28 June 2018
EMA/508732/2018
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Jinarc

International non-proprietary name: tolvaptan

Procedure No. EMEA/H/C/002788/II/0009

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# Table of contents

**1. Background information on the procedure ..... 3**
1.1. Type II variation ..... 3
1.2. Steps taken for the assessment of the product ..... 4

**2. Scientific discussion ..... 4**
2.1. Introduction ..... 4
2.2. Non-clinical aspects ..... 5
2.3. Clinical aspects ..... 6
2.3.1. Introduction ..... 6
2.4. Clinical efficacy ..... 6
2.4.1. Main study ..... 6
2.4.2. Discussion on clinical efficacy ..... 16
2.4.3. Conclusions on the clinical efficacy ..... 18
2.5. Clinical safety ..... 18
2.5.1. Discussion on clinical safety ..... 21
2.5.2. Conclusions on clinical safety ..... 22
2.5.3. PSUR cycle ..... 22
2.6. Risk management plan ..... 22
2.7. Update of the Product information ..... 32
2.7.1. User consultation ..... 32

**3. Benefit-Risk Balance ..... 32**

**4. Recommendations ..... 33**

**5. EPAR changes ..... 34**

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Otsuka Pharmaceutical Europe Ltd submitted to the European Medicines Agency on 4 January 2018 an application for a variation.

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, II and IIIB |

Extension of Indications based on the results of a completed Post Authorisation Efficacy Study (PAES, Trial 156-13-210) as mandated by Annex II of the Product Information with tolvaptan (ANX 006). Trial 156-13-210 is a Phase 3b, Multi-centre, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease.

Updates to SmPC Sections 4.1, 4.8 (to add 'abdominal pain' to the table of adverse events and present the data in line with QRD recommendations) and 5.1 are being proposed. The Package Leaflet is updated in accordance. Minor additional editorial changes to the PI were also carried out.

Version 13.2 of the RMP was submitted, updated to reflect the study results.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0347/2017 on the agreement of a paediatric investigation plan (PIP).

However, the PIP P/0347/2017 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

### *Scientific advice*

The applicant did not seek Scientific Advice for this procedure at the CHMP.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Greg Markey Co-Rapporteur: Daniela Melchiorri

| Timetable | Actual dates |
|---|---|
| Submission date | 4 January 2018 |
| Start of procedure: | 27 January 2018 |
| CHMP Rapporteur Assessment Report | 23 March 2018 |
| PRAC Rapporteur Assessment Report | 23 March 2018 |
| PRAC members comments | 4 April 2018 |
| Updated PRAC Rapporteur Assessment Report | 5 April 2018 |
| PRAC Outcome | 12 April 2018 |
| CHMP members comments | 16 Apr 2018 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 19 April 2018 |
| Request for supplementary information (RSI) | 26 April 2018 |
| PRAC Rapporteur Assessment Report | 01 June 2018 |
| PRAC members comments | 06 June 2018 |
| Updated PRAC Rapporteur Assessment Report | 12 June 2018 |
| CHMP Rapporteur Assessment Report | 13 June 2018 |
| PRAC Outcome | 14 June 2018 |
| CHMP members comments | 18 June 2018 |
| Updated CHMP Rapporteur Assessment Report | 19 June 2018 |
| Opinion | 28 June 2018 |

# 2. Scientific discussion

## *2.1. Introduction*

Tolvaptan is a vasopressin receptor antagonist and was approved in 2015 for the orphan indication: treatment of autosomal dominant polycystic kidney disease (ADPKD). Of note, tolvaptan tablets 15 and 30 mg also have a separate MA under a different brand name (Samsca, EU/1/09/539/001-004) authorised on 3 August 2009 for the *treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion*.

The pivotal trial in ADPKD [TEMPO 3:4] was a 3 year randomised, placebo controlled trial comparing long-term safety and efficacy of oral split dose tolvaptan regimens (titrated between 60 mg/day and 120

mg/day) to placebo, in 1445 adults with ADPKD. The primary objective was to evaluate the long-term efficacy using change in total kidney volume (TKV). The rate of TKV increase over 3 years was significantly less for tolvaptan-treated subjects than for subjects receiving placebo: 2.80% per year vs 5.51% per year, respectively. The key secondary composite endpoint (ADPKD progression) was time to multiple clinical progression events of:

- worsening kidney function - defined as a persistent [reproduced over at least 2 weeks] 25% reduction in reciprocal serum creatinine during treatment [from end of titration to last on-drug visit]
- medically significant kidney pain - defined as requiring prescribed leave, last-resort analgesics, narcotic and anti-nociceptive, radiologic or surgical interventions
- worsening hypertension
- worsening albuminuria.

The relative rate of ADPKD-related events was decreased by 13.5% in tolvaptan-treated patients, (HR, 0.87; 95% CI, 0.78 to 0.97; p=0.0095). The result of the key secondary composite endpoint was primarily attributed to effects on worsening kidney function and medically significant kidney pain. The renal function events were 61.4% less likely for tolvaptan compared with placebo (hazard ratio, 0.39; 95% CI, 0.26 to 0.57; nominal p=0.007). In contrast, there was no effect of tolvaptan on either progression of hypertension or albuminuria. The efficacy assessment and extrapolation to long term outcomes was largely based on the surrogate parameter TKV. Furthermore, the study population in the pivotal trial had a relatively large renal volume consistent with rapid cystic growth, but at least 50% preservation of renal function.

Patients with early, but rapidly progressive disease, were hoped to benefit from therapy and to have a prognosis for observable changes or outcomes during a 3-year trial. More extensive long term data and data on patients in later stages of the disease were therefore needed to confirm efficacy assumption based on hard clinical outcomes. This was reflected in two post-authorisation efficacy studies at the time of Jinarc's approval.

The first was study 156-08-271 [TEMPO 4:4], which was assessed in procedure EMEA/H/C/002788/II/0006. This 2 year open-label extension to the pivotal trial [total of 5 years] showed tolvaptan continued to have an effect on the rate of renal function decline over several more years. Longer term data are not currently available to show whether long-term therapy with tolvaptan continues to slow the rate of renal function decline and affect clinical outcomes of ADPKD, including delay in the onset of end-stage renal disease.

The second post-marketing commitment aimed to further define the efficacy of tolvaptan in patients with more advanced renal dysfunction, on a primary endpoint related to estimated glomerular filtration rate (eGFR) rather than TKV. The company was required to submit the final report of study 156-13-210 by February 2018. This is the subject of the current variation assessment. The results have been published [Torres et al, N Engl J Med 2017; 377:1930-1942, REPRISE study].

## *2.2. Non-clinical aspects*

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

### GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

| | |
|---|---|
| Clinical trial 156-13-210 | Phase 3b, Multi-centre, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease Between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease. |

This is a completed Post-Authorisation Efficacy Study (PAES) as mandated by the CHMP at the time of initial approval of tolvaptan for the use in adults to treat autosomal dominant polycystic kidney disease (ADPKD).

## *2.4. Clinical efficacy*

### 2.4.1. Main study

### Title of Study

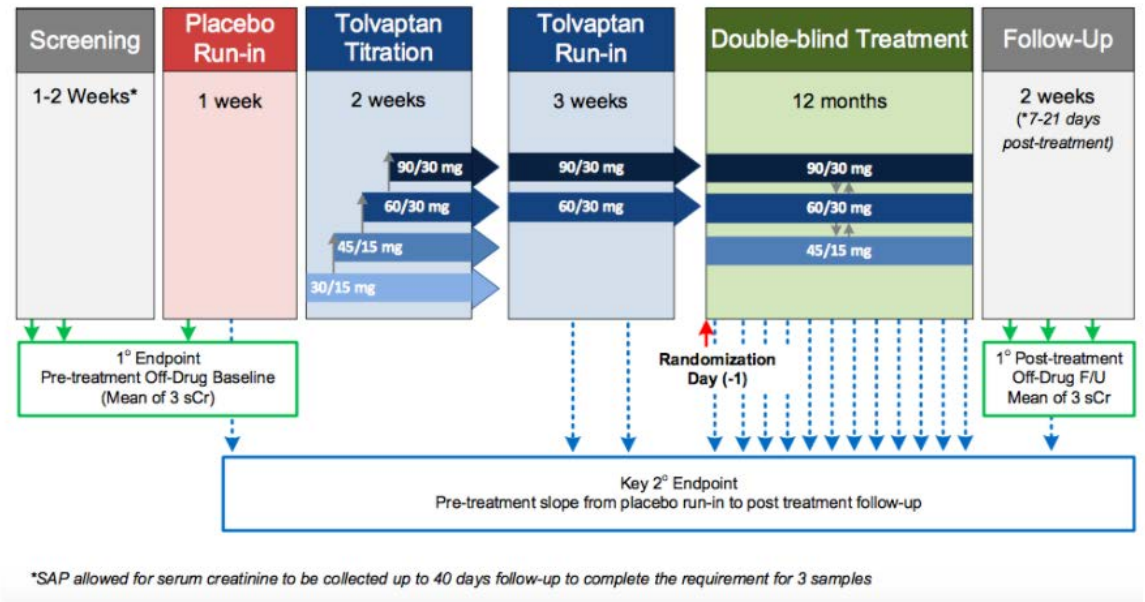
*Clinical trial 156-13-210:* Phase 3b, Multi-centre, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease Between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease.

### *Methods*

The design and objectives of study 156-13-21- were noted already during the initial MAA for Jinarc. The study was a Phase 3b, multi-centre, randomized-withdrawal, placebo-controlled, double-blind, parallel-group trial to compare the efficacy and safety of tolvaptan (45 to 120 mg/day, Split-dose) in subjects with chronic kidney disease between late stage 2 to early stage 4 due to ADPKD. The trial employed a pre-randomization phase comprising placebo run-in, tolvaptan treatment titration, and tolvaptan run-in periods. The titration and run-in periods were designed to test tolerability, exclude subjects unlikely to tolerate tolvaptan's aquaretic effects prior to the randomization period, minimize post-randomization withdrawal, and enrich the trial population with patients who might benefit from long-term treatment. The placebo run-in period was used to establish a pre-randomization baseline of eGFR for each treatment assignment and facilitate straightforward calculation of eGFR slope for all subjects, the key secondary endpoint. After randomisation there was a 1 year double-blind treatment phase, with subjects then

eligible for an open-label extension phase. Tolvaptan, or matching placebo, was administered at 60/30 or 90/30 mg, as split doses, with down-titrations to 45/15 and 30/15 mg as needed for tolerability

Figure 1: Study design




*SAP allowed for serum creatinine to be collected up to 40 days follow-up to complete the requirement for 3 samples

## Study participants

Subjects were required to meet the following inclusion criteria:

1. Male and female subjects 18 to 55 years of age (inclusive) with eGFR between 25 and 65 mL/min/1.73 $m^2$
2. Male and female subjects 56 to < 66 years of age with eGFR between 25 and 44 mL/min/1.73 $m^2$ with evidence of ADPKD progression, i.e., eGFR decline of > 2.0 mL/min/1.73 $m^2$ /year, based on historical eGFR data and medical monitor discretion
3. Male and female subjects who were tolvaptan naïve
4. Diagnosis of ADPKD by modified Pei-Ravine criteria

Exclusion criteria included the need for chronic diuretic use, hepatic impairment or liver function abnormalities other than that expected for ADPKD, advanced diabetes and subjects with additional significant renal disease not due to ADPKD.

## Treatments

See above, section Methods.

## Objectives

This trial was conducted to extend the understanding of the efficacy and safety of tolvaptan treatment in autosomal dominant polycystic kidney disease (ADPKD) subjects with late Stage 2 to early Stage 4 chronic kidney disease (CKD). Focusing on the estimated glomerular filtration rate (eGFR) calculated by the CKD-Epidemiology (CKD EPI) formula (hereafter referred to as “eGFR”), this trial was expected to

provide kidney function data that were complementary to the data demonstrating the benefits previously observed primarily in ADPKD subjects with earlier stages of disease.

## Outcomes/endpoints

The primary objective was the treatment difference in the change of eGFR, as calculated using Chronic Kidney Disease-Epidemiology (CKD-EPI) formula, from pre-treatment baseline to post-treatment follow-up, divided by each subject's trial duration. The pre and post treatment eGFR results were each calculated from the mean of 3 serum creatinine measurements. The secondary efficacy endpoint was the treatment difference in annualized slope of eGFR calculated for individual subjects using eGFR data observed in the placebo run-in, tolvaptan run-in (not including tolvaptan titration), double-blind treatment, and post-treatment follow-up (not including data collected in the first week after the last IMP dose) periods.

## Sample size

Based on a Mixed Model Repeated Measurements analysis of the non-Japanese CKD stage 3 subjects from trial 156-04-251, the treatment difference in renal function at Month 12 was 1.07. Expected intra-subject variance was 14.2 and inter-subject variance 28.05 at Month 12. With 3 repeated measures at pre-treatment baseline and post-treatment follow-up, respectively, the power calculation estimated that, for a 2-sided alpha set at 0.05 for a power of 90%, and with an assumption of 10% dropout rate in the trial, a total sample size of approximately 1300 subjects was needed.

## Randomisation

Randomization was 1:1, tolvaptan to placebo, and utilised an interactive voice response system to ensure appropriate stratification. Subjects were be stratified by their baseline eGFR at a threshold of ≤ 45 or > 45 mL/min/1.73m2 and by age (≤ 55 or > 55 years old). Subjects were also stratified by three TKV criteria (≤ 2000 mL, > 2000 mL, or unknown).

## Blinding (masking)

Placebo was administered in a form identical to the corresponding dose of tolvaptan tablets. Following the screening period, there followed a placebo run-in period (1 week), a tolvaptan titration period (2 weeks), and a tolvaptan run-in period (3 weeks). Subjects were aware they would receive placebo or active treatment during the treatment phase, but they would not know which. The subjects were not told that there was a separate run-in phase and randomization phase, and were not told when formal randomization would occur.

## Statistical methods

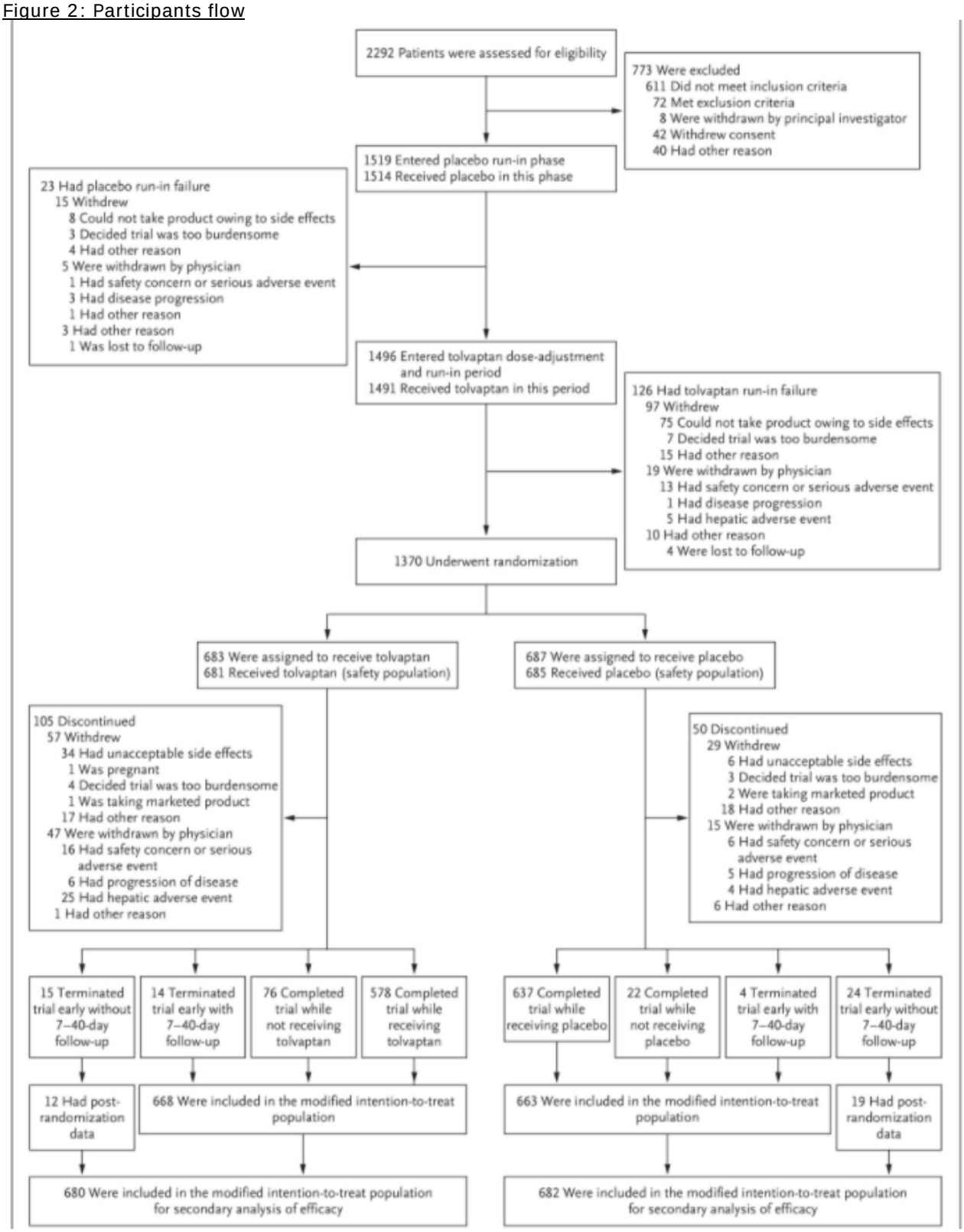
The end points of the trial were ordered hierarchically and tested sequentially with gatekeeping procedures; if the primary end point was found to be significant, analysis of the secondary end point would be justified. A modified intention-to-treat population or full analysis set was used for the analysis of the primary end point. All patients with any data to inform the primary or secondary end points or safety were included in the modified intention-to-treat and safety populations. The primary end point was analysed by means of a weighted analysis of covariance with trial group and randomization stratification factors as factor and baseline covariates. The key secondary end point was also assessed in the modified

intention-to-treat population and was analysed with the use of a linear mixed-effect model with effects of time (as a continuous variable), trial group, interaction of time and trial group, acute hemodynamic effect, stratification factors at randomization, and baseline covariate (of the primary end point) to fit the estimated GFR data. This trial's estimand was the difference in outcome improvement if all subjects tolerated and adhered to their treatment. Data missing at random (MAR) was assumed in the primary analysis. A sensitivity analysis was provided to address the concern of data missing not at random (MNAR).

## *Results*

## Participant flow

Figure 2: Participants flow



## Recruitment

A total of 2292 subjects were screened. After 2 weeks of screening, 1519 subjects entered the 6-week single-blind pre-randomization phase, and subsequently 1370 subjects were randomized and treated during the 12-month double-blind period. Subjects who were randomized, took IMP up to Month 12 (-7/+2 days), and completed some or all of their required trial visits/assessments to the end of the trial (including the Month 12 visit and at least 1 follow-up serum creatinine assessment) were defined as "On-treatment completers."

Subjects who needed to discontinue treatment prior to Day 358 (or never began treatment), and completed some or all of their required trial visits/assessments to the end of the trial (including the Month 12 visit and at least 1 follow-up serum creatinine assessment) were defined as "Off-treatment completers." Subjects who were randomized, took IMP (or never began treatment), but did not complete the Month 12 visit and at least 1 end-of-treatment follow-up serum creatinine assessment were defined as "Non-completers." The percentage of on-treatment completers (i.e., randomized subjects who received IMP up to Month 12 and completed some or all of their required trial assessments to the end of the trial, including the Month 12 visit and ≥ 1 follow-up serum creatinine assessment) was 84.6% in the tolvaptan arm and 92.7% in the placebo arm. The percentage of "off-treatment completers" (i.e., randomized subjects who took IMP, but discontinued treatment prior to Day 358 or never began treatment, and completed some or all assessments to the end of the trial, including the Month 12 visit and ≥ 1 follow-up serum creatinine assessment) was 11.1% in the tolvaptan arm and 3.2% in the placebo arm. Based on these data, 96% of patients in both groups were considered to complete the study; approximately 4% in each treatment group were non-completers.

The difference between groups in time to discontinuation from the IMP was statistically significant ($p < 0.0001$). Among the 6.3% of subjects who chose to discontinue the IMP prior to Month 12, the reason was most frequently that the IMP was not tolerable (8.3% in the tolvaptan group; 0.9% in the placebo group). For the 4.5% of subjects for whom the physician decided to withdraw IMP treatment, the reason was most frequently due to hepatic AEs (3.7% in the tolvaptan arm; 0.6% in the placebo arm). In both treatment arms, the percent of subjects lost to follow-up was low (0.1% in the tolvaptan arm; 0.6% in the placebo arm).

## Conduct of the study

Note that the country-specific amendment for France added the following as an exclusion criterion: Tolvaptan is contraindicated in patients who are known to have hypersensitivity to tolvaptan or 1 of the excipients, are hypovolemic (volume depletion), and cannot perceive thirst. Additionally, subjects with baseline screening abnormalities of serum sodium concentrations (hyponatremia or hypernatremia) could not be enrolled in the trial until these abnormalities resolved, and then the subjects were required to be monitored accordingly.

## Baseline data

Baseline demographics and CKD characteristics are shown in the table below, for the randomised population. Subjects were most frequently in CKD Stage 3b (45.1%), followed by Stage 3a (30.0%), Stage 4 (19.5%), and Stage 2 (5.2%). The majority of subjects (64.2%) had eGFR (CKD-EPI) ≤ 45 mL/min/1.73 m2 . For most subjects (80.4%) the TKV was not known.

Table 1: Baseline Demographics and CKD Characteristics - Randomized Population

| Variable | | Tolvaptan (N=683) | Placebo (N=687) | Total (N=1370) |
|---|---|---|---|---|
| **Age [years]** | | | | |
| | Mean (SD) | 47.3 (8.2) | 47.2 (8.2) | 47.3 (8.2) |
| | Range | 23, 65 | 21, 65 | 21, 65 |
| **Gender** | | | | |
| Male | n (%) | 347 (50.8 ) | 333 (48.5 ) | 680 (49.6 ) |
| Female | n (%) | 336 (49.2 ) | 354 (51.5 ) | 690 (50.4 ) |
| **Height [cm]** | | | | |
| | Mean (SD) | 173.7 (10.4) | 172.8 (10.2) | 173.3 (10.3) |
| | Range | 134.0, 206.0 | 145.0, 205.0 | 134.0, 206.0 |
| **Weight [kg]** | | | | |
| | Mean (SD) | 84.6 (19.9) | 83.2 (19.3) | 83.9 (19.6) |
| | Range | 46.0, 227.0 | 41.9, 193.6 | 41.9, 227.0 |
| **Body Mass Index (kg/m$^2$)** | | | | |
| | Mean (SD) | 28.0 (5.8) | 27.7 (5.6) | 27.8 (5.7) |
| | Range | 17.1, 78.5 | 16.5, 52.0 | 16.5, 78.5 |
| **Race** | | | | |
| White | n (%) | 626 (91.7 ) | 632 (92.0 ) | 1258 (91.8 ) |
| Black or African American | n (%) | 25 (3.7 ) | 23 (3.3 ) | 48 (3.5 ) |
| American Indian or Alaska Native | n (%) | 3 (0.4 ) | 1 (0.1 ) | 4 (0.3 ) |
| Asian | n (%) | 22 (3.2 ) | 19 (2.8 ) | 41 (3.0 ) |
| Native Hawaiian or Other Pacific Islander | n (%) | 0 (0.0 ) | 0 (0.0 ) | 0 (0.0 ) |
| Other | n (%) | 7 (1.0 ) | 12 (1.7 ) | 19 (1.4 ) |
| **Ethnicity** | | | | |
| Hispanic or Latino | n (%) | 44 (6.4 ) | 35 (5.1 ) | 79 (5.8 ) |
| Not Hispanic or Latino | n (%) | 632 (92.5 ) | 647 (94.2 ) | 1279 (93.4 ) |
| Unknown | n (%) | 7 (1.0 ) | 5 (0.7 ) | 12 (0.9 ) |
| **CKD Stage** | | | | |
| CKD 2 | n (%) | 32 (4.7 ) | 39 (5.7 ) | 71 (5.2 ) |
| CKD 3a | n (%) | 209 (30.6 ) | 202 (29.4 ) | 411 (30.0 ) |
| CKD 3b | n (%) | 303 (44.4 ) | 315 (45.9 ) | 618 (45.1 ) |
| CKD 4 | n (%) | 139 (20.4 ) | 128 (18.6 ) | 267 (19.5 ) |
| UNKNOWN | n (%) | 0 (0.0 ) | 3 (0.4 ) | 3 (0.2 ) |
| **Age** | | | | |
| ≤ 55 years old | n (%) | 585 (85.7) | 588 (85.6) | 1173 (85.6) |
| > 55 years old | n (%) | 98 (14.3) | 99 (14.4) | 197 (14.4) |
| **eGFR (CKD-EPI)** | | | | |
| ≤ 45 ml/min/1.73 m² | n (%) | 442 (64.7) | 438 (63.8) | 880 (64.2) |
| > 45 ml/min/1.73 m² | n (%) | 241 (35.3) | 249 (36.2) | 490 (35.8) |
| **Total kidney volume** | | | | |
| ≤ 2000 mL | n (%) | 76 (11.1) | 73 (10.6) | 149 (10.9) |
| > 2000 mL | n (%) | 60 ( 8.8) | 60 ( 8.7) | 120 ( 8.8) |
| **Variable** | | **Tolvaptan (N=683)** | **Placebo (N=687)** | **Total (N=1370)** |
| Not known | n (%) | 547 (80.1) | 554 (80.6) | 1101 (80.4) |

SD = standard deviation.

Note: CKD stages were defined as follows: Stage 1 = ≥ 90 mL/min/1.73 m$^2$; Stage 2 = 60-89 mL/min/1.73 m$^2$; Stage 3a = 45-59 mL/min/1.73 m$^2$; Stage 3b = 30-44 mL/min/1.73 m$^2$; Stage 4 = 15-29 mL/min/1.73 m$^2$. The 3 subjects with CKD stage of "unknown" were randomized based on their eGFR level (rate blank method).

Source: CT-3.1.1, CT-3.1.4, and CT-3.2.1.

## Numbers analysed

A total of 2292 subjects were screened. After 2 weeks of screening, 1519 subjects entered the 6-week single-blind pre-randomization phase, and subsequently 1370 subjects were randomized and treated during the 12-month double-blind period.

## Outcomes and estimation

***Primary efficacy endpoint***

The primary efficacy endpoint was the treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, annualized (divided) by each subject's trial duration. The primary endpoint results demonstrate a statistically significant difference ($p < 0.0001$) in favour of tolvaptan of 1.271 mL/min/1.73 $m^2$ /year (95% CI 0.859 to 1.684).

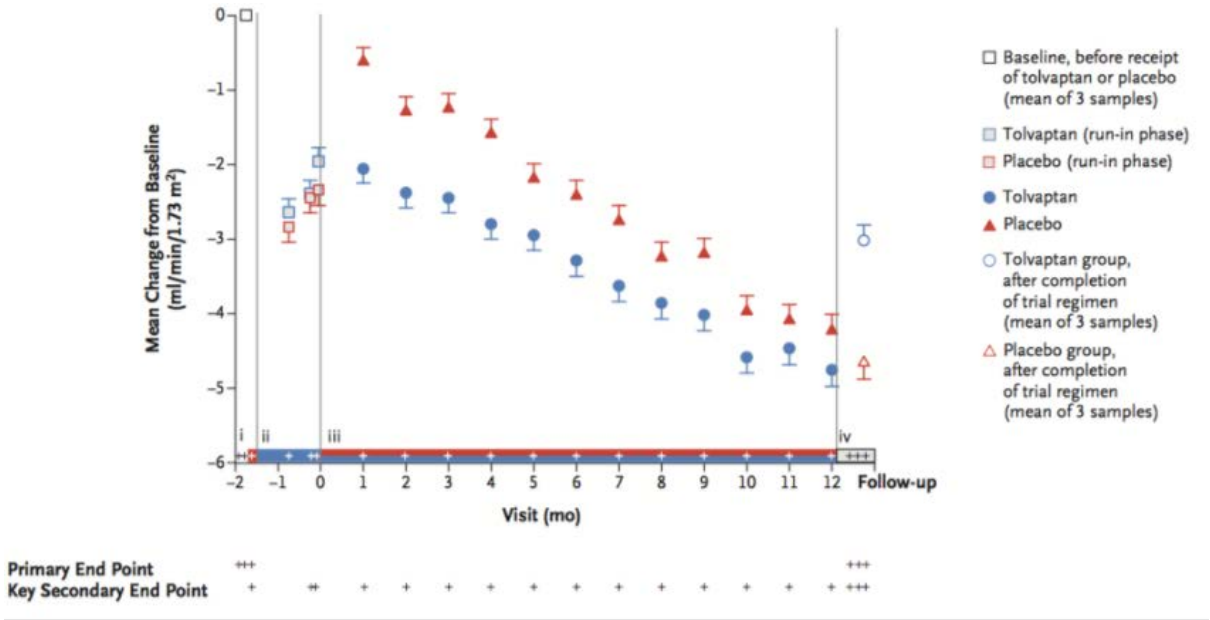
The LS mean change in eGFR was −2.339 mL/min/1.73 $m^2$ /year for tolvaptan vs. −3.610 mL/min/1.73 $m^2$ /year for placebo, which corresponds to a difference of ~ 35%

Table 2: Weighted ANCOVA of Annualized Change in eGFR (CKD-EPI) from Pre-treatment Baseline to Post-treatment Follow-up (mL/min/1.73 m2 /year) - Primary Endpoint, Efficacy Population

| Summary Statistics | Tolvaptan | Placebo |
|---|---|---|
| N | 668 | 663 |
| Mean rate of change per year | -2.961 | -4.249 |
| LS mean | -2.339 | -3.610 |
| Treatment Effect | 1.271 | |
| 95% CI | (0.859,1.684) | |
| P-value | <.0001 | |

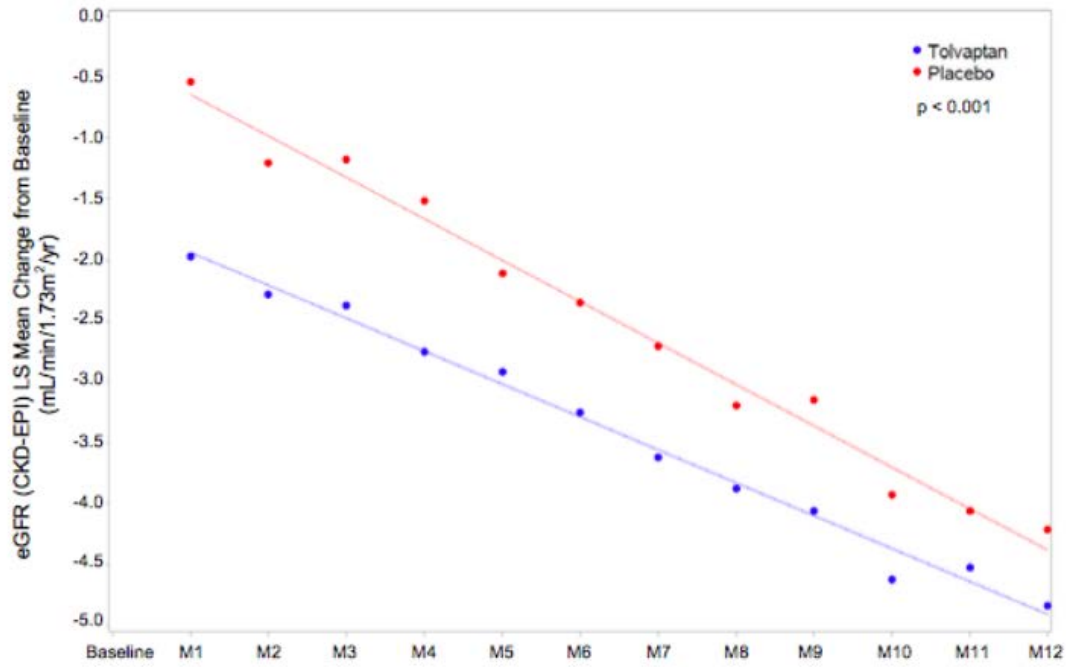
Figure 3 shows the changes in GFR over the 1 year study duration. As in previous data, there is an initial drop in GFR, presumed to be a haemodynamic effect of the drug, which reverses on drug cessation.

Figure 3: change in estimated GFR throughout the course of the trial




The next figure compares the mean slope of change in the eGFR.

Figure 4: mean slope of change in the eGFR between tolvaptan versus placebo




The primary endpoint results according to key subgroups are shown in figure 5 below. The subgroup analysis of the primary endpoints by CKD stage (table 3) demonstrated significant treatment effects for subjects in Stages 3a, 3b, and 4 at baseline – however the result was driven by benefits in those with

stage 3a disease. Patients who were non-white, aged over 55y or with stage 2 CKD at baseline did not seem to benefit from tolvaptan, although there were small numbers of patients in these subgroups.

Figure 5: Subgroup analyses

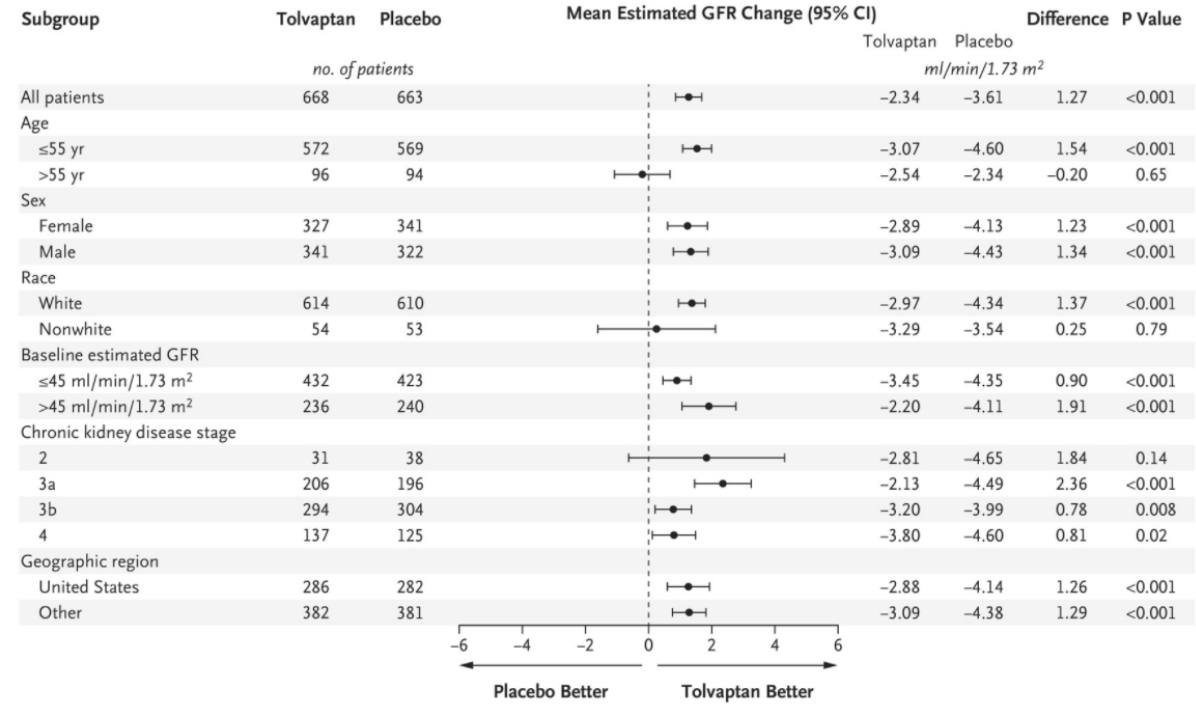



Table 3: Subgroup Analysis of Primary Endpoint according to baseline CKD stage: Weighted ANCOVA of Annualized Change in eGFR (CKD-EPI) from Pre-treatment Baseline to Post-treatment Follow-up (mL/min/1.73 m2 /year) - Primary Endpoint Efficacy Population

| Subgroup | Summary Statistics | Tolvaptan | Placebo |
|---|---|---|---|
| Baseline CKD Stage 2 | N | 31 | 38 |
| | Mean rate of change per year | -0.541 | -4.589 |
| | LS mean | -2.808 | -4.646 |
| | Treatment Effect | 1.838 | |
| | 95% CI | (-0.634,4.310) | |
| | **P-value** | **0.1424** | |
| Baseline CKD Stage 3A | N | 206 | 196 |
| | Mean rate of change per year | -2.061 | -4.379 |
| | LS mean | -2.134 | -4.489 |
| | Treatment Effect | 2.355 | |
| | 95% CI | (1.460,3.250) | |
| | **P-value** | **<.0001** | |
| Baseline CKD Stage 3B | N | 294 | 304 |
| | Mean rate of change per year | -3.344 | -3.982 |
| | LS mean | -3.204 | -3.987 |
| | Treatment Effect | 0.783 | |
| | 95% CI | (0.208,1.358) | |
| | **P-value** | **0.0077** | |
| Baseline CKD Stage 4 | N | 137 | 125 |

| | | | |
|---|---|---|---|
| | Mean rate of change per year | -4.041 | -4.590 |
| | LS mean | -3.797 | -4.602 |
| | Treatment Effect | 0.805 | |
| | 95% CI | (0.122,1.488) | |

A pre-specified subgroup analysis suggested that tolvaptan had less of an effect in patients older than 55 years of age, which correlated with a slower rate of decline of CKD in this subgroup.

***Secondary endpoints***

The key secondary endpoint was the linear mixed effect model of annualized eGFR change slope. This showed a statistically significant difference of 1.011 mL/min/1.73 $m^2$ /year ($p < 0.0001$) in favour of tolvaptan. The subgroup analysis of the secondary endpoints by CKD stage demonstrated significant treatment effects for subjects in Stages 3a, 3b, and 4 at baseline. The exploratory ANCOVA of the primary endpoint by modal dose showed statistically significant dose-response analysis of modal doses of 60, 90, and 120 mg (with 30 and 45 mg doses pooled to 60 mg due to sample sizes of 1 and 6 respectively) ($p = 0.0225$ for the dose trend).

## Ancillary analyses

Not applicable.

## *Summary of main study*

For Trial 156-13-210, statistical significance for both the primary and key secondary endpoints were met at $p < 0.05$ ($p < 0.0001$), which provides confirmatory evidence for the efficacy of tolvaptan in slowing renal function decline and extends the understanding of the effects of tolvaptan to later stages of the disease. All pre-specified sensitivity analyses were also positive (all $p < 0.0001$, except 1 with $p = 0.0005$). Missing data sensitivity analyses demonstrated the robust treatment effect of tolvaptan in slowing eGFR decline against the data MNAR assumption. Subgroup analysis for the primary endpoint demonstrated consistent treatment effects of tolvaptan for subjects in CKD Stages 2, 3a, 3b, and 4, with the latter 3 subgroups showing p-values ≤ 0.02. Similar results were observed for the key secondary endpoint. For both endpoints, significant treatment effects in favour of tolvaptan were observed across most other subgroup categories; for some subgroup categories (e.g., CKD Stage 2), the non-significant results may be partially attributable to low subject numbers.

## 2.4.2. Discussion on clinical efficacy

The key differences from the previous pivotal trial are the enrolment of subjects with later stages of CKD, and the use of GFR as primary endpoint rather than total kidney volume. For comparison, in the pivotal study the mean pre-titration eGFR was around 80. There are no significant issues with the overall design, conduct and analysis of the trial. The key endpoints have been discussed in previous Jinarc assessments.

Overall, characteristics of patients at baseline were balanced between the two groups. Most patients assigned to the tolvaptan group, and who completed the trial, were taking 90 mg morning and 30 mg afternoon doses daily.

Statistical significance for both the primary and key secondary endpoints were met, according to the applicant's pre-specified analyses. In the primary endpoint, the LS mean change in eGFR was −2.339 mL/min/1.73 $m^2$ /year for tolvaptan vs. −3.610 mL/min/1.73 $m^2$ /year for placebo, which corresponds to

a decline of ~ 35%. This corresponds to a treatment effect of 1.271 mL/min/1.73 m2 /year (95% CI 0.859 to 1.684, p < 0.0001). This is very similar to the effect size in the pivotal trial.

To put the eGFR results into context, rapid progression of renal impairment is generally defined in CKD as a sustained decline in eGFR of more than 5 ml/min/1.73 $m^2$/year. Once eGFR decreases below 30 mL/min, there is a progressive impact of complications related to renal impairment. Although primarily dependent on symptoms, the need for renal replacement therapy often occurs in a GFR range between 5 and 10 ml/min/1.73 $m^2$.

In the trial, the baseline estimated GFR was 41.1 ml per minute per 1.73 $m^2$ and declined over a 1-year period by 4.17 ml per minute per 1.73 $m^2$ with placebo. The authors note that if this effect were maintained, the time to chronic kidney disease of stage 5 would be extended from 6.2 years to 9.0 years. Such a delay could buy time for pre-emptive transplant. A larger benefit might be expected if treatment were started earlier, but this assumes that patients would tolerate long-term tolvaptan.

The key secondary endpoint was the linear mixed effect model of annualized eGFR change slope. This showed a statistically significant difference of 1.011 mL/min/1.73 $m^2$ /year (p < 0.0001) in favour of tolvaptan. This endpoint requires modelling assumptions to adjust for the estimated hemodynamic effects of tolvaptan.

To minimize withdrawal resulting from adverse drug effects, only patients who had an acceptable burden of side effects from tolvaptan during a pre-randomization period that included sequential placebo and tolvaptan phases underwent randomization. Therefore these results are specifically for a subset of patients who could take the treatment without an unacceptable level of side effects. Despite selection based upon ability to tolerate the drug, the trial still had a 9.5% dropout rate for tolvaptan, and this would be higher in unselected patients. Several approaches were used to account for the impact of missing data. Although the applicant provided sensitivity analyses of the key endpoints giving results that are in line with primary analyses, the sensitivity analysis do not address a treatment policy estimand and these were requested. However, since the primary results are highly statistically significant, the statistical conclusions of the trial are unlikely to alter. The requested analysis generates very similar results to those seen in the original primary analysis, demonstrating the robustness of the trial results to the method of handling missing data.

The subgroup analysis of the primary endpoints by CKD stage demonstrated significant treatment effects for subjects in Stages 3a, 3b, and 4 at baseline. There were 262 patients in the efficacy population with severe CKD (stage 4, eGFR 15- mL/min/1.73 $m^2$) at baseline – in this subgroup- the LS mean change in eGFR was −3.797 mL/min/1.73 $m^2$ /year for tolvaptan vs. −4.602 mL/min/1.73 $m^2$ /year for placebo. Patients over 55 were required to have an estimated GFR of 25 to 44 ml per minute per 1.73 $m^2$ and historical evidence of a decline in the estimated GFR that exceeded 2.0 ml per minute per 1.73 $m^2$ per year. This presumably followed recommendations of the European Renal Association/European Dialysis and Transplant association, which argue against treating patients aged >50 years who still have an eGFR >45 mL/min/1.73 $m^2$ (CKD stages 1–3a), because these patients have a high probability of slowly progressive disease. Despite the more stringent entry criteria for older patients, tolvaptan had less of an effect in patients older than 55 years of age, which correlated with a slower rate of decline of CKD in this subgroup.

The overall risks versus benefits will need to be carefully considered before starting tolvaptan in patients with late-stage ADPKD. In particular, the speed of ADPKD progression should be weighed against the risk of intolerability and of compliance with monitoring aimed at reducing the risk of hepatic adverse events. However, in selected patients with stage 4 CKD, treatment with tolvaptan would seem to have benefit.

The current SmPC already restricts the indication to rapidly progressing disease, and notes that treatment must be initiated and monitored under the supervision of physicians with expertise in managing ADPKD

and a full understanding of the risks of tolvaptan therapy, including hepatic toxicity and monitoring requirements.

This was a 1 year study, and further the effectiveness of treatment with tolvaptan over the long term remains to be determined. There remains no clinical rationale for the use of tolvaptan in ADPKD patients with end-stage renal failure, and the SmPC states that the treatment should be discontinued if the stage of renal insufficiency progresses to CKD stage 5.

### 2.4.3. Conclusions on the clinical efficacy

The key differences between the previous pivotal trial and the current one are the enrolment of subjects with later stages of CKD, and the use of GFR as primary endpoint rather than total kidney volume. Statistical significance for both the primary and key secondary endpoints was met, according to the applicant's pre-specified analyses. The LS mean change in eGFR was very similar to the effect size in the pivotal trial, and would be considered clinically relevant.

## *2.5. Clinical safety*

### *Introduction*

The pharmacodynamically predictable and most commonly reported adverse reactions are thirst, polyuria, nocturia, and pollakiuria (frequent urination) – with the resulting risk of fluid and electrolyte abnormalities. An increase in serum uric acid is also well documented, and a small reversible reduction in GFR has been observed in ADPKD trials at the initiation of tolvaptan treatment. Furthermore, tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST) with infrequent cases of concomitant elevations in total bilirubin.

In the pivotal ADPKD trial, elevation (> 3 × upper limit of normal [ULN]) of ALT was observed in 4.4 % (42/958) of patients on tolvaptan and 1.0 % (5/484) of patients on placebo, while elevation (> 3 × ULN) of AST was observed in 3.1 % (30/958) of patients on tolvaptan and 0.8 % (4/484) patients on placebo. Two (2/957, 0.2 %) of these tolvaptan treated-patients, as well as a third patient from an extension open label trial, exhibited increases in hepatic enzymes (> 3 × ULN) with concomitant elevations in BT (> 2 × ULN). The period of onset of hepatocellular injury (by ALT elevations > 3 × ULN) was within 3 to 14 months after initiating treatment and these increases were reversible, with ALT returning to < 3 × ULN within 1 to 4 month. In the pivotal trial, the incidence of elevated transaminase levels for tolvaptan subjects (> 3 × ULN) was approximately 3 to 4-fold higher than for placebo subjects. No association with tolvaptan dose or exposure was found at MAA for hepatic events.

In post-marketing experience, anaphylaxis (including anaphylactic shock and rash generalised) has been reported very rarely following administration of tolvaptan.

### *Patient exposure*

Cumulative exposure is shown in table 4 below. Through Month 12 inclusive, the cumulative percentage of subjects continuing on IMP, decreased to 84.5% and 92.6% for the tolvaptan and placebo arms, respectively. At Month 12, the average daily dose was 108.2 mg and 111.8 mg for the tolvaptan and placebo arms, respectively.

Table 4: Extent of Exposure to Trial Medication, Average Cumulative Dose - Randomized Subjects

| | Tolvaptan (n = 683) | | | Placebo (n = 687) | | |
|---|---|---|---|---|---|---|
| | Last Dose | Cumulative[a] | Average Daily Dose[b c] | Last Dose | Cumulative[a] | Average Daily Dose[b c] |
| Exposure up to | n (%) | n (%) | (mg) | n (%) | n (%) | (mg) |
| Tolvaptan Titration/Run-In | 2 ( 0.3) | 683 ( 100) | 99.7 | 2 ( 0.3) | 687 ( 100) | 99.4 |
| Month 1 | 12 ( 1.8) | 681 (99.7) | 111.8 | 7 ( 1.0) | 685 (99.7) | 112 |
| Month 2 | 10 ( 1.5) | 669 (98.0) | 111 | 3 ( 0.4) | 678 (98.7) | 112.1 |
| Month 3 | 18 ( 2.6) | 659 (96.5) | 110.3 | 3 ( 0.4) | 675 (98.3) | 112 |
| Month 4 | 11 ( 1.6) | 641 (93.9) | 110.1 | 3 ( 0.4) | 672 (97.8) | 112 |
| Month 5 | 11 ( 1.6) | 630 (92.2) | 109.5 | 2 ( 0.3) | 669 (97.4) | 111.8 |
| Month 6 | 5 ( 0.7) | 619 (90.6) | 109.3 | 6 ( 0.9) | 667 (97.1) | 111.8 |
| Month 7 | 3 ( 0.4) | 614 (89.9) | 108.8 | 6 ( 0.9) | 661 (96.2) | 111.7 |
| Month 8 | 6 ( 0.9) | 611 (89.5) | 108.3 | 3 ( 0.4) | 655 (95.3) | 111.7 |
| Month 9 | 9 ( 1.3) | 605 (88.6) | 108 | 4 ( 0.6) | 652 (94.9) | 111.7 |
| Month 10 | 8 ( 1.2) | 596 (87.3) | 107.7 | 4 ( 0.6) | 648 (94.3) | 111.7 |
| Month 11 | 11 ( 1.6) | 588 (86.1) | 107.8 | 8 ( 1.2) | 644 (93.7) | 111.6 |
| Month 12 | 537 (78.6) | 577 (84.5) | 108.2 | 596 (86.8) | 636 (92.6) | 111.8 |
| >month 12 | 40 ( 5.9) | 40 ( 5.9) | 105.8 | 40 ( 5.8) | 40 ( 5.8) | 105 |

## *Adverse events*

For the single, blind, tolvaptan run-in period, any AE reported after a subject had received the first dose of tolvaptan was considered a TEAE. During this period, of the 1491 subjects treated, 1051 (70.5%) subjects experienced a TEAE – the most frequently reported TEAEs were polyuria (31.9%), thirst (28.8%), and nocturia (20.7%). One subject died; serious TEAEs were reported for 43 (2.9%) subjects. Discontinuations of IMP due to an AE were reported for 101 (6.8%) subjects.

During the double-blind treatment period, TEAEs were reported for 85.3% and 82.3% of subjects in the tolvaptan and placebo groups, respectively. The most frequently occurring TEAEs (tolvaptan vs. placebo) were renal pain (16.6% vs. 19.0%), hypertension (10.7% vs. 11.5%), viral upper respiratory tract infection (10.6% vs. 12.3%), upper respiratory tract infection (8.7% vs. 8.5%), diarrhoea (6.9% vs. 3.4%), fatigue (6.8% vs. 3.5%), polyuria (5.3% vs. 1.6%); urinary tract infection (5.7% vs. 8.0%), and peripheral oedema (4.4% vs. 6.6%).

Overall, 1 subject died (placebo group); 12.5% and 8.8% of subjects in the tolvaptan and placebo groups, respectively, experienced serious TEAEs; and 9.5% and 2.2% of subjects in the tolvaptan and placebo groups, respectively, experienced IMP discontinuation due to AEs. An overview of AEs is given in table 5 below.

Table 5: Overview of Adverse Events (All Causalities), Primary and Secondary Safety Populations, Single- and Double-blind Treatment Periods

| | Tolvaptan | Placebo | Total |
|---|---|---|---|
| **Tolvaptan single-blind period** | | | |
| Subjects treated | 1491 (100.0) | | |
| Subject years of drug exposure | 139.2 | | |
| Subjects with adverse events | 1051 (70.5) | | |
| Adverse events | 3100 | | |
| Subjects with treatment-emergent adverse events | 1051 (70.5) | | |
| Treatment-emergent adverse events | 2978 | | |
| Subjects with serious treatment-emergent adverse events | 43 (2.9) | | |
| | **Tolvaptan** | **Placebo** | **Total** |
| Subjects with non-serious treatment-emergent adverse events | 1040 (69.8) | | |
| Subjects with severe treatment-emergent adverse events | 59 (4.0) | | |
| Subjects discontinued investigational medicinal product due to adverse events | 101 (6.8) | | |
| Deaths | 1 (0.1) | | |
| **Randomized subjects** | | | |
| Subjects treated | 681 (100.0) | 685 (100.0) | 1366 (100.0) |
| Subject years of drug exposure | 612.5 | 651.5 | 1263.9 |
| Subjects with adverse events | 581 (85.3) | 564 (82.3) | 1145 (83.8) |
| Adverse events | 2744 | 2537 | 5281 |
| Subjects with treatment-emergent adverse events | 581 (85.3) | 564 (82.3) | 1145 (83.8) |
| Treatment-emergent adverse events | 2425 | 2263 | 4688 |
| Subjects with serious treatment-emergent adverse events | 85 (12.5) | 60 (8.8) | 145 (10.6) |
| Subjects with non-serious treatment-emergent adverse events | 569 (83.6) | 556 (81.2) | 1125 (82.4) |
| Subjects with severe treatment-emergent adverse events | 70 (10.3) | 50 (7.3) | 120 (8.8) |
| Subjects discontinued investigational medicinal product due to adverse events | 65 (9.5) | 15 (2.2) | 80 (5.9) |
| Deaths | 0 (0.0) | 1 (0.1) | 1 (0.1) |

### *Serious adverse event / deaths / other significant events*

There were no deaths in the study considered to be related to IMP. One subject died from a Pulmonary Embolism during the tolvaptan titration and run-in period and another subject died from a Road Traffic Accident during the double-blind treatment period (assigned to placebo)

During the single-blind treatment period, 43 (2.9%) subjects experienced ≥ 1 serious TEAE. The majority of the serious TEAEs were reported by 1 subject. The most frequently reported serious TEAEs in descending order were alanine aminotransferase increased (4 subjects, 0.3%), polyuria (4 subjects, 0.3%), and nocturia (3 subjects, 0.2%). The majority of these serious TEAEs were assessed as severe in intensity.

During the double-blind treatment period, serious TEAEs were reported for 85 (12.5%) subjects in the tolvaptan group vs. 60 (8.8%) subjects in the placebo group. The most frequently reported serious TEAEs were (in descending overall order, tolvaptan vs. placebo): hepatic enzyme increased (1.6% vs. 0.1%), alanine aminotransferase increased (1.2% vs. 0.0%), liver function test increased (0.6% vs. 0.3%), renal cyst haemorrhage (0.4% vs. 0.3%), and renal impairment (0.3% vs. 0.4%). The majority of the serious TEAEs were reported for 1 or 2 subjects overall (0.1% overall). Most serious TEAEs were considered to be severe in intensity.

## Adverse events of particular interest

*Hepatic toxicity:* Treatment emergent AEs related to liver injury in the double-blind treatment period were reported for 10.9% and 5.3% of subjects in the tolvaptan and placebo groups, respectively. The most frequently reported were increased alanine aminotransferase (3.7% vs. 1.3%), increased aspartate aminotransferase (2.2% vs. 1.6%), increased hepatic enzymes (2.5% vs. 0.4%), and increased transaminases (1.5% vs. 0.7%). Serious TEAEs were reported for 31 (4.6%) and 4 (0.6%) subjects in the tolvaptan group and placebo groups, respectively. The most frequently reported TEAEs overall were (tolvaptan vs. placebo): 11 subjects with hepatic enzyme increased (1.6% vs. 0.1%) and 8 subjects with alanine aminotransferase increased (1.2% vs. 0.0%). However, no subject during the trial had concurrent transaminase and bilirubin elevations that met Hy's Law laboratory criteria (i.e., no subject had peak transaminase > 3 x ULN plus peak bilirubin > 2 x ULN).

For the 29 subjects in the tolvaptan group who discontinued the IMP after reporting a potential clinically significant increased ALT (> 3 x ULN), the values returned toward normal after the IMP was discontinued. For the 9 subjects in the tolvaptan group who did not discontinue the IMP after reporting a potential clinically significant increased ALT (> 3 x ULN), the ALT values returned toward normal for all except for 1 subject - that subject had 4 serious TEAEs of liver function test increased, the last of which resulted in discontinuation of the IMP; the subject recovered from all 4 serious TEAEs.

It is noted that monthly monitoring of LFTs was done in this study, more frequent that the majority of patients in the previous pivotal study. However the frequency is in line with the current SmPC, which requires monitoring of liver function tests on a monthly basis during the first 18 months of treatment and 3 monthly thereafter.

*Hyperuricaemia*: There were 7 TEAE of increased blood uric acid in the tolvaptan group (1%) in the double-blind treatment period, compared to no cases in the placebo group. The corresponding figures for the AE of gout were 12 (1.8%) vs 5 (0.7%).

*Skin neoplasm*: A possible signal of skin neoplasm was noted at the time of initial MAA. In study 156-13-210, tolvaptan conversely had a smaller incidence in skin neoplasm compared with placebo, although numbers were small.

*Glaucoma*: A possible signal of glaucoma was noted at the time of initial MAA. There were no observed cases of with glaucoma in study 156-13-210.

## 2.5.1. Discussion on clinical safety

The titration and run-in periods in the clinical trial were designed to test tolerability, exclude subjects unlikely to tolerate tolvaptan's aquaretic effects prior to the randomization period, minimize post-randomization withdrawal. The adverse event profile is being reviewed with this in mind.

Generally, the reported adverse events were in line with those established in the pivotal trial and there are no new signals of concern. In the pivotal trial, the most notable safety issue associated with chronic tolvaptan use in ADPKD was the potential for idiosyncratic hepatic toxicity. At the time of granting the initial marketing authorisation, the risk was considered manageable in the context of the RMP and SmPC restrictions (including contra-indications, monitoring and stopping rules).

In the currently submitted trial 156-13-210, TEAEs related to liver injury in the double-blind treatment period were reported for 10.9% and 5.3% of subjects in the tolvaptan and placebo groups, respectively. However, no subject during the trial had concurrent transaminase and bilirubin elevations that met Hy's Law laboratory criteria (i.e., no subject had peak transaminase > 3 x ULN plus peak bilirubin > 2 x ULN)

and all cases were reversible. One caveat is that the currently estimated "window of susceptibility" for hepatic AEs was estimated at around 18 months, whilst the submitted trial ran for 1 year.

It is noted that monthly monitoring of LFTs was performed in this study, more frequent that the majority of patients in the previous pivotal study. However the frequency is in line with the current SmPC recommendations, which requires monitoring of liver function tests on a monthly basis during the first 18 months of treatment and 3 monthly thereafter.

It is known that at the initiation of tolvaptan therapy, there is a small and reversible reduction in GFR, the mechanism for this is not fully defined. Data at the time of initial MAA suggested that the absolute decrease was lower in patients with more severe renal impairment, although the numbers of such patients are limited. Even if the decline is small, in patients with more severe renal impairment it can become more significant as a percentage of residual renal function. The CHMP requested further data on the initial change in GFR when starting therapy with tolvaptan overall and analysed by baseline CKD stage. The applicant explained that in the pivotal AKPD trials, a reversible haemodynamic reduction in GFR was observed at the initiation of tolvaptan treatment, and this is also stated in section 4.4 of the SmPC. In these new data, a similar effect was seen. There is a trend for a lower initial decrease with worsening baseline renal function and this was also seen in the pivotal AKPD trials. A greater effect was seen in some individuals, but, there were no subjects in CKD Stages 3a, 3b, and 4 that crossed their CKD stage boundary due to the initial change in eGFR, and this initial drop in eGFR recovered once a subject stopped taking tolvaptan.

There was a small difference in the TEAE of abdominal pain versus placebo and this is reflected in the SmPC.

### 2.5.2. Conclusions on clinical safety

Generally, the reported adverse events were in line with those established in the pivotal trial and there are no new signals of concern.

### 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.6. Risk management plan*

The PRAC considered that the risk management plan version 13.3 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 13.3 with the following content:

### *Safety concerns*

| **Summary of safety concerns for Jinarc** | |
|---|---|
| Important identified | • Volume depletion and dehydration |

| Summary of safety concerns for Jinarc | |
|---|---|
| risks | • Dehydration associated renal dysfunction<br>• Too rapid rise of serum sodium and neurologic sequelae (encephalopathy, osmotic demyelination)<br>• Hyper-/hypoglycemia and new onset diabetes mellitus (DM)<br>• Hyperuricemia, gout<br>• Hypernatremia in patients with underlying heart failure<br>• Hyperkalaemia in patients with underlying heart failure<br>• Interaction with CYP3A4 inhibitors<br>• Interaction with CYP3A4 inducers<br>• Interaction with vasopressin receptor agonists<br>• Pharmacodynamic interaction tolvaptan and combined administration of diuretics leading to dehydration and renal dysfunction<br>• Liver injury in ADPKD patients<br>• Anaphylaxis |
| Important potential risks | • Acute urinary retention (in patients with urinary outflow obstruction)<br>• Allergic skin reactions<br>• Raised intraocular pressure/glaucoma<br>• Interaction tolvaptan and serum potassium concentration-increasing substances<br>• Pharmacodynamic interaction tolvaptan and combined administration ACE-I possibly leading to dehydration and renal dysfunction<br>• Pharmacodynamic interaction tolvaptan and combined administration ARB possibly leading to dehydration and renal dysfunction<br>• Interaction tolvaptan and combined administration of warfarin and antiplatelet agents in patients with underlying heart failure<br>• Cardiac arrhythmias secondary to electrolyte shifts in patients with underlying heart failure<br>• Post-treatment myocardial ischemia in patients with worsening underlying heart failure<br>• Dyspnoea in patients with underlying heart failure<br>• Hypercoagulability (stroke, myocardial infarction) in patients with underlying heart failure<br>• Gastrointestinal bleeding in patients with underlying cirrhosis<br>• Teratogenicity<br>• Skin neoplasms (basal cell carcinoma) in ADPKD patients |
| Missing information | • Pediatric use<br>• Pregnancy outcome data<br>• Use in breast-feeding<br>• Off-label use<br>• Use in hepatic impaired patients<br>• Use in ADPKD patients with renal function other than stage 1-3 |

| Summary of safety concerns for Jinarc | |
|---|---|
| | • Use in patients over 50 in ADPKD patients<br>• Long term use of Jinarc in routine medical practice |

## *Pharmacovigilance plan*

| Study/activity Type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or FSR |
|---|---|---|---|---|
| Category 3<br>**Study I156-00-003**<br>Study Drug Use-Results Survey of Samsca in ADPKD in Japan | To obtain details on the occurrence of AEs in the post-marketing phase in Japan | Adverse events with Samsca in ADPKD patients in Japan in particular liver injury | Started: 02-May-2014 | Planned Q3 2023 |
| Category 1<br>**Jinarc PASS 156-12-299** | Jinarc PASS: The objective of the PASS is to prospectively collect information on the safety of Jinarc when used in a real-life setting. A retrospective study to assess safety concerns associated with longer term use will also be included. | Hepatotoxicity, and other identified and potential risks including glaucoma and skin neoplasms and missing information. In addition, ADPKD related morbidity and mortality will be assessed. | Started: 31-Oct-2016 | Planned Q4 2022 |

## *Risk minimisation measures*

| Safety Concern | Routine Risk Minimization Measures | Additional Risk Minimization Measures |
|---|---|---|
| ***Important Identified Risks*** | | |
| Volume depletion and dehydration | **Jinarc SmPC**<br>• **Section 4.4** Special warnings and precautions for use; the text states: *Tolvaptan may cause adverse reactions related to water loss such as thirst, dry mouth and dehydration (see section 4.8). Therefore, patients must have access to water (or other aqueous fluids) and be able to drink sufficient amounts of these fluids (see section 4.2). Patients have to be instructed to drink water or other aqueous fluids at the first sign of thirst in order to avoid excessive thirst or dehydration. Additionally, patients have to drink 1-2 glasses of fluid before bedtime regardless of perceived thirst and replenish fluids overnight with each episode of nocturia*<br>• **Section 4.3** Contraindications: Volume | None |

| Safety Concern | Routine Risk Minimization Measures | Additional Risk Minimization Measures |
|---|---|---|
| | depletion is added. | |
| Dehydration associated renal dysfunction | **Jinarc SmPC**<br>• *Volume status must be monitored in patients taking tolvaptan because treatment with tolvaptan may result in severe dehydration which constitutes a risk factor for renal dysfunction. If dehydration becomes evident, take appropriate action which may include the need to interrupt or reduce the dose of tolvaptan and increase fluid intake. Special care must be taken in patients having diseases that impair appropriate fluid intake or who are at an increased risk of water loss eg, in case of vomiting or diarrhoea.* | None |
| Too rapid rise of serum sodium and neurologic sequelae (encephalopathy, osmotic demyelination) | **Jinarc SmPC**<br>• **Section 4.4** Special warnings and precautions for use; the text states: *Fluid and electrolyte status must be monitored in all patients. Administration of tolvaptan induces copious aquaresis and may cause dehydration and increases in serum sodium (see section 4.8) and is contraindicated in hypernatremia patients (see section 4.3). Therefore, serum creatinine, electrolytes and symptoms of electrolyte imbalances (eg, dizziness, fainting, palpitations, confusion, weakness, gait instability, hyper-reflexia, seizures, coma) have to be assessed prior to and after starting tolvaptan to monitor for dehydration. During long-term treatment electrolytes have to be monitored at least every three months. Pre-treatment sodium abnormalities (hyponatraemia or hypernatremia) must be corrected prior to initiation with tolvaptan therapy.* | None |
| Hyper-/hypoglycemia and new onset diabetes mellitus (DM) | **Jinarc SmPC**<br>• **Section 4.8** Hyperglycemia is a common undesirable effects<br>• **Section 4.4** Class effect warning: *Diabetic patients with an elevated glucose concentration (eg, in excess of 300 mg/dl) may present with pseudohyponatraemia. This condition should be excluded prior and during treatment with tolvaptan. Tolvaptan may cause hyperglycaemia (see section 4.8). Therefore, diabetic patients treated with tolvaptan should be managed cautiously. In particular this applies to patients with inadequately controlled type II diabetes.* | None |
| Hyperuricemia, gout | **Jinarc SmPC**<br>• **Section 4.8** in clinical trials with other indications hyperuricemia is a common adverse event<br>• **Section 4.4** states : *Decreased uric acid clearance by the kidney is a known effect* | None |

| Safety Concern | Routine Risk Minimization Measures | Additional Risk Minimization Measures |
|---|---|---|
| | *of tolvaptan. In a double-blind, placebo-controlled trial of patients with ADPKD, potentially clinically significant increased uric acid (greater than 10 mg/dL) was reported at a higher rate in tolvaptan-patients (6.2%) compared to placebo-treated patients (1.7%). Adverse reactions of gout were reported more frequently in tolvaptan-treated patients (28/961, 2.9%) than in patients receiving placebo (7/483, 1.4%). In addition, increased use of allopurinol and other drugs used to manage gout were observed in the double-blind, Placebo-controlled trial. Effects on serum uric acid are attributable to the reversible renal hemodynamic changes that occur in response to tolvaptan's effects on urine osmolality and may be clinically relevant. However, events of increased uric acid and/or gout were not serious and did not cause discontinuation of therapy in the double-blind, placebo-controlled trial. Uric acid concentrations are to be evaluated prior to initiation of Jinarc therapy, and as indicated during treatment based on symptoms.* | |
| Hypernatremia in patients with underlying heart failure | **Jinarc SmPC**<br>• **Section 4.3** Hypernatraemia is a contraindication.<br>• **Section 4.8** Hypernatraemia is a common undesirable effect | None |
| Hyperkalaemia in patients with underlying heart failure | **Jinarc SmPC**<br>• Not applicable | None |
| Interaction with CYP3A4 inhibitors | **Jinarc SmPC**<br>• Warning in SmPC **Section 4.5** *Concomitant use of medicinal products that are moderate (eg, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil) or strong (eg, itraconazole, ketoconazole, ritonavir, clarithromycin) CYP 3A inhibitors increase tolvaptan exposure. Co-administration of tolvaptan and ketoconazole resulted in a 440% increase in area under time-concentration curve (AUC) and 248% increase in maximum observed plasma concentration (Cmax) for tolvaptan. Co-administration of tolvaptan with grapefruit juice, a moderate to strong CYP3A inhibitor, produced a doubling of peak tolvaptan concentrations (Cmax). Dose reduction of tolvaptan is recommended for patients while taking moderate or strong CYP 3A inhibitors (see section 4.2).* | None |

| Safety Concern | Routine Risk Minimization Measures | Additional Risk Minimization Measures |
|---|---|---|
| Interaction with CYP3A4 inducers | **Jinarc SmPC**<br>• Warning in SmPC **Section 4.5** *Tolvaptan plasma concentrations have been decreased by up to 87% (AUC) after the administration of CYP3A4 inducers. Caution should be exercised in co-administering CYP3A4 inducers (eg, rifampicin, barbiturates) with tolvaptan. In healthy subjects, tolvaptan, a CYP3A4 substrate, had no effect on the plasma concentrations of some other CYP3A4 substrates (eg, warfarin or amiodarone). Tolvaptan increased plasma levels of lovastatin by 1.3 to 1.5-fold. Even though this increase has no clinical relevance, it indicates tolvaptan can potentially increase exposure to CYP3A4 substrates.* | None |
| Interaction with vasopressin receptor agonists | **Jinarc SmPC**<br>• **Section 4.5** *In addition to its renal aquaretic effect, tolvaptan is capable of blocking vascular vasopressin V2 receptors involved in the release of coagulation factors (eg, von Willebrand factor) from endothelial cells. Therefore, the effect of vasopressin analogues such as desmopressin may be attenuated in patients using such analogues to prevent or control bleeding when co-administered with tolvaptan.* | None |
| Pharmacodynamic interaction tolvaptan and combined administration of diuretics leading to dehydration and renal dysfunction | **Jinarc SmPC**<br>• **Section 4.5** Diuretics: *Tolvaptan has not been extensively studied in ADPKD in combination with diuretics. While there does not appear to be a synergistic or additive effect of concomitant use of tolvaptan with loop and thiazide diuretics, each class of agent has the potential to lead to severe dehydration, which constitutes a risk factor for renal dysfunction. If dehydration or renal dysfunction becomes evident, appropriate action must be taken which may include the need to interrupt or reduce doses of tolvaptan and/or diuretics and increased fluid intake. Other potential causes of renal dysfunction or dehydration must be evaluated and addressed.* | None |
| Liver injury in ADPKD patients | **Jinarc SmPC**<br>• **Section 4.4**, Warning and Precautions for Use, contains language that includes the need for monthly liver function test monitoring in the first 18 months of Jinarc use and every 3 months thereafter, and guidelines on when to interrupt or discontinue Jinarc therapy | Several education materials were launched:1. Prescriber's education, certification in the prescriber's registry and reassurance of prescriber's certification prior to the dispensation of |

| Safety Concern | Routine Risk Minimization Measures | Additional Risk Minimization Measures |
|---|---|---|
| | | Jinarc in accordance with local legislation. 2. Educational material on need for liver monitoring while on tolvaptan and guide to early recognition of liver injury. 3.Checklist for the prescriber to evaluate eligibility of ADPKD patient for tolvaptan treatment. 4. Patient education brochure and medication alert card for the patient on tolvaptan |
| Anaphylaxis | **Jinarc SmPC**<br>• **Section 4.8** undesirable effects (anaphylactic shock and rash generalized) and a warning statement in SmPC **Section 4.4** *In post-marketing experience, anaphylaxis (including anaphylactic shock and rash generalised) has been reported very rarely following administration of tolvaptan. This type of reaction occurred after the first administration of tolvaptan. If an anaphylactic reaction or other serious allergic reactions occur, administration of tolvaptan must be discontinued immediately and appropriate therapy initiated. Since hypersensitivity is a contraindication (see section 4.3) treatment must never be restarted after an anaphylactic reaction or other serious allergic reactions.* | None |
| ***Important Potential Risks*** | | |
| Acute urinary retention (in patients with urinary outflow obstruction) | **Jinarc SmPC**<br>• *Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention.* | None |
| Allergic skin reactions | **Jinarc SmPC**<br>• **Section 4.3** Contraindications: Hypersensitivity to the active substance or to any of the excipients<br>• **Section 4.8** Pruritic rash is an uncommon adverse event in clinical trials with other indications | None |
| Raised intraocular | None | None |

| Safety Concern | Routine Risk Minimization Measures | Additional Risk Minimization Measures |
|---|---|---|
| pressure/glaucoma | | |
| Interaction tolvaptan and serum potassium concentration increasing substances | **Jinarc SmPC**<br>• Includes the following text: *Fluid and electrolyte status should be monitored in all patients. Administration of tolvaptan induces copious aquaresis and may cause dehydration and increases in serum sodium and is contraindicated in hypernatremia patients. Therefore, serum creatinine, electrolytes and symptoms of electrolyte imbalances (eg, dizziness, fainting, palpitations, confusion, weakness, gait instability, hyper-reflexia, seizures, coma) should be assessed prior to and after starting tolvaptan to monitor for dehydration.* | None |
| Pharmacodynamic Interaction tolvaptan and combined administration ACE-I possibly leading to dehydration and renal dysfunction | None | None |
| Pharmacodynamic Interaction tolvaptan and combined administration ARB possibly leading to dehydration and renal dysfunction | None | None |
| Interaction tolvaptan and combined administration of warfarin and antiplatelet agents in patients with underlying heart failure | None | None |
| Cardiac arrhythmias secondary to electrolyte shifts in patients with underlying heart failure | None | None |
| Post-treatment myocardial ischemia in worsening heart failure patients | None | None |
| Dyspnoea in patients with underlying heart failure | None | None |
| Hypercoagulability (stroke, myocardial infarction) in patients with underlying heart | None | None |

| Safety Concern | Routine Risk Minimization Measures | Additional Risk Minimization Measures |
|---|---|---|
| failure | | |
| Gastrointestinal bleeding in patients with underlying cirrhosis | None | None |
| Teratogenicity | **Jinarc SmPC**<br>• **Section 5.3** states: *Teratogenicity was noted in rabbits given 1000 mg/kg/day (15 times the exposure from the recommended human dose on an AUC basis). No teratogenic effects were seen in rabbits at 300 mg/kg/day (about 2.5 to 5.3 times the exposure in humans at the recommended dose, based on AUC). In a peri- and post-natal study in rats, delayed ossification and reduced pup bodyweight were seen at the high dose of 1000 mg/kg/day. The toxic potential of tolvaptan was also investigated in juvenile rats by 6-week repeated oral administration starting from 25 days of age (4 days after weaning). Tolvaptan was orally administered by gavage at doses of 30, 100, and 1000 mg/kg/day. No animal died and, overall, treatment-related changes were generally qualitatively comparable to those observed in adult rat toxicity studies of tolvaptan.*<br>• **Section 4.3** contraindication: *Tolvaptan shall not be used during pregnancy. One pregnancy in an ADPKD trial resulted in spontaneous abortion. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.*<br>• **Section 4.6** states: *Women of childbearing potential should use adequate contraceptive measures during Jinarc use. Jinarc must not be used during pregnancy (see section 4.3).* | None |
| Skin Neoplasms (basal cell carcinoma) in ADPKD patients | None | None |
| ***Missing Information*** | | |
| Pediatric use | **Jinarc SmPC**<br>• *The safety and efficacy of tolvaptan in children and adolescents has not yet been established. Tolvaptan is not recommended in the pediatric age group* | None |
| Pregnancy outcome data | **Jinarc SmPC**<br>• **Section 4.6** *Studies in animals have shown reproductive toxicity (see Section 5.3). The potential risk for humans is unknown. Women of childbearing potential should use adequate contraceptive measures during tolvaptan use. Jinarc must not be used during pregnancy (See section 4.3).* | None |

| Safety Concern | Routine Risk Minimization Measures | Additional Risk Minimization Measures |
|---|---|---|
| Use in breast-feeding | **Jinarc SmPC**<br>• **Section 4.6** *It is unknown whether tolvaptan is excreted in human breast milk. Studies in rats have shown excretion of tolvaptan in breast milk. The potential risk for humans is unknown. Jinarc is contraindicated during breastfeeding (see Section 4.3).* | None |
| Off-label use | **Jinarc SmPC**<br>• SmPC and package information leaflet instruct prescribers and patients on proper use of tolvaptan in ADPKD. The Jinarc PASS will survey the drug utilisation pattern. | None |
| Use in hepatic impaired patients | **Jinarc SmPC**<br>• **Section 4.2** *The effect of hepatic impairment on the treatment of ADPKD has not been investigated. In patients with severe hepatic impairment the benefits and risks of treatment with Jinarc must be evaluated carefully. Patients must be managed carefully and liver enzymes must be monitored regularly (see section 4.4). Jinarc is contraindicated in patients with elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment that meet the requirements for permanent discontinuation of tolvaptan (see sections 4.3 and 4.4). No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B).* | None |
| Use in ADPKD patients with renal function other than stage 1-4 | **Jinarc SmPC**<br>• **Section 4.1** Therapeutic Indications, language is included to highlight the intended use in adults with ADPKD who have CKD stage 1 to 4 at initiation of treatment.<br>• **Section 4.2** Renal impairment language states *Dose adjustment is not required in patients with renal impairment. No clinical trials in subjects with a creatinine clearance <10 mL/min or in patients undergoing dialysis have been conducted. The risk of hepatic damage in patients with severely reduced renal function (ie, eGFR < 20) may be increased; these patients should be carefully monitored for hepatic toxicity. Data for patients in CKD stage 3 are more limited than for patients in stage 1 or 2* | None |
| Use in patients over 50 in ADPKD patients | **Jinarc SmPC**<br>• **Section 4.2** under the Elderly Population states that *Increasing age has no effect on tolvaptan plasma concentrations. However, safety and effectiveness of tolvaptan in ADPKD patients aged over 50 years has not yet been established.* | None |
| Long term use of | **Jinarc SmPC** | None |

| Safety Concern | Routine Risk Minimization Measures | Additional Risk Minimization Measures |
|---|---|---|
| Jinarc in routine medical practice | • **Section 5.1** of the SmPC states *Data are not currently available to show whether long-term therapy with Jinarc continues to slow the rate of renal function decline and affect clinical outcomes of ADPKD, including delay in the onset of end-stage renal disease.* | |

### *2.7. Update of the Product information*

As a consequence of the data submitted in support of this new indication, sections 4.1, 4.8 and 5.1 of the SmPC have been updated.

Section 4.1 now specifies that Jinarc is indicated in adults with CKD stage 1 to 4 at initiation of treatment, as follows: "*Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to ~~3~~ **4** at initiation of treatment with evidence of rapidly progressing disease (see section 5.1).*"

Section 4.8 now lists 'abdominal pain' in the table of adverse events and presents the data in line with QRD recommendations.

Section 5.1 now includes a description of Study 156-13-210 and its results.

The Package Leaflet has been updated accordingly.

Reference to the obligation to carry out Condition 'ANX 006' has been deleted from the Annex II for Jinarc.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed and accepted by the CHMP.

### 2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

## 3. Benefit-Risk Balance

Clinical trial 156-13-210 was a Phase 3b, Multi-centre, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease Between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease.

This is a completed Post-Authorisation Efficacy Study (PAES) as mandated by the CHMP at the time of initial approval of tolvaptan for the use in adults to treat autosomal dominant polycystic kidney disease. The study design was acceptable and the characteristics of patients at baseline were balanced between the two groups. Statistical significance for both the primary and key secondary endpoints was met, according to the MAH's pre-specified analyses. The safety analysis did not reveal any new adverse events.

Therefore, the CHMP concluded that the efficacy and safety of Jinarc in patients with CKD stage 4 is not different from that in the already treated patients with stage 1-3 and agreed on the proposed extension of indication.

The overall B/R of Jinarc is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | II | I, II and IIIB |

Extension of Indications to the treatment of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 4, based on the results of a completed Post Authorisation Efficacy Study (PAES, Trial 156-13-210). Trial 156-13-210 is a Phase 3b, Multi-centre, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease. Submission of these results fulfils the corresponding condition mandated by Annex II of the Product Information for tolvaptan (ANX 006).

Sections 4.1, 4.8 and 5.1 of the SmPC and the package leaflet were updated accordingly. Changes in line with QRD template and other minor additional editorial changes were also carried out.

Version 13.3 of the RMP, updated to reflect the study results, was approved.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Package Leaflet and to the Risk Management Plan (RMP).

The CHMP is of the opinion that the following obligation has been fulfilled, and therefore recommends its deletion from the Annex II:

*"Post-authorisation efficacy study (PAES): In order to further define the efficacy of tolvaptan in patients with more advanced renal dysfunction on a primary endpoint related to GFR rather than TKV the MAH should submit the Final study report of Study 156-13-210 by: Feb-2018."*

# 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

### *Scope*

Please refer to the Recommendations section above.

### *Summary*

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-09'