy information should be collected. The applicant explained that as “kidney volume” is rarely measured in clinical practice, the symptoms and findings of ADPKD over time such as renal function and renal pain will be investigated. However, since the long-term efficacy of tolvaptan and the efficacy of tolvaptan initiated in patients with more advanced ADPKD are important issues to be investigated, information on changes in kidney volume should be collected by MRI etc., wherever possible. The details of post-marketing surveillance, including identification of safety specification and the appropriateness of risk classification and the appropriateness of pharmacovigilance activities and risk minimization activities based on “Risk Management Plan Guidance” (PFSB/SD Notification No.0411-1 and PFSB/ELD Notification No.0411-2 dated April 11, 2012), will be further reviewed, taking also account of comments from the Expert Discussion.

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

The assessment is currently underway and its results and conclusion by PMDA are reported in the Review Report (2).

IV. Overall Evaluation

As a result of the above review, PMDA considers as follows:

Based on the submitted data, the efficacy of tolvaptan in slowing kidney volume growth in patients with ADPKD has been demonstrated. Although there is a serious safety concern, i.e. the risk of serious hepatic

dysfunction, given that ADPKD is a rare, progressive, irreversible disease with no established curative therapies, tolvaptan can be made available in clinical practice under the following conditions: that tolvaptan is only administered under prescription by an appropriate physician; that patients with a rapidly increasing kidney volume who are deemed to be at high risk for rapidly progressing disease and who have given informed consent are appropriately selected for treatment with tolvaptan; and that rapid responses etc. to signs of hepatic dysfunction and adverse events related to the aquaretic effects of tolvaptan can be assured. Tolvaptan offers a new therapeutic option for ADPKD and has clinical relevance. A decision to approve or not to approve based on the risks and benefits, taking account of the risk of serious hepatic dysfunction, eligible patients for treatment with tolvaptan, the details of post-marketing surveillance, and other issues will be further reviewed, taking account of comments from the Expert Discussion.

Tolvaptan may be approved for ADPKD if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

February 7, 2014

I. Product Submitted for Registration

[Brand name]	(a) Samsca Tablets 7.5 mg (b) Samsca Tablets 15 mg (c) Samsca Tablets 30 mg
[Non-proprietary name]	Tolvaptan
[Applicant]	Otsuka Pharmaceutical Co., Ltd.
[Date of application]	May 30, 2013

II. Content of the Review

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

1. Clinical positioning of tolvaptan

PMDA has concluded on the clinical positioning of tolvaptan as follows:

Given that no curative therapies for autosomal dominant polycystic kidney disease (ADPKD) currently exist and that ADPKD is progressive and may lead to end-stage renal disease or dialysis, tolvaptan will be a therapeutic option for ADPKD because a multinational phase III trial in ADPKD patients (TEMPO trial) showed that tolvaptan reduces renal cyst growth and can slow renal function decline. However, it should be noted that tolvaptan is associated with the risk of serious hepatic dysfunction. In light of the above benefits and risks of tolvaptan, as long as the use of tolvaptan is limited to ADPKD patients with a predicted poor renal prognosis where renal function is preserved but the condition is worsening rapidly due to particularly rapid renal cystic growth and patients treated with tolvaptan are closely monitored for hepatic dysfunction, making tolvaptan available as a therapeutic option for ADPKD in clinical practice is of significance.

PMDA's conclusion was supported by the expert advisors.

2. Efficacy of tolvaptan

2.(1) Efficacy endpoint

PMDA has concluded that the primary efficacy endpoint (the rate of change in total kidney volume) and the secondary composite endpoint (worsening renal function, clinically significant renal pain, new or worsening hypertension, and new or worsening albuminuria) for the TEMPO trial are justified and that the

efficacy of tolvaptan can be evaluated with a comprehensive and integrated assessment of the results for the secondary composite endpoint and its components as well as the primary endpoint.

The expert advisors made the following comments on the above conclusions by PMDA:

- PMDA's conclusions are appropriate.
- While there is certainly an association between kidney volume growth and the rate of renal function decline in ADPKD patients, there is no evidence that tolvaptan delays the onset of end-stage renal disease or dialysis initiation (the true endpoint). Therefore, it is necessary to conduct a clinical study to evaluate the true endpoint after tolvaptan is approved for the treatment of ADPKD.

PMDA explained as follows:

A large, long-term placebo-controlled study is necessary to rigorously verify the efficacy of tolvaptan against the true endpoint in patients with progressing ADPKD in whom the benefits of tolvaptan are expected to outweigh the risks, but its feasibility is low and the conduct of such study cannot be imposed as a condition for approval etc. Meanwhile, comparison with appropriate controls cannot be made, but efficacy information including kidney volume and renal function can be collected via drug use-results survey of ADPKD patients treated with tolvaptan after approval. Thus, a drug use-results survey covering all patients treated with tolvaptan will be conducted to collect data from patients chronically treated with tolvaptan and investigate the occurrence of the true endpoint wherever possible.

In the end, the expert advisors supported PMDA's decision to evaluate the usefulness of tolvaptan based on assessments in the TEMPO trial.

2.(2) Efficacy in Japanese patients

The following conclusion by PMDA was supported by the expert advisors:

According to tolvaptan efficacy results from the TEMPO trial, tolvaptan significantly reduced the annualized growth rate of total kidney volume (the primary endpoint) in the overall trial population and the results in the Japanese subgroup were also consistent with those in the overall trial population. It can be concluded that the overall results, including the results of the secondary composite endpoint and its components, were similar between the overall trial population and Japanese subgroup. Therefore, the efficacy of tolvaptan as demonstrated in the entire TEMPO trial can be expected also in Japanese patients with ADPKD.

2.(3) Clinical relevance of the efficacy of tolvaptan demonstrated in the TEMPO trial

PMDA has concluded on the clinical relevance of tolvaptan as follows:

The TEMPO trial suggested that tolvaptan can slow renal function decline, which is the most important finding in treating ADPKD, albeit slight improvement, showing the clinical relevance of tolvaptan. Whether tolvaptan continues to provide the same level of efficacy from the early phase of treatment until several years later (a more advanced stage of disease) is unknown. However, ADPKD is a progressive, irreversible disease with no curative treatment, and tolvaptan showed clinically relevant efficacy, at least

for the pivotal portion of the TEMPO trial. Thus, as long as tolvaptan is used selectively in patients with a rapidly increasing kidney volume deemed to be at high risk for rapidly progressing disease and periodic liver function tests etc. are performed to carefully watch for serious adverse drug reactions such as hepatic dysfunction, clinically relevant efficacy can be achieved.

These conclusions by PMDA were discussed at the Expert Discussion, and the expert advisors made the following comment and identified the following issues:

- The conclusions by PMDA are appropriate.
- The clinical relevance of the effect of tolvaptan in slowing total kidney volume growth as demonstrated in the TEMPO trial is unknown.
- The therapeutic effects of tolvaptan seemed to be attenuated at 3 years after the start of treatment compared with early phase of treatment in the TEMPO trial.
- It is not clear whether the therapeutic effects of tolvaptan persist or the disease progresses rapidly after discontinuation of treatment with tolvaptan.

In the end, the expert advisors agreed as follows:
Given that there are currently no therapies with clinically proven efficacy against kidney volume growth in ADPKD, tolvaptan is acceptable as a therapeutic option, as long as tolvaptan is indicated only for patients with rapidly progressing ADPKD, like the population of the TEMPO trial, the frequency of testing etc. comparable to those in the TEMPO trial is specified, and patients treated with tolvaptan are closely monitored, allowing for early detection of hepatic dysfunction and hypernatraemia, as described later.

2.(4) Assurance of blinding of TEMPO trial

The following conclusion by PMDA was supported by the expert advisors:
Although there is a possibility that the blinding of the TEMPO trial was not maintained due to adverse drug reactions such as increased urine volume and thirst related to the pharmacological effects of tolvaptan, the efficacy of tolvaptan can be evaluated based on the results of between-treatment comparison in the TEMPO trial, because it is inferred that there were no serious breaks of the blinding for subjects or physicians that would overturn the interpretation of the results of between-treatment comparison in the TEMPO trial, taking also account of the results for total kidney volume and multiple renal function-related endpoints, which are considered objective endpoints.

3. Intended population and indication

3.(1) Population studied in TEMPO trial

The following conclusions by PMDA were supported by the expert advisors:
It was justifiable to study patients with a total kidney volume ≥750 mL, in whom kidney volume growth was expected to occur within the trial period, in the TEMPO trial in order to evaluate the efficacy of tolvaptan, and the inclusion criteria as to kidney volume were appropriate.

3.(2) Intended population and indication for tolvaptan

PMDA has concluded as follows:

The appropriate indication for tolvaptan should be "slowing of the progression of autosomal dominant polycystic kidney disease" and the "Precautions for Indications" section etc. should stipulate that tolvaptan is indicated for patients who clearly benefit from tolvaptan, i.e. patients deemed to be at high risk for rapidly progressing disease, as with patients enrolled into the TEMPO trial.

The above conclusions by PMDA were discussed at the Expert Discussion and the expert advisors made the following comments:

- PMDA's conclusions by are appropriate.
- A certain number of ADPKD patients do not progress to end-stage renal disease or have very slowly progressing disease (Higashihara E. *Clin Exp Nephrol.* 2012;16:622). Taking account of the design and results of the TEMPO trial, the significance of making tolvaptan available in clinical practice under the indication allowing use, regardless of ADPKD conditions, cannot be explained at present. Therefore, the use of tolvaptan should be limited to the patient population as with those studied in the TEMPO trial.
- Given that tolvaptan is associated with the risk of serious adverse reactions such as hypernatraemia due to its potent aquaretic effects, as well as the risk of serious hepatic dysfunction, the intended patient population should be defined in the "INDICATIONS" section, instead of the "Precautions for Indications" section etc., in order to more rigorously select patients to be treated with tolvaptan in clinical practice so that tolvaptan is not initiated in patients with early ADPKD in whom the progression of renal impairment is unpredictable.
- Taking also into account that a retrospective study in the UK (Thong KM. *Q J Med.* 2013;106:639-646) and an observational study in Japan (Higashihara E. *Clin Exp Nephrol.* 2012;16:622) have shown that the rate of renal function decline varies among patients, it is not appropriate to hurry to initiate tolvaptan in, for example, patients in whom the rate of renal function decline is not high based on the result obtained after at least 6 months of observation, and about 6 months to 1 year of observation does not cause significant disadvantages (loss of a therapeutic opportunity) to patients.

The expert advisors agreed that the "INDICATIONS" section should state that tolvaptan is indicated for patients with rapidly progressing disease, as with the population of the TEMPO trial.

Moreover, the expert advisors commented as follows:

Based on the efficacy endpoints tested in the TEMPO trial, the "INDICATIONS" section should explicitly indicate that the primarily expected effect of tolvaptan is "to slow kidney volume growth" in ADPKD patients.

PMDA explained as follows:

While the reduction in the rate of kidney volume increase, the primary endpoint, was assessed in the TEMPO trial, improvement of clinical symptoms of ADPKD including slowing of renal function decline

was also focused and assessed, which demonstrated efficacy, etc. Thus, "slowing of the progression" of ADPKD is also considered to reflect the clinical effects of tolvaptan observed in the TEMPO trial.

PMDA has concluded that the "INDICATIONS" section and the "Precautions for Indications" section should be as below based on the above discussion and considering: that "patients with a rapid estimated rate of kidney volume increase as indicated by a total kidney volume ≥750 mL" were studied in the TEMPO trial; that since renal functional decline is evident only after kidney volume reaches a certain level, it is practical to use kidney volume growth as a measure of the rate of disease progression; that the mean rate of change in total kidney volume in the placebo group was approximately 5%/year in the TEMPO trial; and how cut-off values for specific parameters pertaining to the intended population for other drugs are described.

In the end, the above conclusions by PMDA were supported by the expert advisors.

Indications

Slowing of the progression of autosomal dominant polycystic kidney disease in patients who have an already-large and rapidly increasing kidney volume

Precautions for Indications

For autosomal dominant polycystic kidney disease

- Samsca is indicated only if both of the following criteria are met.
  1) The total kidney volume is ≥750 mL.
  2) The growth rate of kidney volume is approximately ≥5%/year.
  [Patients with a rapid estimated rate of kidney volume increase as indicated by a total kidney volume of ≥750 mL were enrolled into a clinical trial.] [See the "Clinical Studies" section.]
- The efficacy and safety of Samsca in patients with creatinine clearance <60 mL/min at treatment initiation have not been established. [Patients with creatinine clearance ≥60 mL/min at treatment initiation were enrolled into a clinical trial.] [See the "Clinical Studies" section.]

3.(3) Use of tolvaptan in dialysis patients and patients with significantly advanced renal impairment

The following conclusions by PMDA were supported by the expert advisors:

tolvaptan should be contraindicated in patients with markedly decreased residual renal function (eGFR <15 mL/ min) and dialysis patients etc. Moreover, since it cannot be ruled out that renal function may be further decreased due to decreased renal blood flow associated with the aquaretic effects of tolvaptan, the package insert should advise that the indication of tolvaptan in patients who have not developed end-stage renal disease but have particularly advanced renal impairment should be determined carefully.

Based on the above discussion, PMDA instructed the applicant to contraindicate tolvaptan in "patients with serious renal impairment (eGFR <15 mL/min)" and list "patients with decreased renal function" in the "Careful Administration" section, and the applicant responded appropriately.

3.(4) Details of regulatory review in the US

[redacted]

[redacted] On the other hand, PMDA has concluded that the results from the TEMPO trial including the results of the primary endpoint, secondary composite endpoint and its components, and other renal function-related endpoints demonstrated the clinically relevant efficacy of tolvaptan in ADPKD patients. This conclusion by PMDA was supported by the expert advisors.

4. Dosage and administration

4.(1) Recommended dose

PMDA has concluded as follows:

While no Japanese or foreign parallel-group comparison study assessed the dose response relationship between dose levels from 60 mg/day to 120 mg/day of tolvaptan for efficacy, the distribution of doses of the investigational product administered in the TEMPO trial and efficacy results by modal dose have indicated a certain significance of the initial dose of 60 mg/day with titration up to 120 mg/day. The results in the Japanese subgroup were also consistent with the results in the overall trial population; the significance of dose titration from 60 mg/day to 120 mg/day has been suggested in the Japanese subgroup as in the overall trial population. Therefore, provided that the package insert adequately advises that attention should be paid to the possible occurrence of aquaretic adverse events during treatment with tolvaptan, especially, immediately after up-titration, the same dosing regimen as used in the TEMPO trial should be recommended in Japan.

The expert advisors made the following comments on these conclusions by PMDA:

- PMDA's conclusions are appropriate.
- Generally, the incidence of adverse drug reactions is likely to increase with increasing dose and a dose increase to 120 mg does not necessarily result in increased efficacy but may only lead to an increase in the incidence of adverse drug reactions. A wording that conveys this point should be incorporated in the Dosage and Administration section.
- Since the incidence of hepatic dysfunction was high, especially in the high dose (120 mg/day) group compared to other dose groups, a warning about the need for liver function tests after up-titration, etc. should be included in the package insert.

PMDA has concluded as follows:

In the TEMPO study, efficacy has been verified based on the trial dosage and administration, in which the dose was to be increased up to 120 mg/day wherever possible if tolerated, and about half of the subjects were receiving 120 mg/day at Month 36 and there was a trend towards a greater effect with a higher dose. Thus, it cannot be said that a dose increase to 120 mg/day does not result in increased efficacy. The appropriate dosage and administration statement should be as shown below, and a precautionary statement about adverse reactions to high-dose tolvaptan should be included in the package insert.

In the end, PMDA's conclusions were supported by the expert advisors.

Dosage and Administration

The usual initial adult dose of tolvaptan is 60 mg per day as a split-dose oral regimen of 45 mg/15 mg (morning/evening). When tolvaptan is tolerated at 60 mg per day for ≥1 week, the initial dose may be increased to 90 mg (60 mg/30 mg) per day and then to 120 mg (90 mg/30 mg) per day in a step-wise manner with a ≥1-week interval between titrations. The dose may be adjusted, as appropriate, based on tolerability, but the maximum dose should not exceed 120 mg per day.

Based on the above discussion, PMDA instructed the applicant to include the following statement in the "Important Precautions" section: "The incidence of adverse drug reactions tended to increase with increasing dose and serious hepatic dysfunction occurred at 120 mg/day. Adequate attention should be paid to the possible occurrence of adverse reactions to high-dose tolvaptan, especially hepatic dysfunction."

The applicant responded appropriately.

4.(2) CYP3A4 inhibitor coadministration

The following conclusion by PMDA was supported by the expert advisors:

The package insert should include a precautionary statement to the effect that while use with CYP3A4 inhibitors should basically be avoided, if temporary coadministration of tolvaptan with CYP3A4 inhibitors is inevitable, the dose of tolvaptan should be reduced to one-quarter when coadministered with strong CYP3A4 inhibitors and to one-half when coadministered with weak or moderate CYP3A4 inhibitors.

4.(3) Patients with severe renal impairment

PMDA has concluded as follows:

The concentration of tolvaptan unbound to plasma proteins was increased approximately 2-fold in subjects with CLcr <30 mL/min compared with those with CLcr >60 mL/min in a clinical pharmacology study, and tolvaptan has never been administered at doses higher than 120 mg/day to Japanese ADPKD patients. Thus, the package insert should advise that the dose should be reduced in patients with severe renal impairment.

Some of the expert advisors commented that tolvaptan should be contraindicated in patients with severe renal impairment. However, PMDA's conclusion was supported by the expert advisors in the end, taking also account of discussion in "3.(3) Use of tolvaptan in dialysis patients and patients with significantly advanced renal impairment."

Based on the above, PMDA instructed the applicant to include in the "Precautions for Dosage and Administration" section a statement to the effect that the dose should be reduced in patients with severe renal impairment. The applicant responded appropriately.

5. Safety

5.(1) Risk of hepatic dysfunction

PMDA has concluded on the risk of hepatic dysfunction associated with tolvaptan as follows:

Based on the results from the TEMPO trial, it is inferred that tolvaptan is associated with the risk of serious hepatic dysfunction and the possibility that the risk of hepatic dysfunction associated with tolvaptan is high, especially in Japanese patients, cannot be ruled out. It should be noted that the incidence of hepatic dysfunction in the Japanese subgroup was particularly high when tolvaptan was administered at the high dose (120 mg/day). The results of clinical trials showed that liver function tended to recover over time after discontinuation of tolvaptan in many subjects with hepatic dysfunction and resolution tended to be faster in subjects who discontinued tolvaptan early after the onset of hepatic dysfunction than in subjects who continued treatment even after the onset of hepatic dysfunction. Thus, tolvaptan should be made available in clinical practice under the following conditions: that patients with co-morbidities related to liver disorder are excluded from treatment with tolvaptan; and that blood testing for liver function is performed at regular intervals during treatment with tolvaptan and if hepatic dysfunction is suggested, treatment will be discontinued immediately. In accordance with the monitoring requirements of the TEMPO trial in Japan, liver function tests should be performed after each up-titration and then monthly during treatment with tolvaptan. Moreover, considering the incidence of hepatic dysfunction associated with tolvaptan and the seriousness of potential hepatic dysfunction, physicians who are familiar with the safety and efficacy profiles of tolvaptan should administer tolvaptan to ADPKD patients. The use of tolvaptan should be limited to patients who have been fully informed of the possible occurrence of adverse drug reactions including hepatic dysfunction that can lead to a serious outcome during chronic use of tolvaptan and the need for appropriate hydration and periodic monitoring by blood testing etc. and who have provided informed consent.

The expert advisors made the following comments on the above conclusions by PMDA:

- PMDA's conclusions are appropriate.
- The wording "patients with liver disorder or a history of liver disorder" in the CONTRAINDICATIONS section is vague and ambiguous. At least, tolvaptan should be contraindicated in patients with hepatic cirrhosis and patients with advanced chronic liver disorder equivalent to hepatic cirrhosis, and consideration should be given to the use of tolvaptan in patients with mild liver disorder with conditions such as "The use of tolvaptan should be considered through consultation with a hepatologist."
- If tolvaptan is contraindicated in patients with a history of hepatic dysfunction, patients with a history of hepatitis acute who have normal liver function, etc. will also have to be excluded. Thus, this may be inappropriate.
- Handling of hepatic cysts in ADPKD should be defined.

PMDA explained as follows:

Patients with a history of liver disorder, compared to those without a history of liver disorder, may be at higher risk for hepatic dysfunction and it cannot be ruled out that the risks of tolvaptan outweigh its

benefits. Contraindications and handling of hepatic cysts in ADPKD will be described specifically.

The above conclusions by PMDA were supported by the expert advisors.

Based on the above discussion, PMDA instructed the applicant to contraindicate tolvaptan in "patients with hepatic dysfunction such as chronic hepatitis and drug-induced hepatic dysfunction (excluding hepatic cysts in autosomal dominant polycystic kidney disease) or a history of hepatic dysfunction" and include the statements described below in the "WARNINGS" section and the "Important Precautions" section. The applicant responded appropriately.

WARNINGS

- Samsca should be used under the supervision of a physician with adequate knowledge about autosomal dominant polycystic kidney disease, only if the expected therapeutic benefits outweigh the possible risks. Prior to treatment initiation, patients should give informed consent after being fully informed of the efficacy and risks of tolvaptan, i.e. Samsca is not a drug to cure disease; serious hepatic dysfunction may occur; appropriate hydration and periodic monitoring by blood testing etc. are required, etc.
- Cases of serious hepatic dysfunction associated with Samsca have been reported. Liver function tests including serum transaminases and total bilirubin must be performed prior to treatment initiation and after up-titration, and liver function tests should be performed at least monthly during treatment. If any abnormalities are detected, treatment should be discontinued immediately and appropriate measures should be taken.

Important Precautions

Serious hepatic dysfunction may occur following treatment with Samsca. Prior to treatment initiation, patients should be fully informed of such adverse reactions and instructed to see a physician promptly if they have symptoms.

5.(2) Risk associated with an increase in serum sodium levels

The following conclusions by PMDA were supported by the expert advisors:

In accordance with the requirements of the TEMPO trial, monthly monitoring of serum sodium should be advised in the "WARNINGS" section and the "Important Precautions" section. If hyponatraemia is detected, its cause should be identified and serum sodium should be corrected. Whether tolvaptan should be indicated should also be determined carefully. Then, the patient should be more closely monitored during treatment with tolvaptan.

Taking also account of the above discussion, PMDA instructed the applicant to include the following statements in the package insert and the applicant responded appropriately.

WARNINGS

Adverse drug reactions such as dehydration and hypernatraemia, associated with excessive aquaresis, may

occur, especially after the initiation or up-titration of Samsca. At least, Samsca should be initiated in a hospital and guidance regarding the need for appropriate hydration should be provided. Serum sodium should be measured at least monthly during treatment with Samsca.

Important Precautions

- Hypernatraemia may occur. Serum sodium should be measured at each visit during the initial dose titration phase and then at least monthly during treatment with Samsca. If abnormalities are detected, the dose should be reduced or discontinued.
- Serum sodium should be measured prior to treatment initiation. If hyponatraemia is detected, the cause of hyponatraemia should be identified and serum sodium should be corrected, as rapid increases in serum sodium can cause central pontine myelinolysis. Whether Samsca should be indicated should be determined carefully. Then, treatment should be initiated only if the use of Samsca is considered appropriate.

5.(3) Risk associated with the aquaretic effects of tolvaptan

The following conclusions by PMDA were supported by the expert advisors:

With respect to aquaretic adverse events such as dehydration, dizziness, and syncope reported in the tolvaptan group in the TEMPO trial etc., the incidence itself was high (aquaretic adverse events tended to frequently occur especially in the early phase of treatment) and serious or severe events were also observed. Therefore, adequate attention should be paid to the possible occurrence of aquaretic adverse events. The principles of warnings/precautions for adverse events related to the aquaretic effects of tolvaptan in the draft package insert presented by the applicant, are acceptable.

5.(4) Risk of hyperkalaemia

The following conclusions by PMDA were supported by the expert advisors:

The results from the TEMPO trial etc. showed no obvious trend towards an increased risk for hyperkalaemia for tolvaptan compared to placebo. However, the aquaretic effects of tolvaptan may cause hyperkalaemia, and it is expected that antihypertensives which may cause hyperkalaemia, such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, will be commonly used with tolvaptan in ADPKD patients with hypertension and that the risk of hyperkalaemia related to renal impairment will be further increased along with the progression of ADPKD. Thus, adequate attention should be paid to the risk of hyperkalaemia. The precautionary statements about hyperkalaemia in the draft package insert presented by the applicant are appropriate.

5.(5) Risk of gout/hyperuricaemia

The following conclusion by PMDA was supported by the expert advisors:

The TEMPO trial and other clinical trials indicate the risk of gout/hyperuricaemia associated with tolvaptan. Compared with patients treated with tolvaptan under the approved indications who have already been shown to be at risk of increased blood uric acid, ADPKD patients are treated with tolvaptan at high doses. Thus, the following statement in the “Important Precautions” section of the package insert is

appropriate: “Blood uric acid concentrations may be increased due to decreased uric acid clearance by the kidney following Samsca treatment. Attention should be paid to blood uric acid concentrations during treatment with Samsca.”

5.(6) Need for patient management in a hospital for administration of tolvaptan

PMDA has concluded as follows:

As long as tolvaptan is contraindicated in “patients who cannot sense thirst or who have difficulty in ingestion of fluid” and adequate patient education is provided prior to the initiation of tolvaptan treatment, it is not essential to initiate and up-titrate tolvaptan in ADPKD patients in a hospital.

The above conclusion by PMDA was discussed and the expert advisors made the following comments:

- PMDA’s conclusion is appropriate.
- Whether or not patient guidance is appropriately understood greatly depends on individual patients and their families. Thus, at least, treatment should be initiated in a hospital to ensure monitoring and patient guidance.
- Even for the approved indications, it is advised that tolvaptan should be initiated in a hospital as a rule. Compared with patients treated with tolvaptan under the approved indications, ADPKD patients are treated with tolvaptan at higher doses. Thus, tolvaptan should be used more carefully.

In the end, the expert advisors agreed that at least, tolvaptan should be initiated in a hospital.

Based on the above discussion, PMDA instructed the applicant to include in the “WARNINGS” section a statement to the effect that at least Samsca should be initiated in a hospital. The applicant responded appropriately.

5.(7) Risk associated with long-term treatment with tolvaptan

The following conclusion by PMDA was supported by the expert advisors:

Regarding the long-term safety of tolvaptan, only the information on up to 3 years of treatment has been obtained at present. Thus, it is necessary to collect post-approval information on the long-term safety of tolvaptan beyond 3 years.

6. Draft risk management plan

Based on the review described in “3.(iii).B.(6) Post-marketing investigations” of the Review Report (1) and the above-mentioned comments from the expert advisors, PMDA has concluded that a post-marketing surveillance study should include all ADPKD patients treated with tolvaptan and investigate the following issues additionally.

- Long-term safety
- Safety and efficacy in patients with more advanced ADPKD (CLcr <60 mL/min) than the population of the TEMPO trial
- Effects on hepatic and pancreatic cysts and the occurrence of cerebral aneurysms and cerebral

haemorrhage
- Renal function and kidney volume over time and the length of time to renal failure or dialysis (including clinical course after discontinuation of tolvaptan)

PMDA instructed the applicant to investigate the above issues via post-marketing surveillance. The applicant submitted an appropriate draft post-marketing surveillance plan [Table 19].

The expert advisors also agreed with the following conclusions by PMDA, as described in "5.(1) Risk of hepatic dysfunction":
Considering the incidence of hepatic dysfunction associated with tolvaptan and the seriousness of potential hepatic dysfunction, tolvaptan should be prescribed only by physicians who are familiar with the safety and efficacy profiles of tolvaptan. The use of tolvaptan should be limited to patients who have provided informed consent after being informed of the benefits and risks of tolvaptan and precautions during treatment with tolvaptan.

Accordingly, PMDA instructed the applicant to consider measures to ensure proper use of tolvaptan after approval.

The applicant responded as follows:
The following measures will be taken in order to ensure that tolvaptan is prescribed only by physicians who are familiar with the pathology of ADPKD and the safety and efficacy profiles of tolvaptan. First, physicians who are likely to prescribe tolvaptan for ADPKD will be identified in advance and information on proper use will be communicated to them immediately after approval. Then, they will be requested to attend learning sessions, be certified, and obtain written informed consent from patients prior to the initiation of tolvaptan treatment for ADPKD. Prescribing physicians will be requested to attend on-line learning sessions (e-Learning) to ensure that they prescribe tolvaptan after fully understanding the pathology of ADPKD, the intended patient population, the profiles of tolvaptan, the importance of liver function tests and serum sodium measurement, and the need to obtain written informed consent from patients prior to treatment initiation. In addition, the pharmacies of all hospitals and dispensing pharmacies to which tolvaptan will be delivered will be requested to verify that prescribing physicians are certified, prior to dispensing prescriptions of tolvaptan for ADPKD patients.

Although the details need to be discussed and it is essential to prepare a system for proper use before approval, PMDA has concluded that an outline of the measures to ensure proper use after approval presented by the applicant is appropriate and accepted the applicant's response.

Based on the above discussion, PMDA has concluded that the safety specification and efficacy considerations as shown in Table 17 should be included in the current risk management plan and that additional pharmacovigilance activities [see Table 19 for a draft drug use-results survey (all-case survey) plan] and risk minimization activities as shown in Table 18 should be conducted.

Table 17. Safety specification and efficacy considerations of risk management plan

Safety specification		
Important identified risks	Important potential risks	Important missing information
・Thirst ・Hypernatraemia ・Dehydration ・Thrombosis/Thromboembolism ・Renal failure/Renal impairment ・Hepatic dysfunction ・Gout/Hyperuricaemia ・Dizziness ・Syncope/Loss of consciousness ・Hyperkalaemia ・Diabetes mellitus, Hyperglycaemia ・Glaucoma ・Hepatic encephalopathy ・Shock, Anaphylaxis ・Excessive fall in blood pressure, Ventricular fibrillation, Ventricular tachycardia	・Central pontine myelinolysis ・Skin neoplasms (basal cell carcinoma, malignant melanoma) ・Drug interactions (coadministration with CYP3A4 inhibitors) ・Gastrointestinal haemorrhage	・Effects on mid- and long-term prognosis (heart failure) ・Patients with serum sodium <125 mEq/L (heart failure, hepatic cirrhosis) ・Use with existing therapies (heart failure, hepatic cirrhosis) ・Patients with renal impairment (heart failure, hepatic cirrhosis) ・Patients with advanced ADPKD (CLcr <60 mL/min) (ADPKD) ・Elderly (ADPKD) ・Long-term safety (ADPKD)
Efficacy considerations		
・Efficacy of reduced dose (heart failure, hepatic cirrhosis) ・Long-term efficacy (ADPKD) ・Patients with advanced ADPKD (CLcr <60 mL/min) (ADPKD)		

Table 18. Summary of additional pharmacovigilance activities and risk minimization activities in risk management plan for the additional indication

Additional pharmacovigilance activities	Additional risk minimization activities
・Early Post-marketing Phase Vigilance (EPPV) for ADPKD ・Drug use-results survey for ADPKD (all-case survey) ・ADPKD post-marketing clinical study [a]	・EPPV for ADPKD ・Develop and provide materials for healthcare professionals ・Develop and provide materials for patients ・Publish data on the incidences of adverse drug reactions etc. on the company's website ・Ensure the use of tolvaptan by physicians with expertise/experience ・Promote careful selection of patients to be treated ・Promote explanation to patients and understanding prior to treatment initiation ・Promote certain tests

a: After tolvaptan is approved, an extension study will be reclassified as a post-marketing clinical study and continued until tolvaptan will become available at each medical institution.

Table 19. Outline of draft drug use-results survey (all-case survey) plan

Objective	To evaluate the safety and efficacy of tolvaptan in routine clinical settings
Survey method	All-case registration
Patients to be surveyed	Patients with autosomal dominant polycystic kidney disease
Survey period	8 years
Observation period	From treatment initiation until the end of survey period
Planned sample size	1600 patients
Main information to be collected	・Patient information (age, body weight, height, etc.) ・Patient characteristics (age of diagnosis of ADPKD, kidney volume, renal function, complications, medical history, etc.) ・Administration of tolvaptan (daily dose, start date, end date, reason for dose change/interruption) ・Use of tolvaptan (ongoing; completion; discontinuation, reason for discontinuation) ・Kidney volume, renal function, and clinical symptoms of ADPKD over time (kidney volume, renal function, blood pressure, albuminuria, renal pain, etc.) ・Concomitant medications and therapies ・Adverse events (name of event, date of onset, seriousness, outcome, date of outcome assessment, causality to tolvaptan, etc.)

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

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

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA has concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

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

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-01, 5.3.5.2-02, 5.3.5.2-03, 5.3.5.2-04). As a result, failure to retain some of the source data (MRI images) appropriately and failure to document the communication of the information to subjects and the confirmation of their willingness to continue participation in the trial prior to retesting that was not mentioned in the written information were found at some trial sites. Although these findings requiring improvement were noted, the relevant cases were handled appropriately. Therefore, PMDA has concluded that the clinical trials as a whole were conducted in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that tolvaptan may be approved for the indication and dosage and administration as shown below, with the following conditions. Since tolvaptan has been designated as an orphan drug for the indication of ADPKD, its re-examination period should be 10 years for the indications and dosage and administration proposed in the current application.

[Indications]

Samsca Tablets 7.5 mg

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

・Treatment of fluid retention in hepatic cirrhosis when treatment with other diuretics including loop diuretics is not sufficiently effective.

・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.

Samsca Tablets 15 mg

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

・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.

Samsca Tablets 30 mg

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.

(Underline denotes new additions proposed in the current application and double underline denotes additions proposed as of September 13, 2013 after the submission of the current application.)

[Dosage and Administration]

Samsca Tablets 7.5 mg

・For the treatment of fluid retention in heart failure

The usual adult dosage of tolvaptan is 15 mg once daily administered orally.

・For the treatment of fluid retention in hepatic cirrhosis

The usual adult dosage of tolvaptan is 7.5 mg once daily administered orally.

・For slowing the progression of autosomal dominant polycystic kidney disease

The usual initial adult dosage of tolvaptan is 60 mg per day as a split-dose oral regimen of 45 mg/15 mg (morning/evening). When tolvaptan is tolerated at 60 mg per day for ≥1 week, the initial dose may be increased to 90 mg (60 mg/30 mg) per day and then to 120 mg (90 mg/30 mg) per day in a step-wise manner with a ≥1-week interval between titrations. The dose may be adjusted, as appropriate, based on tolerability, but the maximum dose should not exceed 120 mg per day.

Samsca Tablets 15 mg

・For the treatment of fluid retention in heart failure

The usual adult dosage of tolvaptan is 15 mg once daily administered orally.

・For slowing the progression of autosomal dominant polycystic kidney disease

The usual initial adult dosage of tolvaptan is 60 mg per day as a split-dose oral regimen of 45 mg/15 mg

(morning/evening). When tolvaptan is tolerated at 60 mg per day for ≥1 week, the initial dose may be increased to 90 mg (60 mg/30 mg) per day and then to 120 mg (90 mg/30 mg) per day in a step-wise manner with a ≥1-week interval between titrations. The dose may be adjusted, as appropriate, based on tolerability, but the maximum dose should not exceed 120 mg per day.

Samsca Tablets 30 mg

The usual initial adult dosage of tolvaptan is 60 mg per day as a split-dose oral regimen of 45 mg/15 mg (morning/evening). When tolvaptan is tolerated at 60 mg per day for ≥1 week, the initial dose may be increased to 90 mg (60 mg/30 mg) per day and then to 120 mg (90 mg/30 mg) per day in a step-wise manner with a ≥1-week interval between titrations. The dose may be adjusted, as appropriate, based on tolerability, but the maximum dose should not exceed 120 mg per day.

(Underline denotes new additions proposed in the current application and double underline denotes additions proposed as of September 13, 2013 after the submission of the current application.)

[Conditions for approval]

Samsca Tablets 7.5 mg and Samsca Tablets 15 mg to be used for slowing the progression of autosomal dominant polycystic kidney disease in patients with an increased kidney volume and a rapid rate of kidney volume increase

The applicant is required to:

1. Take necessary measures prior to marketing to ensure that Samsca is prescribed only by physicians who fully understand the treatment of autosomal dominant polycystic kidney disease and the risks of Samsca and who comply with the proper use of Samsca with regard to selection of eligible patients and periodic monitoring of liver function and serum sodium concentrations and that medical institutions/pharmacies verify that Samsca has been prescribed by a relevant physician, prior to dispensing Samsca.
2. Conduct a post-marketing surveillance study, which will cover all patients treated with Samsca, until data from a specific number of patients are collected, in order to collect data on the safety and efficacy of Samsca as early as possible and to take necessary measures to ensure the proper use of Samsca. Periodically report the collected results.

Samsca Tablets 30 mg

The applicant is required to:

1. Take necessary measures prior to marketing to ensure that Samsca is prescribed only by physicians who fully understand the treatment of autosomal dominant polycystic kidney disease and the risks of Samsca and who comply with the proper use of Samsca with regard to selection of eligible patients and periodic monitoring of liver function and serum sodium concentrations and that medical institutions/pharmacies verify that Samsca has been prescribed by a relevant physician, prior to dispensing Samsca.
2. Conduct a post-marketing surveillance study, which will cover all patients treated with Samsca, until data from a specific number of patients are collected, in order to collect data on the safety and efficacy

of Samsca as early as possible and to take necessary measures to ensure the proper use of Samsca. Periodically report the collected results.

(Underline denotes new additions.)