Otsuka Pharmaceutical Development & Commercialization, Inc.

Final Study Report

Study ID 156-12-299

CONFIDENTIAL – PROPRIETARY INFORMATION

Post-Authorisation Safety Study (PASS) information

Title	A 7.5-year, Multicentre, Non-interventional, Post-authorisation Safety Study for Patients Prescribed JINARC® for Autosomal Dominant Polycystic Kidney Disease
Version identifier of the FSR	1.0
Date of last version of the FSR	20 Nov 2024
EU Post-Authorisation Study register number	ENCEPP/SDPP/12842
Active substance	Tolvaptan
Medicinal product	JINARC®
Product reference	EMEA/H/C/002788
Procedure number	EMEA/H/C/PSP/0028
Marketing Authorisation Holder (MAH)	Otsuka Pharmaceutical Netherlands B.V.
Joint PASS	No
Research question and objectives	The primary focus of this PASS is to characterise and quantify the identified risk of idiosyncratic liver injury in JINARC treated patients with autosomal dominant polycystic kidney disease (ADPKD) in routine clinical practice.
Countries of study	United Kingdom, Germany, Italy, Spain, France, Norway, Sweden, Finland, Denmark, Austria, Netherlands, Belgium, Luxemburg, Switzerland, and others where JINARC is available.
Author	PPD Phone: PPD

Marketing Authorisation Holder

MAH(s)	Otsuka Pharmaceutical Netherlands B.V. Herikerbergweg 292 1101 CT, Amsterdam Netherlands
MAH contact person	PPD Phone: PPD PPD

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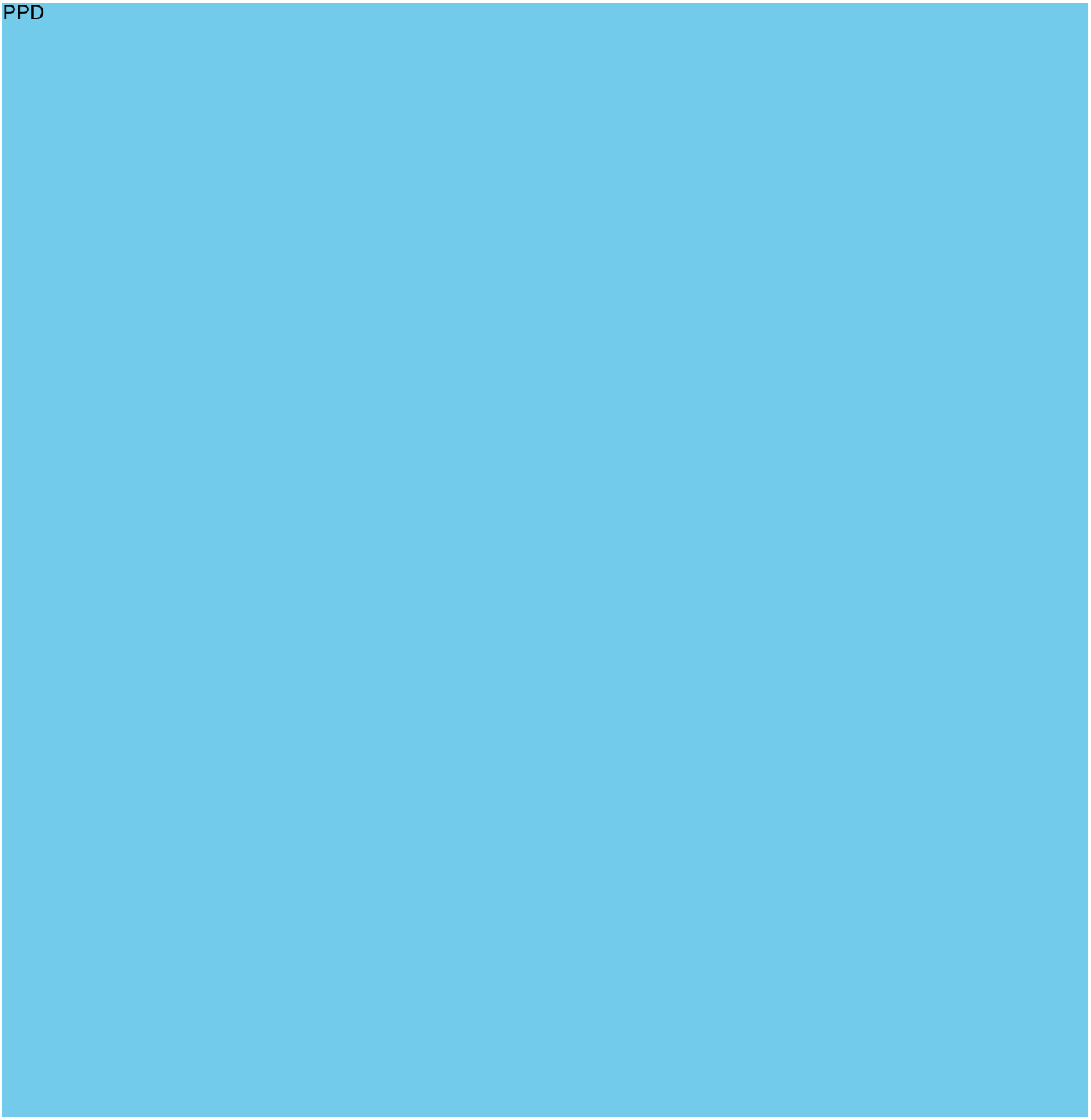

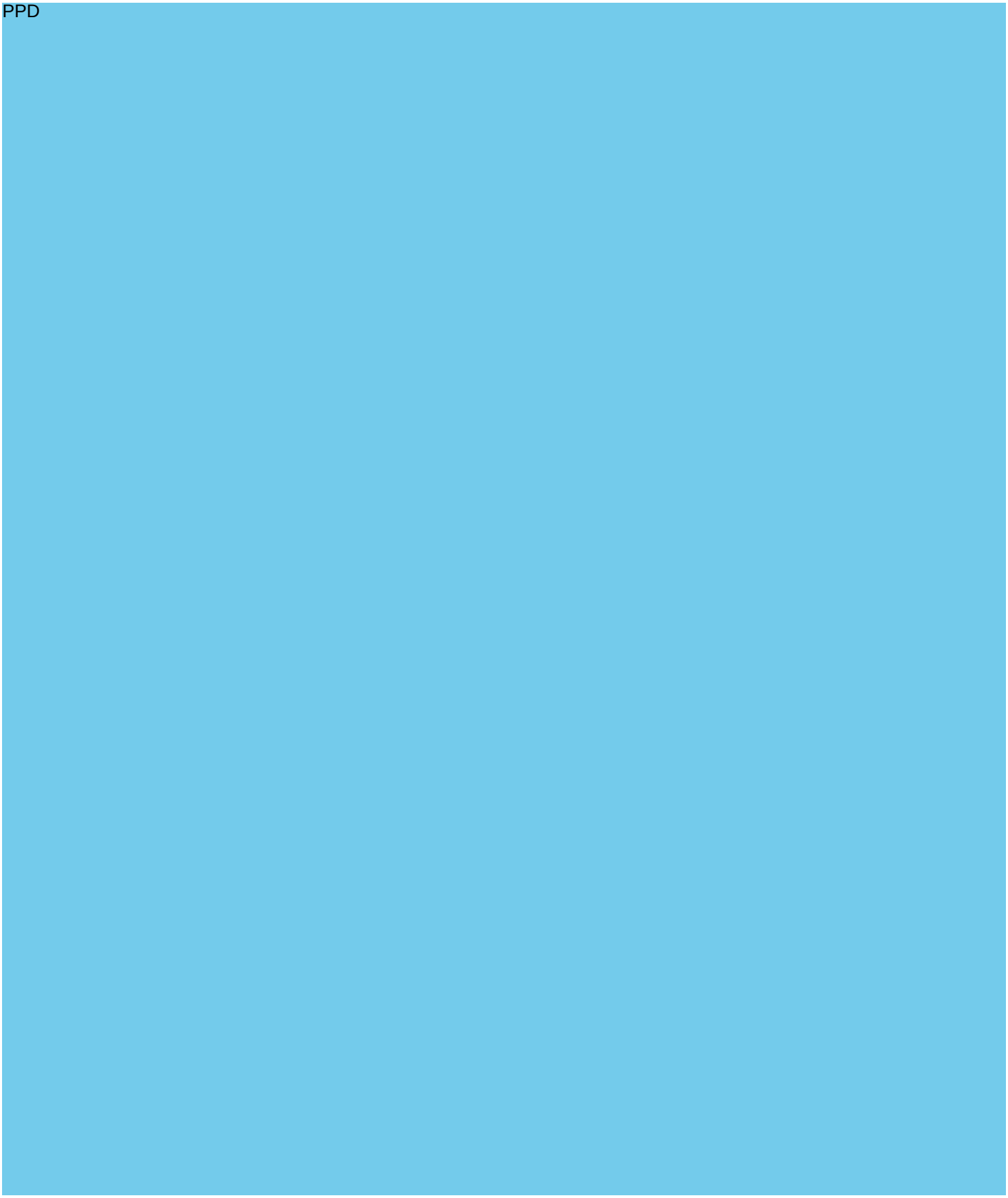
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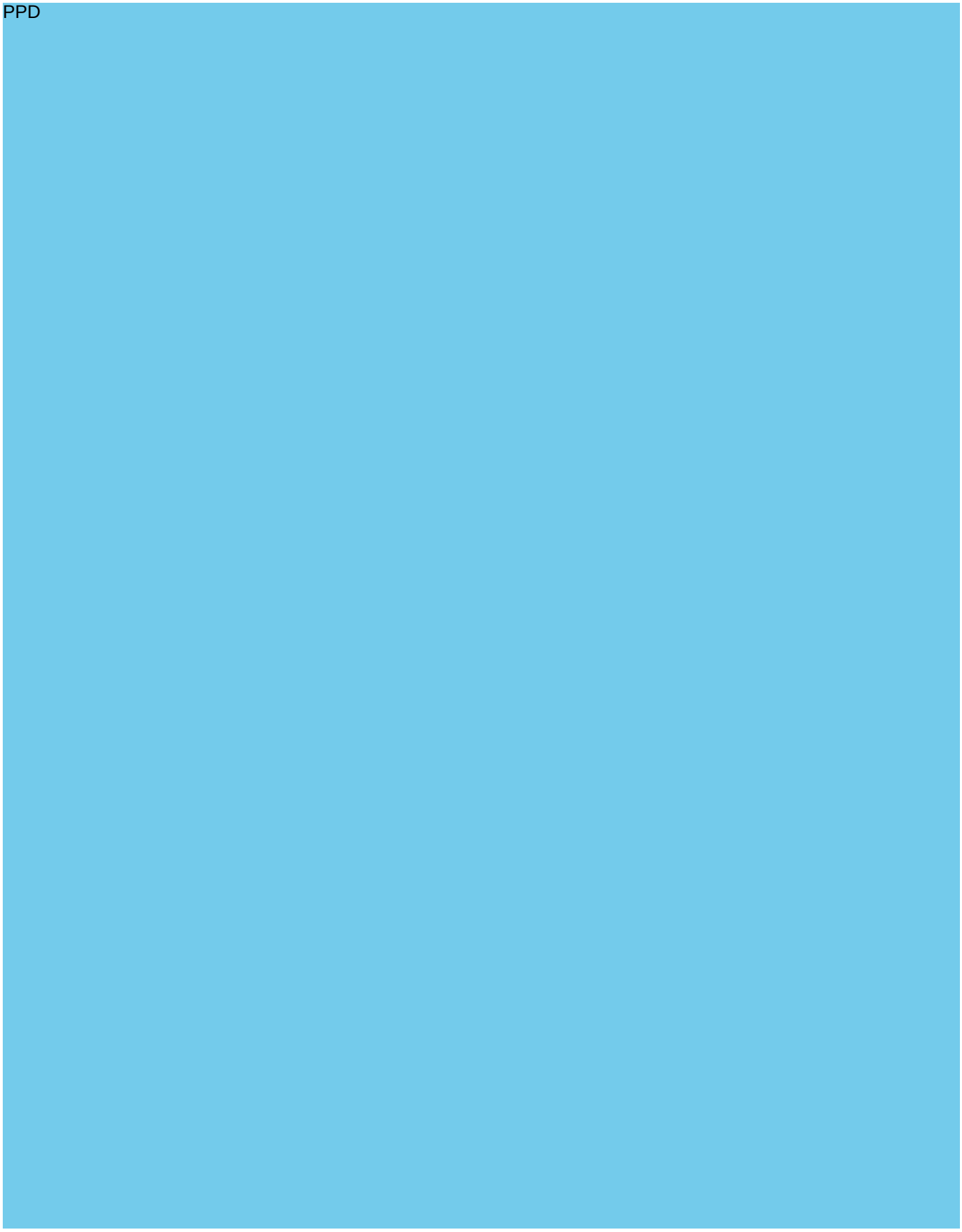
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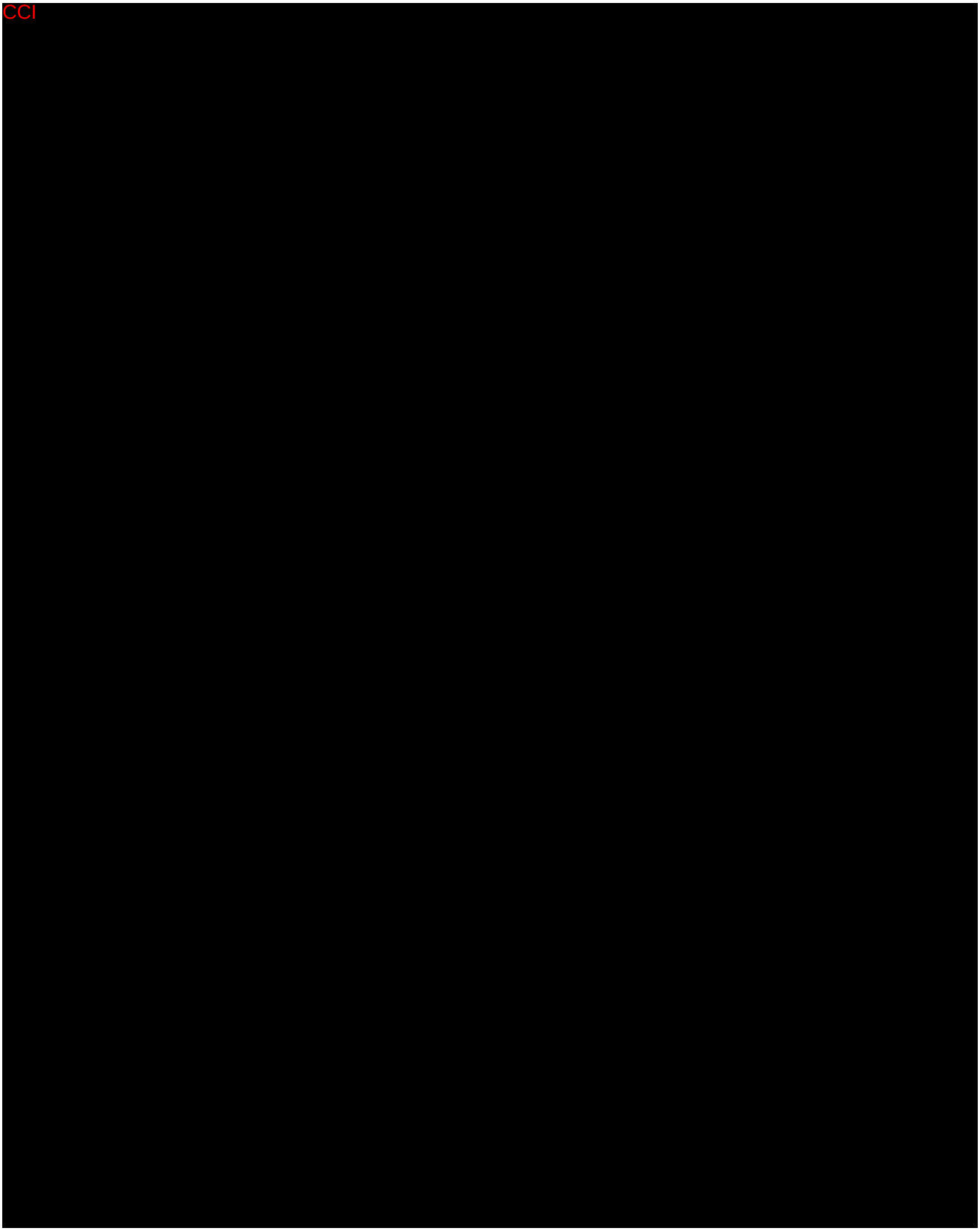

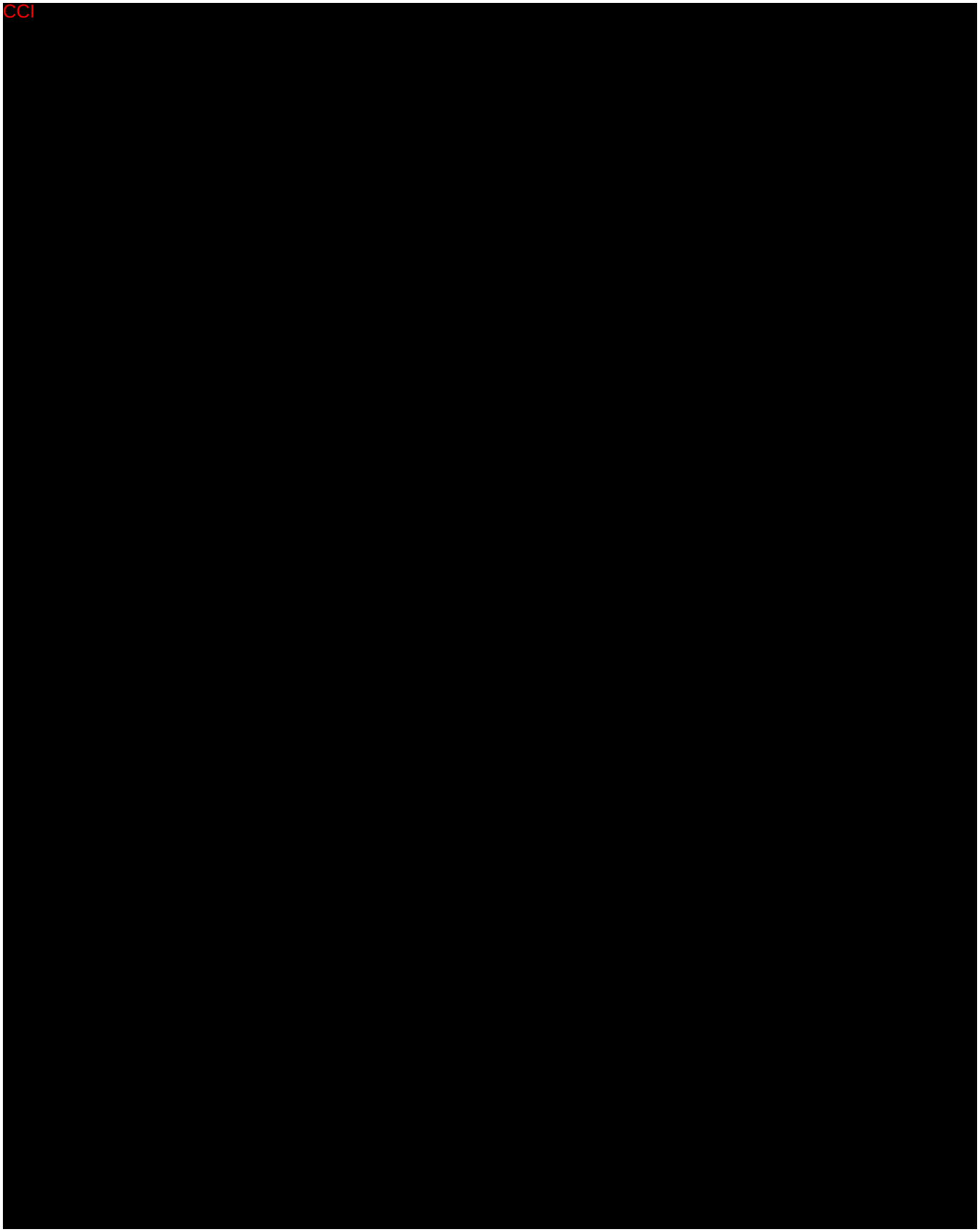
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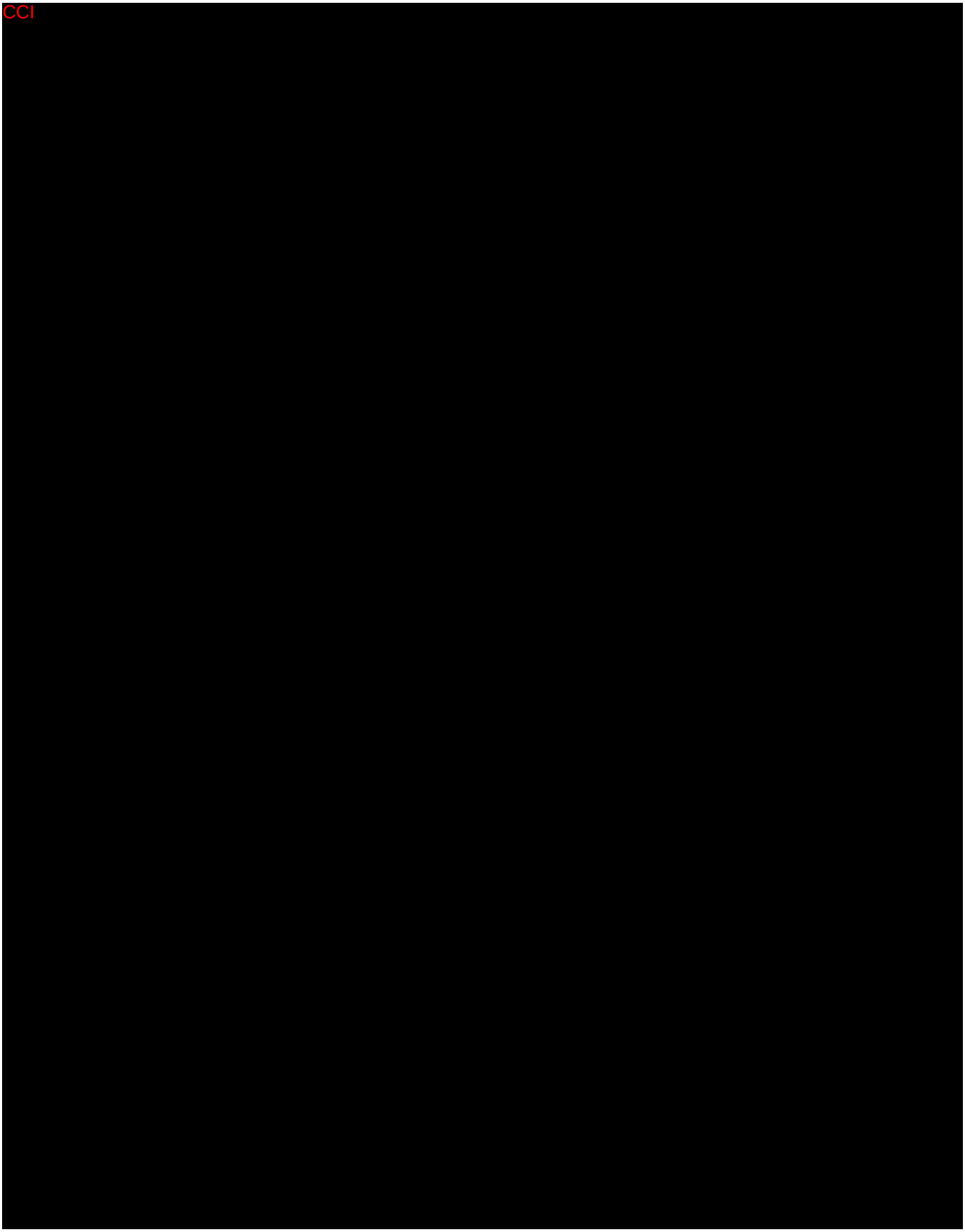
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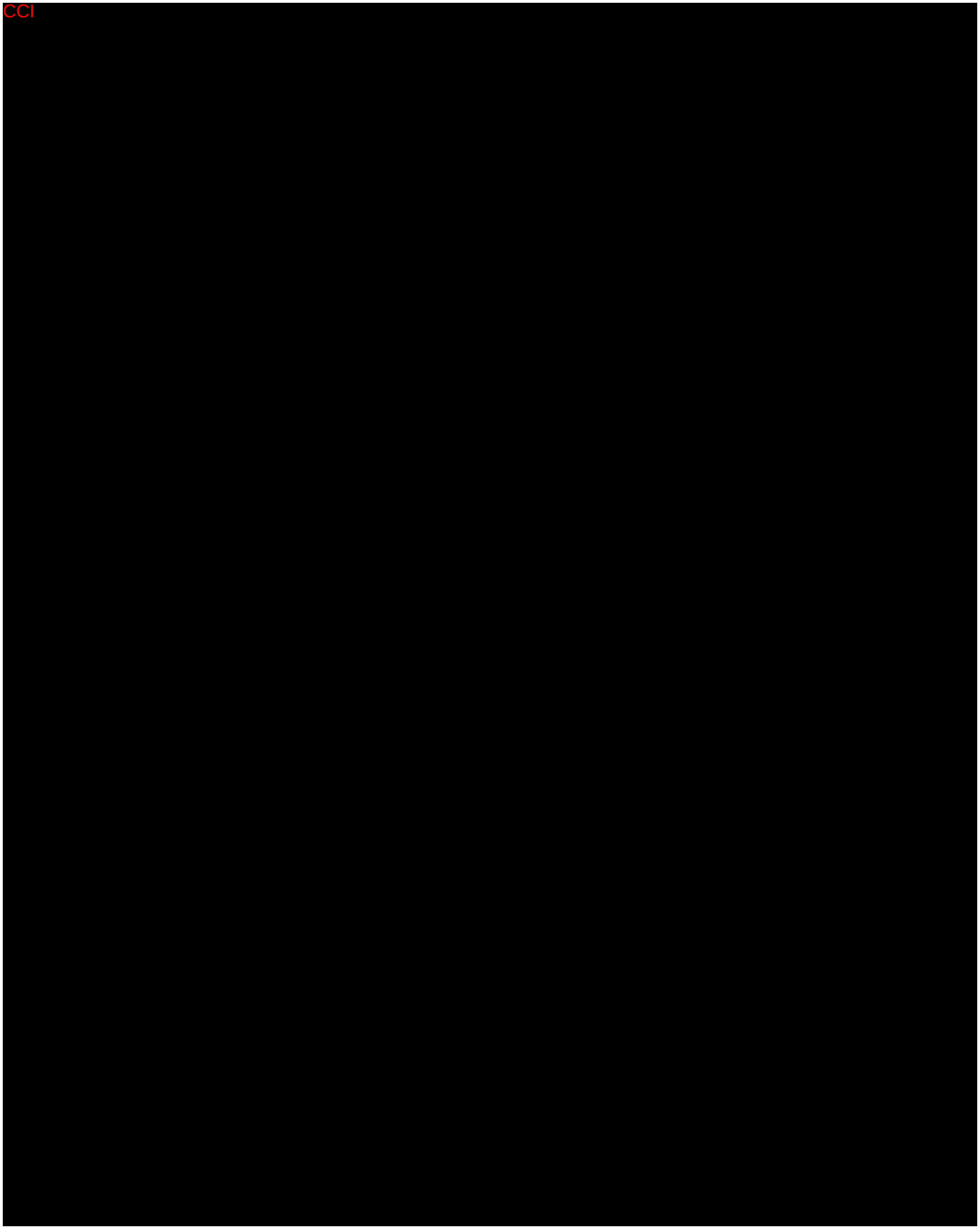
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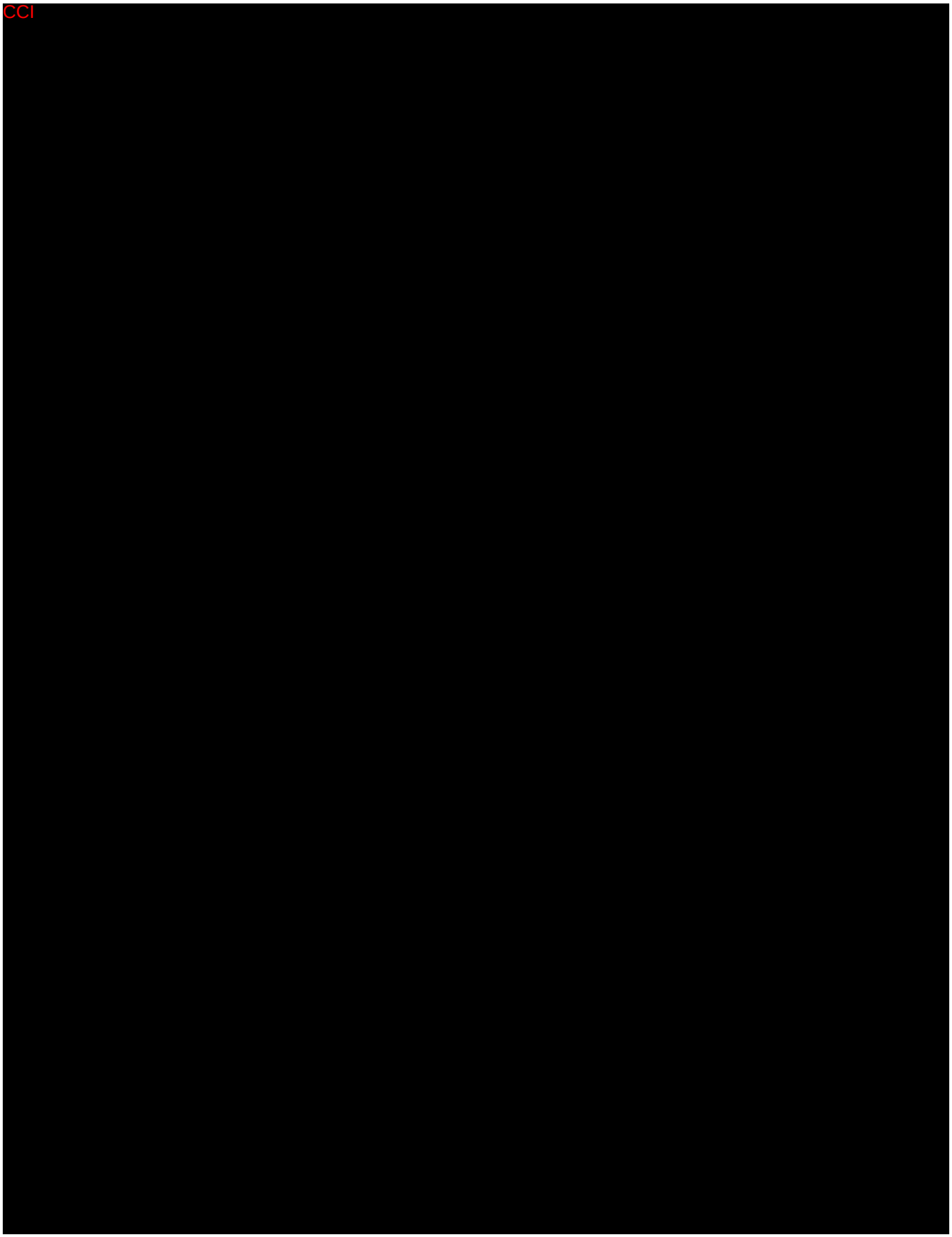
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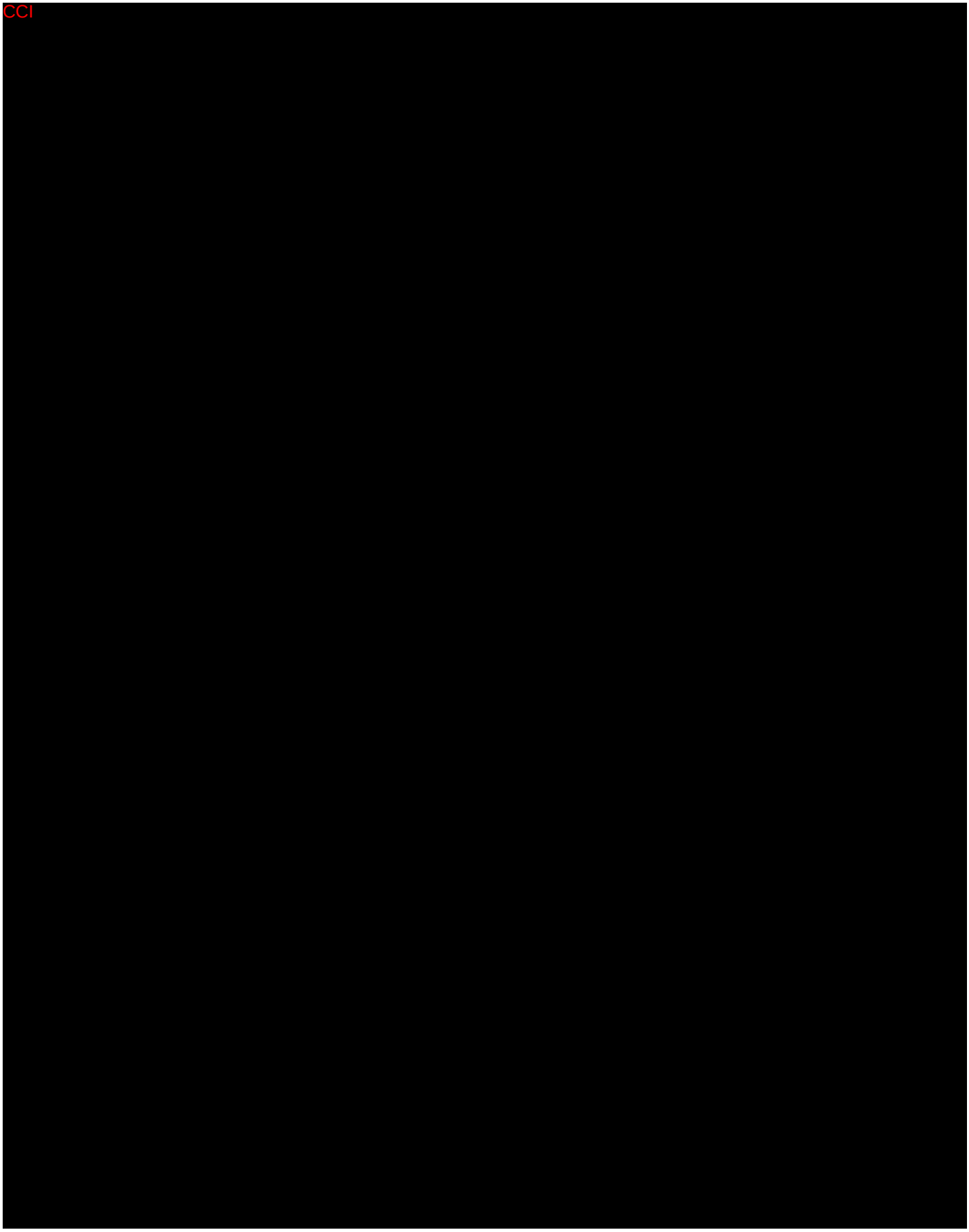
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1 Abstract

Title

A 7.5-year, Multicentre, Non-interventional, Post-authorisation Safety Study for Patients Prescribed JINARC® for Autosomal Dominant Polycystic Kidney Disease

Date of abstract: 20 November 2024

Authors:

PPD Otsuka Pharmaceutical Development and Commercialization Europe GmbH

Keywords

Post-authorisation Safety Study, tolvaptan, Autosomal Dominant Polycystic Kidney Disease (ADPKD).

Rationale and Background

Autosomal dominant polycystic kidney disease is a hereditary disorder and a leading cause of chronic renal failure. The disease is characterised by development of progressive enlargement of renal cysts resulting in end-stage renal disease (ESRD) typically in mid to late adulthood. The estimated prevalence of ADPKD in Europe is between 3.76 and 3.96 per 10,000.[1]

Tolvaptan is the only treatment option for slowing the progression of kidney disease in patients with ADPKD. Except for tolvaptan, all other currently available treatment options for ADPKD are palliative and directed at minimising complications of the disease rather than addressing underlying renal pathophysiology or pathognomonic cyst formation. Patients with ADPKD who progress to ESRD require renal transplantation frequently after years of renal dialysis.

Tolvaptan is a selective vasopressin V_2-receptor antagonist. Tolvaptan blocks vasopressin and slows cystogenesis and renal function decline in patients with ADPKD. The indication is explicitly described in the Summary of Product Characteristics (SmPC).[2] The indication statement is: "JINARC is indicated to slow the progression of cyst development and renal insufficiency of ADPKD in adults with chronic kidney disease (CKD) Stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease."

Tolvaptan has the potential to cause life threatening idiosyncratic liver injury in patients receiving or administering therapy prescribed for the treatment of ADPKD. In

post-marketing experience with tolvaptan in ADPKD, acute liver failure requiring liver transplantation has been reported. The primary focus of the Post-authorisation Safety Study (PASS) was to characterise and quantify an identified risk for idiosyncratic liver injury in JINARC treated patients with ADPKD in routine clinical practice. Safety information on other potential risks through characterisation of adverse events (AEs) and other safety information generated from patterns of JINARC use in the real-world, use in patients over the age of 50 years, long-term safety, and other ADPKD associated renal outcomes were collected, monitored, and assessed.

The PASS was managed by Otsuka Pharmaceutical Development & Commercialization Inc. (OPDC, Rockville, Maryland, USA) and its designees/vendors on behalf of the Marketing Authorisation Holder (MAH), Otsuka Pharmaceutical Netherlands B.V.

Research Question and Objectives

The goal of this study was to assess the long-term safety profile of JINARC when prescribed under usual practice for treatment of patients with ADPKD.

Primary:

- To characterise and quantify the identified risk of idiosyncratic liver injury in JINARC treated patients with ADPKD in routine clinical practice.

Secondary

- To evaluate patterns of JINARC use in a real-world setting, including the following:
  - Use and potential risks in pregnant women, including the frequency and outcome of pregnancies associated with the use of JINARC.
  - Prescriber compliance with the SmPC.
- To evaluate the use and potential risks in patients over the age of 50 years.
- To assess the effectiveness of risk minimisation measures among JINARC prescribers.
- To evaluate the incidence and potential risks and adverse drug reactions (ADRs) which may be found with long-term use.

Additional exploratory objectives were also evaluated.

Study Design

This PASS was a multicentre, prospective, observational study of patients being treated with JINARC for ADPKD to better characterise specified known risks in real-world treatment through evaluation of AEs and prescribing habits, and collection of data from patients with limited information from clinical trials. Study participation was available to physicians who completed the appropriate education in all countries in Europe where JINARC is launched and commercially available by prescription. Physicians and patients from other regions could also have been included for comprehensive or separate analysis. This study did not require any additional diagnostic, therapeutic, or monitoring procedures outside of normal medical practice.

This was a study of real-world treatment practices in patients newly initiated on treatment with JINARC for ADPKD to evaluate treatment patterns and outcomes in patients treated in the post-marketing setting. Patients were followed for a minimum of 2 years (or for as long as they participate in the study) and to a maximum of 6 years depending on their recruitment date.

Data was collected and evaluated to address the following endpoints:

Primary Endpoint:

- The incidence of patients with acceptable levels of transaminases at screening who experience an elevation of transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) ≥ 3 × upper limit of normal (ULN), or an AE consistent with hepatotoxicity.

Secondary Endpoints:

- The incidence of patients who meet Hy's laboratory criteria (AST or ALT > 3 × ULN and total bilirubin [BT] > 2 × ULN in the absence of elevated alkaline phosphatase [AP]).
- The frequency of all AEs by duration of treatment and by dose of JINARC in patients treated for < 6 months, 6 to 12 months, 12 to 24 months, ≥ 24 months and overall, including the incidence of hepatic AEs and the incidence of patients who meet Hy's Law laboratory criteria.
- The incidence of patients who intentionally or unintentionally conceive during JINARC use, including the outcomes of that pregnancy (full term/healthy birth, spontaneous abortion, intentional abortion, congenital anomaly, foetal malformation, foetal death, and perinatal death).
- The incidence of JINARC initiation in patients > 50 to 64 years and ≥ 65 years of age.
- The proportion of prescribers who did not adhere to the recommendations of the SmPC in the selection, treatment, and monitoring of patients prescribed JINARC.

Additional exploratory endpoints were also assessed.

CCI [redacted]

Setting

All prescribers within countries that have launched JINARC who completed the appropriate education were certified and invited to participate in the study. Thus, the eligible population included all patients with a diagnosis of ADPKD who were newly prescribed JINARC by a prescriber participating in the PASS.

Marketing authorisation was granted in the second quarter (Q2) of 2015 and following endorsement of the initial protocol by Pharmacovigilance Risk Assessment Committee (PRAC), and upon the product being made available by country, the first patient was enrolled in October 2016 and the last patient, last visit was 19 Feb 2024.

Subject Population

Inclusion Criteria: Patients were eligible for participation in this study if they were:

- Tolvaptan naïve (have never taken tolvaptan including as part of a cross-over or open-label trial).
- Prescribed JINARC for ADPKD by an appropriately certified prescriber who had completed the required educational training.
- Willing and able to provide informed consent/legal guardian consent; understand the requirements of participation in the study and able to comply with the study and data collection processes.

Exclusion Criteria: Patients were not eligible for participation in this study if they were:

- Currently or previously a recipient of tolvaptan.
- Prescribed JINARC for ADPKD in a manner not according to the SmPC or if the appropriately certified prescriber had not completed the required educational training.

Variables and Data Sources

Variables include definition of exposure, hepatotoxicity monitoring, potential risks with long-term use, ADPKD progression, patterns of JINARC use, CCI [redacted] and characterisation of patients and physicians.

This study was operated by a contract research organisation (CRO) on behalf of OPDC. Patient-level data for all patients enrolled in the study was provided proactively by participating prescribers.

Results

- Two thousand one hundred and thirty-six patients were enrolled into the study. Of these, 2091 (97.9%) patients received at least one dose of study medication and are included in the safety analysis. A total of 1564 (73.2%) patients completed the study.
- The overall mean age of patients in the PASS was 43.0 years (standard deviation [SD] 10.4). At treatment initiation, the majority of patients (1601 [76.6%]) were ≤ 50 years of age, 444 (21.2%) patients were > 50 to 64 years, and 45 (2.2%) patients were ≥ 65 years of age. The proportion of male to female patients is slightly higher for male patients (1096 vs 1038).
- A total of 258 patients with elevation of hepatic transaminases and/or hepatic events potentially associated with the risk of liver injury were identified.
- Elevated ALT or AST levels (≥ 3 × ULN) were reported for 80 (4.0%) patients. The initial incidence of elevated ALT or AST (≥ 3 × ULN) was stratified by treatment dosage; 12 patients experienced ALT or AST ≥ 3 × ULN at 60 mg, 14 at 90 mg, and 40 at 120 mg.
- Forty-nine patients had ALT or AST > 5 × ULN, 15 patients had ALT or AST > 10 × ULN, and 5 patients had ALT or AST > 20 × ULN. A total of 27 (1.4%) patients experienced > 2 × ULN total BT; no patient met Hy's Law laboratory criteria.
- A total of 244 hepatic AEs were reported with discontinuation of JINARC in response to the hepatic AEs occurring in 65 (3.1%) patients.
- Of the 1014 female patients in the safety sample, 607 (59.9%) met the criteria of childbearing potential. A total of 168 (16.6%) female patients received a pregnancy test, with 21 (2.1%) positive test results. Two (0.1%) patients had premature babies; 1 experienced neonatal disorder, and neither patient was taking JINARC at the time of delivery. An additional 10 cases indicating pregnancies from review of all safety data were identified. Thirteen cases showed no maternal exposure during pregnancy was reported (planned pregnancies). In 12 cases maternal exposure was identified; 6 patients discontinued treatment the same day when pregnancy was detected. Four cases reported pregnancy of partner, 3 cases had exposure up to 3 months, and in 2 cases insufficient information was provided to assess maternal exposure.
- Of the 2091 patients in the safety analysis population, prescribers for 122 (5.8%) patients did not adhere to the recommendations of the SmPC, predominantly including patients with a CKD stage of 5; a total of 19 patients were on strong and moderate CYP3A4 inhibitors at starting dose. Sixteen of these patients (84.2%) that were on strong and moderate CYP3A4 inhibitors started JINARC at 45/15 mg. Per the JINARC SmPC, patients on moderate CYP3A inhibitor should have been started at a split 15 mg and 15 mg dose, and those on strong CYP3A inhibitor should have been started at 15 mg per day.

- The majority of patients (1963; 93.9%) initiated therapy at a starting dose of 60 mg. The overall mean (SD) duration of exposure in the PASS was 976.0 (677.0) days, with the minimum duration of exposure at 1 day, and maximum at 2319 days.
- Across all age groups, the majority of patient's baseline CKD stages were Stage 2 (549, 26.3%), Stage 3b (459, 22.0%), and Stage 3a (455, 21.8%). The majority baseline CKD stage for patients > 50 years was Stage 3b (197 patients; 9.4%), followed by Stage 3a (120 patients; 5.7%), and Stage 2 (64 patients; 3.1%). As of the final CKD stage recorded, stages were Stage 1 (189; 9.0%), Stage 2 (349; 16.7%), Stage 3a (340; 16.3%), Stage 3b (448; 21.4%), Stage 4a (141; 6.7%), Stage 4b (283; 13.5%), and Stage 5 (125; 6.0%). No trend was identified when CKD stage shifts were evaluated by age group.
- In the 36 patients who initiated treatment at doses higher than 60 mg, the most frequently reported treatment-emergent AEs (TEAEs) within 10 days of treatment initiation were polyuria (6 [16.7%] patients), and thirst and nocturia (3 [8.3%] patients, each). The frequency of these events was comparable or higher in patients who initiated treatment at 60 mg compared with patients in the higher dose group.
- One patient received a liver transplant during the study. The patient had a medical history of polycystic liver disease and underwent elective liver transplant. The transplant was not related to JINARC, and treatment was discontinued after the event.
- Majority of patients (1533/2091; 73.3%) experienced TEAEs within < 6 months of treatment exposure. Incidence of TEAEs was 49.1% (829 patients) from 6 to 12 months, 56.1% (859 patients) from 12 to 24 months, 49.5% (639 patients) from 24 to 36 months, and 60.4% (550 patients) from 36 months of treatment exposure. Analysis of the incidence of TEAEs by treatment dosage did not identify a trend.
- Treatment-emergent AEs were experienced by 1839 (87.9%) patients who reported a total of 10167 events. Treatment-emergent AEs were equally distributed between age groups, < 50 years of age (1346/1528, 88.1%), ≥ 50 and < 65 years of age (450/517, 87.0%), and ≥ 65 years of age (42/45, 93.3%). The most frequently reported TEAEs by preferred term (PT) (incidence ≥ 10% of all patients) were polyuria (743 [35.5%] patients), nocturia (595 [28.5%] patients), renal pain (321 [15.4%] patients), thirst (268 [12.8%] patients), fatigue (262 [12.5%] patients), COVID-19 (238 [11.4%] patients), polydipsia (228 [10.9%] patients), hypertension (223 [10.7%] patients), and headache (217 [10.4%] patients).
- A total of 1374 (65.7%) patients experienced TEAEs that were assessed to be potentially drug-related by the investigator. The incidence of potentially drug-related TEAEs was similar between patients who were < 50 years of age (1012/1529; 66.2%) and patients who were ≥ 50 years of age (362/562; 64.4%). The most frequently reported TEAEs by PT were polyuria (738 [35.3%] patients), nocturia (585 [28.0%] patients), thirst (264 [12.6%] patients), and polydipsia (226 [10.8%] patients). Most of the events were mild (990/1374) and majority of the mild events (728) occurred in patients < 50 years of age.
- Serious TEAEs were experienced by 412 (19.7%) patients who reported a total of 747 events. Of those 412 patients, 254 were < 50 years of age, and the remaining

158 were ≥ 50 years of age. The most frequently reported serious TEAEs by PT (incidence ≥ 1.0% of all patients) renal cyst infection (37 [1.8%] patients), renal pain (24 [1.1%] patients), pyelonephritis (23 [1.1%] patients), and renal cyst haemorrhage (21 [1.0%] patients). A trend was not identified between serious events and treatment dosage. The majority (127/412) of serious events occurred at 12 to 24 months of treatment exposure.

- A total of 551 (25.8%) patients discontinued the study. Of these discontinuations, 120 (5.6%) were due to loss to follow-up, 105 (4.9%) were due to withdrawal by patient, 92 (4.3%) were due to AEs, 53 (2.5%) were due to physician decision, and 14 (0.7%) were due to noncompliance with the study drug. A total of 141 (6.6%) patients discontinued due to "other" nonspecified reasons.
- Treatment-emergent AEs with a fatal outcome were experienced by 22 (1.1%) patients. All fatal events were not related to JINARC.

Discussion

This study was intended to explore the safety profile and usage of JINARC when used in the real-world setting in Europe, particularly with relation to the risk of liver injury that was identified in the interventional pre-registrational studies.

The data presented in this report indicate that the risk mitigation methods are adequate to identify patients who develop hepatotoxicity and demonstrates the adequacy of the suggested liver monitoring for such events and of the suggested steps for the prescriber to take to protect the patient. The data also suggest that these recommended steps were followed, and patients were thus protected from progression to liver injury. Results show adequate clinical assessment of laboratory values where action was taken (drug withdrawal and interruption) in 79.1% of events. The remaining events the majority were considered mild or moderate and not related or recovered with continuous treatment.

Of the 80 patients with ALT or AST levels ≥ 3 × ULN, only 3 (3.8%) patients were on strong CYP3A4 inhibitors; however, transaminase increase was not associated with concomitant medication. Additionally, only 5 out of 252 (2.0%) patients that ended treatment due to tolerability were also on CYP3A4 inhibitors at the time of treatment discontinuation. One of these patients was on strong CYP3A4 inhibitors while the other 4 patients were on moderate CYP3A4 inhibitors. No patient met Hy's Law laboratory criteria, and no significant safety information was identified from the review of the data in 80 patients with confirmed ALT or AST levels ≥ 3 × ULN.

Of the 2091 patients in the safety analysis population, prescribers for 122 (5.8%) patients did not adhere to the recommendations of the SmPC, predominantly including patients

with a CKD stage of 5. The majority of patients (93.9%) initiated therapy at a starting dose of 60 mg as recommended in the SmPC.

A total of 31 cases of pregnancy were identified over the duration of the study. No trends were observed in the use of JINARC in pregnant women.

The average age at study initiation of the cohort was 43.0 years (range: 18 to 79 years), which is similar to the ages in the interventional studies. Overall, 26.9% of the patients in this study were over 50 years of age at initiation of JINARC. This is important as the first phase 3 study (TEMPO 3:4) limited patients to below 50 years. Thus, the examination of the safety in this group is of particular interest. No notable differences were observed in the types of adverse events experienced by patients who were ≥ 50 years old, and the incidence of AEs was comparable to patients who were < 50 years old, including the incidence of potential liver injury.

The 22 deaths reported in the study are unrelated to JINARC and at least 3 events (subarachnoid haemorrhage) are known complications of ADPKD.

The additional risk minimisation measures implemented for JINARC have proven effective in mitigating the risk of liver injury. These, combined with subsequent patient management, have resulted in no deaths related to liver injury.

Overall, no new safety concerns have been identified.

Marketing Authorisation Holder

Otsuka Pharmaceutical Netherlands B.V.

Herikerbergweg 292

1101 CT, Amsterdam

Netherlands

Names and Affiliations of Principal Investigators

There was no Principal Investigator assigned to this study. See Section 3 for a list of National Coordinating Investigators.

2 List of Abbreviations

ADPKD	autosomal dominant polycystic kidney disease
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BT	total bilirubin
CKD	chronic kidney disease
CRO	contract research organisation
CYP	cytochrome p450
eCRF	electronic case report form
ESRD	end-stage renal disease
EU	European Union
IMP	investigational medicinal product
IRE	immediately reportable event
LFT	liver function tests
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
CCI	[redacted]
OPDC	Otsuka Pharmaceutical Development and Commercialization, Inc.
OPNL	Otsuka Pharmaceutical Netherlands B.V.
PASS	post-authorisation safety study
PRAC	Pharmacovigilance Risk Assessment Committee
PT	preferred term
SAP	Statistical Analysis Plan
SD	standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SOC	system organ class
TEAE	treatment-emergent adverse events
THIN	The Health Improvement Network
ULN	upper limit of normal

3 Investigators

A list of the National Coordinating Investigators in the PASS is displayed in Table 3-1.

Table 3-1 List of Coordinating Investigators

Country	Coordinating Investigator
Austria	PPD
Belgium	
Denmark	
Finland	
France	
Germany	
Italy	
Netherlands	
Norway	
Spain	
Sweden	
Switzerland	
United Kingdom	

4 Other Responsible Parties

Table 4-1 Responsible Parties

	Contact Information
OPNL	Otsuka Pharmaceutical Netherlands B.V. Herikerbergweg 292 1101 CT, Amsterdam Netherlands
OPDC	Otsuka Pharmaceutical Development & Commercialization Inc. 2440 Research Blvd. Rockville, Maryland 20850 United States of America
IQVIA (CRO) RDS Inc.	IQVIA RDS Inc. 4820 Emperor Blvd. Durham, North Carolina 27703 United States of America

OPDC = Otsuka Pharmaceutical Development & Commercialization, Inc.; OPNL = Otsuka Pharmaceutical Netherlands B.V.

5 Milestones

The milestones for the study are displayed in Table 5-1.

Table 5-1 Study Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	31 Oct 2016	31 Oct 2016	The date of the first eCRF was completed was considered the start of data collection.
End of data collection	01 Mar 2022	12 May 2024	-
Registration in the EU PAS register	19 Mar 2019	19 Mar 2019	-
Interim report 1	Q4 2019	22 Oct 2019	-
Interim report 2	Q4 2022	14 Nov 2022	-
Final report of study results	Q1 2025	20 Nov 2024	-

eCRF = electronic case report form; EU = European Union; PAS = post-authorisation study.

6 Rationale and Background

Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary disorder and a leading cause of chronic renal failure. The disease is characterised by development and progressive enlargement of renal cysts resulting in ESRD typically in mid to late adulthood. The estimated prevalence of ADPKD in Europe is between 3.76 and 3.96 per 10000.[1]

Tolvaptan is the only treatment option for slowing the progression of kidney disease in patients with ADPKD. Except for tolvaptan, all other currently available treatment options for ADPKD are palliative and directed at minimising complications of the disease rather than addressing underlying renal pathophysiology of pathognomonic cyst formation. Patients with ADPKD who progress to ESRD require renal transplantation frequently after years of renal dialysis.

Tolvaptan is a selective vasopressin V_2-receptor antagonist. Tolvaptan blocks vasopressin and slows cystogenesis and renal function decline in patients with ADPKD. The indication is explicitly described in the SmPC.[2] The indication statement is: "JINARC is indicated to slow the progression of cyst development and renal insufficiency of ADPKD in adults with chronic kidney disease (CKD) Stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease."

Tolvaptan has the potential to cause life threatening idiosyncratic liver injury in patients receiving or administering therapy prescribed for the treatment of ADPKD. In post-marketing experience with tolvaptan in ADPKD, acute liver failure requiring liver transplantation has been reported. The primary focus of this PASS was to characterise and quantify an identified risk for idiosyncratic liver injury in JINARC treated patients

with ADPKD in routine clinical practice. Safety information on other potential risks through characterisation of adverse events (AEs) and other safety information generated from patterns of JINARC use in the real-world, use in patients over the age of 50 years, long-term safety, and other ADPKD associated renal outcomes was be collected, monitored, and assessed.

The PASS was managed by Otsuka Pharmaceutical Development & Commercialization Inc., (OPDC, Rockville, Maryland, USA) and its designees/vendors on behalf of the MAH, Otsuka Pharmaceutical Netherlands B.V.

7 Research Question and Objectives

The goal of this ongoing study was to assess the long-term safety profile of JINARC when prescribed under usual practice for treatment of patients with ADPKD.

Primary Objective

- To characterise and quantify the identified risk of idiosyncratic liver injury in JINARC treated patients with ADPKD in routine clinical practice.

Secondary Objectives

- To evaluate patterns of JINARC use in a real-world setting, including the following:
  - Use and potential risks in pregnant women, including the frequency and outcome of pregnancies associated with the use of JINARC.
  - Prescriber compliance with the SmPC.
- To evaluate the use and potential risks in patients over the age of 50 years.
- To assess the effectiveness of risk minimisation measures among JINARC prescribers.
- To evaluate the incidence and potential risks and ADRs which may be found with long-term use.

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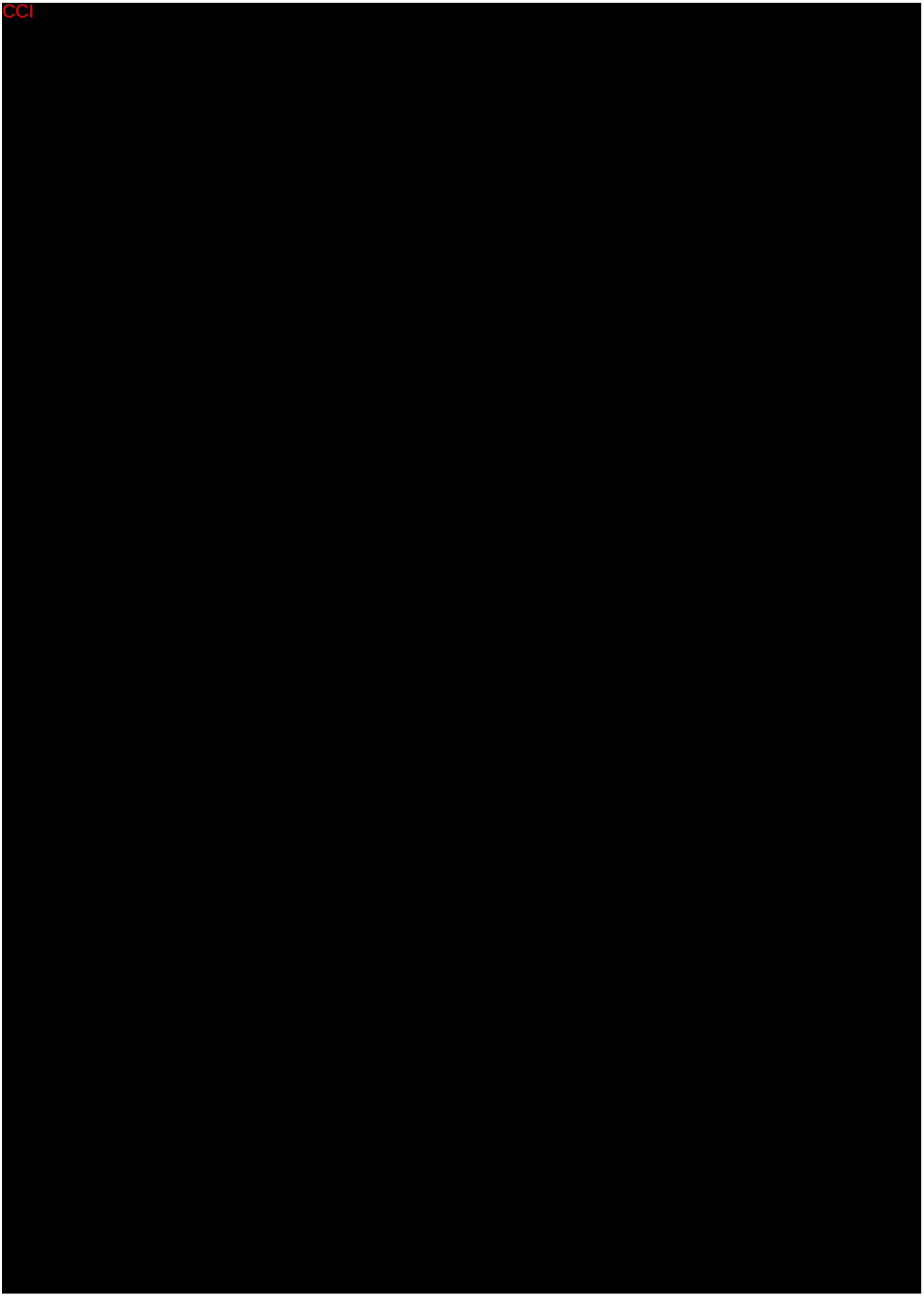
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9 Research Methods

9.1 Study Design

This PASS was designed as a multicentre, prospective, observational study of patients being treated with JINARC for ADPKD to better characterise the specified known risks in real-world treatment through evaluation of AEs and prescribing habits, and collection of data from patients with limited information from clinical trials. Study participation was available to physicians who completed the educational training in all countries in Europe where JINARC is launched and commercially available by prescription. Physicians and patients from other regions could also have been included for comprehensive or separate analysis. This study did not require any additional diagnostic, therapeutic, or monitoring procedures beyond usual medical practice.

This was a study of real-world treatment practices in patients newly initiated on treatment with JINARC for ADPKD to evaluate treatment patterns and outcomes in patients treated in the post-marketing setting. Patients were followed for a minimum of 2 years (or for as long as they participate in the study) and to a maximum of 6 years depending on their recruitment date.

Data regarding the risk of serious hepatotoxicity outside of clinical trials in patients with ADPKD who are treated and monitored in the post-approval setting are not available. Abnormalities of liver function associated with JINARC use in clinical trials occurred within the first 18 months of treatment.

This PASS will further evaluate this known risk, investigate patterns of JINARC use in the real-world, and provide a greater understanding of the overall safety profile of JINARC in a broader patient population.

9.2 Setting

All prescribers within countries that have launched JINARC and who completed the appropriate education were certified and invited to participate in this study. These certified prescribers were invited to enrol patients into the study via the JINARC training portal, and through invitations issued at face-to-face training sessions on the risk minimisation materials. In some countries, training could have been conducted by MAH staff and a personal participation opportunity would have been provided.

Interest in participating in the study was ascertained on an ongoing basis by a CRO. A status list was initiated and maintained by the CRO for each provider approached, and documentation of interest to participate was maintained. Reasons for physician or treatment centre non-participation in the study was also recorded.

The study period was defined as the time from enrolment of the first patient into the study until the last enrolled patient was completely followed. The total study duration was 7.5 years. The study commenced in October 2016 (first patient, first visit) and completed on 19 Feb 2024 (last patient, last visit).

9.3 Subjects

Patients with a diagnosis of ADPKD who were treatment-naïve and were prescribed JINARC by a certified prescriber were eligible for enrolment into the study. The decision to initiate use of JINARC was made independently by the participant and their health care provider and was not mandated by the study design or protocol.

The overall number of patients and sites may have been adjusted during the study to meet enrolment goals, if needed. To the extent possible, consecutive patients meeting inclusion/exclusion criteria were enrolled.

Inclusion Criteria: Patients were eligible for participation in this study if they were:

- Tolvaptan naïve (have never taken tolvaptan including as part of a cross-over or open-label trial).
- Prescribed JINARC for ADPKD in accordance with the SmPC by an appropriately certified prescriber who had completed the required educational training.
- Willing and able to provide informed consent/legal guardian consent; understand the requirements of participation in the study and were able to comply with the study and data collection processes.

Exclusion Criteria: Patients were not eligible for participation in this study if they were:

- Currently or previously a recipient of tolvaptan.
- Prescribed JINARC for ADPKD in a manner not according to the SmPC or if the appropriately certified prescriber had not completed the required educational training.

Withdrawal of Patients: As this was a non-interventional study, no specific withdrawal criteria were specified. Patients were free to withdraw consent at any time. Data was collected up to the time of withdrawal of consent and no additional information was collected after that time. If a patient discontinues treatment with JINARC, but does not withdraw consent to participate in the study, data will continue to be recorded for a minimum of 2 years from the date of first dose.

9.4 Variables

Variables were assessed for the definition of exposure, hepatotoxicity monitoring, potential risks with long-term use, ADPKD progression, patterns of JINARC use, MRU, characterisation of patients (demographic characteristics, including subgroups of interest such as those patients who initiate treatment with JINARC at ≥ 50 years of age), and characterisation of physicians.

9.5 Data Sources and Measurement

This study was initiated and operated by a CRO on behalf of OPDC. Patient-level data for all patients enrolled in the study were provided proactively by participating prescribers and were anonymised.

For the prospective component of the study, patient medical records were the data sources used to collect information on safety and prescribing habits. For the retrospective component of the study, patient/prescription databases and primary care databases were the data sources used to collect information on treated and non-treated JINARC patients, respectively.

Tables of potential clinical primary care, pregnancy, and potential rare AE databases are available in the Section 9.4 of the protocol.

9.6 Bias

This was an observational, prospective study conducted within a real-world setting. Thus, no randomisation was undertaken. As this was a single cohort study, no direct comparator arm was established.

Enrolment bias: Sites were expected to maintain screening logs of all patients meeting eligibility criteria, along with reasons for non-enrolment.

Healthy user bias/depletion of susceptibles: Long-term users of a given medication have generally shown tolerance to the drug and may be at lower risk of liver events than new users. Since patients were enrolled at the time of initiation of a new medication regimen, this should have eliminated bias associated with the study of prevalent medication users.

Follow-up bias: A low loss to follow-up rate of less than 25% was expected, in part due to the ability to follow-up directly with patients even if they did not return to the enrolling centre. Maintaining a low rate of loss to follow-up will lower the risk of bias that could result, for example, if patients with AEs were less likely to return to the study health care provider for follow-up.

Patients were routinely monitored for hepatic function more frequently than was done in the pivotal trial, therefore, events of liver injury may not have been observed as prescribers may have interrupted therapy if liver enzyme elevations were detected. This could have led to a systematic bias in study results.

The participating physicians who were in the study were a self-selected population, and because their activities were being recorded, they were more likely to be motivated to comply with the safety recommendations.

9.7 Study Size

At study initiation, it was expected that 3000 patients would be enrolled over a 6-year period. Due to issues with enrolment, the study protocol was amended on 29 July 2021 to reduce the sample size to 2100 patients (Appendix 1).

A total of 2136 patients were enrolled in the study. Patients were followed-up for at least 2 years or until the study was terminated.

9.8 Data Transformation

A data management plan was created before data collection began and was to describe all functions, processes, and specifications for data collection, cleaning, and validation. The eCRFs include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review was performed based on parameters dictated by the plan. Ad hoc queries were generated within the electronic data capture system and followed-up for resolution.

High data quality standards were maintained, and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality was enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data.

9.9 Statistical Methods

9.9.1 Main Summary Measures

The details on prospective collection of data and data analyses are outlined in the Statistical Analysis Plan (SAP) (Appendix 3).

9.9.2 Main Statistical Methods

The following populations were defined for this study:

- Enrolled: Consists of all patients who were enrolled in the study.
- Safety: Consists of all patients who were enrolled in the study and were administered at least 1 prescription for JINARC.

Study completers are defined as patients who were evaluated at Month 24 during the treatment period. A patient could withdraw consent prior to the end of the trial, but if the withdrawal occurs after Month 24, they were still considered completers.

The core patient population for all safety analyses was based on the safety population.

The main safety analyses were evaluating the risk of serious hepatotoxicity, risk with long-term use, patterns of JINARC use in the real-world (eg, the frequency and outcome

of pregnancies, and prescriber compliance with the SmPC), use and risk in patients over the age of 50 years, and any rare adverse outcomes. Exploratory safety analyses were performed to evaluate morbidity and mortality due to ADPKD progression, and additional safety assessments.

Analysis of prospective data involved evaluating safety (risk of serious hepatotoxicity, rare adverse outcomes, and risk with long-term use) and pattern of use in accordance with the SmPC (in terms of eg, posology, dose and dosage, titration, and dose adjustment for patients taking concomitant cytochrome p450 [CYP] 3A inhibitors, CYP3A inducers, or digoxin).

Analysis of retrospective data involved evaluating the frequency and outcome of pregnancies and use and risk in patients > 50 years of age.

Adverse Events

All AEs were coded by system organ class (SOC) and Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT). The incidence of the AEs was summarised by duration of exposure and dose level: by severity, potentially drug-related, with an outcome of death, serious AEs, and discontinuations due to AEs. For patients with multiple AEs, each AE was counted in its respective category.

Adverse events associated with risks included liver injury, identified by searching the Cholestasis and Jaundice of Hepatic Origin Standard MedDRA Query (SMQ), Hepatic failure and other liver damage-related conditions SMQ, Hepatitis, non-infectious SMQ, Liver-related investigations, signs, and symptoms SMQ, and Liver-related coagulation and bleeding disturbances SMQ.

Adverse events associated with risks also included AEs related to abnormal pregnancy or pregnancy outcome.

Clinical Laboratory Tests

Laboratory measurements that signal the potential for Hy’s Law were reported.

Concomitant Medications

Concomitant medications (including interacting medications) were coded according to PT using the current version World Health Organisation Drug Dictionary and are summarised by preferred drug name.

9.9.2.1 Additional Analyses

Additional endpoints that were analysed include:

- Patient demographic characteristics and reasons for non-enrolment
- The incidence of and reasons for treatment interruption and discontinuation.

All additional endpoints will be summarised by descriptive statistics, eg, proportion, mean, median, SD, minimum and maximum values.

9.9.2.2 Extent of Exposure

Extent of exposure to JINARC is summarised using descriptive statistics for titration and maintenance, respectively, by age (18 to ≤ 50, > 50 to 64 and ≥ 65 years of age), sex, and CKD stage.

9.9.3 Missing Values

The proportion of missing data were reported for each measured variable in the study. No imputations were made on missing values.

9.9.4 Sensitivity Analyses

No sensitivity analysis was run.

9.9.5 Amendments to the Statistical Analysis Plan

The SAP was amended on 12 Oct 2022 to align with the updates in protocol Amendment 4. The current SAP is presented in Appendix 3.

9.10 Quality Control

The Sponsor had ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and the guidelines for Good Pharmacoepidemiology Practices. Training in the protocol and study procedures were conducted via telephone. In addition to telephone and written communication, CRO monitors, or Sponsor representatives may have visited study sites to review protocol compliance and accuracy of data entered in the eCRF. If an onsite monitoring visit was performed, the participating physician must have provided the monitor with full access to all source and study documents.

9.11 Protocol Deviations

The PASS was an observational study of real-world treatment practices with patients newly started on treatment with JINARC with no protocol specified procedures. Only 7 critical protocol deviations were noted throughout the course of the study and included

issues related to the ICF process (2), SAE criteria (3) and other criteria (2 - patient confidentiality and data privacy/enrolment tracking). Tables and listings were not generated for protocol deviations for this study.

9.12 Study Conduct Issues

Issues impacting the conduct of the study include the following:

- Significant delays in patient enrolment - Enrolment was initiated in 2016 but was delayed for multiple reasons including:
  - Delay to expected launch of commercial JINARC
  - Patients not meeting inclusion criteria of being tolvaptan naïve (investigators treated patients prior to consideration for participation in this study)
  - Delay in Ethics Committee approvals following implementation of General Data Protection Regulation in 2018
  - Release of generic tolvaptan in 2021
- Measures taken by the Sponsor and CRO to maximize opportunities for enrolment included increased engagement with sites, provision of additional support, training and communication, identification of additional countries / sites for participation in the study, development of all documents needed to comply with new regulations, and provision of information regarding options for tolvaptan treatment. Enrolment improved over time but remained below targets for the duration of the study.
- COVID-19 pandemic – The multiple restrictions implemented during the start of the pandemic in 2020 caused interruption to enrolment, study visit compliance, site monitoring, and data entry. The Sponsor and CRO supported investigators and site staff to prioritize patient safety as the first measure and many patient visits were cancelled during the initial phases. Remote activities (such as safety monitoring, site identification/initiation, and data monitoring) were encouraged and continued throughout the remainder of the pandemic. Safety reporting, data entry, and query resolution were completed and the impact on the overall conduct of the study was minimised.
- Sample size reduction from 3000 patients to 2100 patients – Lower than expected enrolment occurred throughout the entire recruitment period of the study. Analysis of the available data, however, showed that a reduction of sample size from 3000 to 2100 would have a negligible effect on the ability of the PASS to characterise and quantify the risk of liver injury in the patient population on tolvaptan. The Sponsor believed that the reduction in sample size would not compromise evaluation of patient safety. PRAC approved the reduction in sample size in Nov 2021 (EMEA/H/C/PSA/S/0078.1).

10 Results

10.1 Participants

Two thousand one hundred and thirty-six patients were enrolled into the study. Of those, 2091 (97.9%) patients received at least 1 dose of study medication and were included in the safety analysis. A total of 1564 (73.2%) patients completed the study, 1292 (60.5%) of which had ≥ 24 months of exposure and 272 (12.7%) with < 24 months of exposure. There were 551 (25.8%) patients that discontinued. Patient disposition in the PASS is presented in Table 10.1-1.

Table 10.1-1 Patient Disposition

	Jinarc (N=2136)
Number of Subjects	**n (%)**
Screened	2199
Screen failure	58
Enrolled[a]	2136 (100.0)
Completed	1564 (73.2)
>=24 months of exposure	1292 (60.5)
<24 months of exposure	272 (12.7)
Discontinued	551 (25.8)
Missing completion status	21 (1.0)
Analysed for safety[b]	2091 (97.9)

[a]Received at least one prescription.

[b]Enrolled and received at least one dose of trial medication.
Source: CT-1.1.

10.2 Descriptive Data

The overall mean (SD) age of patients in the PASS was 43.0 years (10.4) (range: 18 to 79 years) with 1558 (73.0%) patients aged < 50 years and 575 (26.9%) patients aged ≥ 50 years; age was not reported for 1 (0.0%) patient. Slightly more male than female patients were enrolled in the study: 1096 patients were male and 1038 patients were female. Racial composition was predominantly white (1967 [92.2%] patients) and not Hispanic or Latino (1757 [82.3%] patients). The overall mean (SD) weight was 82.1 kg (18.0) (range: 34.2 to 175.0 kg).

Patient demographics and baseline characteristics are presented in Table 10.2-1.

Table 10.2-1	Demographics Characteristics, Enrolled Subjects			
Variable		**Male (N=1096)**	**Female (N=1038)**	**Total (N=2134)**
Age [years]				
	N	1095	1038	2133
	Mean (SD)	42.6 (10.6)	43.5 (10.2)	43.0 (10.4)
	Range	18, 78	19, 79	18, 79
Age Group				
Missing Age	n (%)	1 (0.1)	0 (0.0)	1 (0.0)
< 50	n (%)	811 (74.0)	747 (72.0)	1558 (73.0)
>= 50	n (%)	284 (25.9)	291 (28.0)	575 (26.9)
Height [cm]				
	N	876	790	1666
	Mean (SD)	180.6 (8.5)	167.2 (7.1)	174.2 (10.3)
	Range	115.0, 208.0	131.0, 190.0	115.0, 208.0
Weight [kg]				
	N	938	871	1809
	Mean (SD)	88.9 (16.7)	74.8 (16.5)	82.1 (18.0)
	Range	52.0, 175.0	34.2, 143.0	34.2, 175.0
Race				
Missing	n (%)	19 (1.7)	15 (1.4)	34 (1.6)
White	n (%)	1004 (91.6)	963 (92.8)	1967 (92.2)
Black or African American	n (%)	17 (1.6)	20 (1.9)	37 (1.7)
American Indian or Alaska Native	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	n (%)	28 (2.6)	23 (2.2)	51 (2.4)
Native Hawaiian or Other Pacific Islander	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other	n (%)	28 (2.6)	17 (1.6)	45 (2.1)
Ethnicity				
Hispanic or Latino	n (%)	116 (10.6)	106 (10.2)	222 (10.4)
Not Hispanic or Latino	n (%)	902 (82.3)	855 (82.4)	1757 (82.3)
Not Reported	n (%)	16 (1.5)	15 (1.4)	31 (1.5)
Unknown	n (%)	62 (5.7)	62 (6.0)	124 (5.8)
Tobacco				
Current	n (%)	200 (18.2)	153 (14.7)	353 (16.5)
Former	n (%)	152 (13.9)	127 (12.2)	279 (13.1)
Never	n (%)	2 (0.2)	1 (0.1)	3 (0.1)
Missing	n (%)	742 (67.7)	757 (72.9)	1499 (70.2)
Alcohol				
Current	n (%)	367 (33.5)	258 (24.9)	625 (29.3)
Former	n (%)	34 (3.1)	26 (2.5)	60 (2.8)
Never	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	n (%)	695 (63.4)	754 (72.6)	1449 (67.9)
Total Kidney Volume [mL]				
	N	368	328	696
	Mean (SD)	2178.2 (1324.2)	1658.7 (884.3)	1933.4 (1166.7)
	Median	1783.5	1479.0	1645.5
	Range	13.0, 8030.0	293.0, 6350.0	13.0, 8030.0

Note: Percentages are based on the number of subjects enrolled.
Note: Gender is missing for 2 subjects.
Source: CT-3.1.1.

Across all age groups, the majority of patient's baseline CKD stages were Stage 2 (549, 26.3%), followed by Stage 3b (459, 22.0%), and Stage 3a (455, 21.8%), accounting for 70.1% of the study population. Two hundred and ninety-seven (14.2%) patients were Stage 1, 83 (4.0%) were Stage 4a, 30 (1.4%) were Stage 4b, and just 2 (0.1%) were Stage 5 at baseline (ST-13.1). Baseline CKD stage by age group is provided in Table 10.2-2.

Autosomal dominant polycystic kidney disease medical history is provided in CT-3.3.1.

Table 10.2-2 Baseline CKD Stage by Age Group

		Jinarc (N=2091)
Age (Years)	**CKD Stage**	**n (%)[a]**
18 - 35	1	213 (10.2)
	2	145 (6.9)
	3a	53 (2.5)
	3b	28 (1.3)
	4	9 (0.4)
	5	0 (0.0)
36 - 50	1	80 (3.8)
	2	340 (16.3)
	3a	282 (13.5)
	3b	234 (11.2)
	4	51 (2.4)
	5	0 (0.0)
>50	1	4 (0.2)
	2	64 (3.1)
	3a	120 (5.7)
	3b	197 (9.4)
	4	53 (2.5)
	5	2 (0.1)
Any Age	1	297 (14.2)
	2	549 (26.3)
	3a	455 (21.8)
	3b	459 (22.0)
	4	113 (5.4)
	5	2 (0.1)

Note: Percentages are based on the number of enrolled subjects.

[a]Subjects receiving at least one dose of study medication are included in the safety analysis.

Source: ST-1.

10.3 Outcome Data

A total of 2091 (97.9%) of 2136 patients enrolled in the PASS were included in the safety analysis population. The PASS analysis population consists of all patients who were enrolled in the study and have been administered at least 1 prescription for JINARC.

10.4 Main Results

10.4.1 Risk of Drug-induced Liver Injury

Liver function was consistently monitored throughout the study on a single-case level since the baseline visit at monthly visits for 18 months, and every 3 months thereafter. The percentage of patients with liver parameters (liver function leverage) by month is presented in ST-7.

No patient met Hy's Law laboratory criteria (CT-6.1.1). There was one liver transplant during the study, however it was not related to JINARC or potentially liver injury.

In the study there were a total of 258 (12.3%) patients with elevation of hepatic transaminases and/or hepatic events potentially associated with the risk of liver injury were identified (CT-5.1). The incidence of potentially liver injury related laboratory test abnormalities is presented in CT-10.2.1.

Overall, elevated ALT or AST levels (≥ 3 × ULN) was identified in 80 (4.0%) patients in the clinical database (CT-5.1). Eighteen of the 80 patients experienced a second episode of ALT or AST increased ≥ 3 × ULN.

The incidence of elevated ALT or AST was stratified by duration of exposure. Twenty (1.0%) patients had ALT or AST ≥ 3 × ULN < 6 months from the date of the first dose of JINARC, 19 (1.1%) patients had elevation from 6 to 12 months of the first dose, 8 (0.5%) patients had elevation from 12 to 18 months, 2 (0.1%) patients had elevation from 18 to 24 months, 5 (0.4%) patients within 24 to 36 months, and 5 (0.5%) patients from 36 months (ST-22).

The initial incidence of elevated ALT or AST levels (≥ 3 × ULN) was stratified by treatment dosage; 12 patients experienced ALT or AST levels ≥ 3 × ULN at 60 mg, 14 at 90 mg, and 40 at 120 mg (ST-21).

Additional review of the data in the 80 patients with confirmed elevated ALT or AST (≥ 3 × ULN) was conducted. Results of the data analysis are summarised below and presented within narratives in Appendix 4.

Seventy-eight (3.9%) patients experienced ALT or AST > 3 × ULN, 49 patients had ALT or AST > 5 × ULN, 15 patients had ALT or AST > 10 × ULN, and 5 patients had ALT or AST > 20 × ULN (CT-10.2.1).

A total of 27 (1.4%) patients experienced > 2× ULN total bilirubin (BT); but no patient experienced ALT or AST > 3 × ULN and BT > 2 × ULN (CT-10.2.1).

A total of 244 hepatic TEAEs (11.7%) were reported (CT-6.1.2). The majority of these TEAEs were in CKD Stage 2 (75; 13.1%), Stage 3a (60; 12.7%), and Stage 3b (53; 10.5%) (ST-8). The most frequently occurring hepatic TEAEs were ALT increased, hepatic enzyme increased, AST increased, and transaminases increased. Discontinuation of JINARC in response to the hepatic AEs occurred in 65 (3.1%) patients (CT-6.2.1).

It can be concluded from the review of cases of elevated ALT or AST and the incidence of hepatic events, that severity was not the only criterion for the decision for drug withdrawal or end of treatment, but mild cases also resulted in the end of treatment. Data shows that monitoring of patients with mild intermittent hepatic disorders resulted in adequate clinical assessment of laboratory values and resulted in adequate action being taken by the treating physician. Individual case review of elevated ALT or AST is presented in Section 10.4.2.2.

Patient narratives have been described in detail for patients with potential liver injury and patients with transaminases ≥ 3 × ULN (Appendix 4).

10.4.2 Patterns of Use in Real-world Setting

10.4.2.1 Use in Pregnant Women

The incidence of patients who intentionally or unintentionally became pregnant or reported pregnancy of a partner was monitored throughout the PASS. Of the 1014 female patients in the safety sample, 607 (59.9%) met the criteria of childbearing potential. A total of 168 (16.6%) female patients received a pregnancy test after enrolment, with 21 (2.1%) positive test results (ST-2). An additional 10 pregnancies were identified based on manual review of individual CRFs. Thus, a total of 31 cases of pregnancy were identified over the 7.5-year duration of the study.

Individual case review of the 31 pregnancies showed:

- Thirteen cases where there was no maternal exposure, due to the patient stopping treatment before becoming pregnant (ie planned pregnancy).
- Twelve cases where maternal exposure was identified, 6 of which discontinued treatment the same day pregnancy was detected.
- Two cases where insufficient information was provided to assess maternal exposure.
- Four cases that reported pregnancy of partner.

Of the 31 pregnancies, 2 patients had premature babies both of which had pre-eclampsia; 1 experienced neonatal disorder, which resulted in treatment interruption. Neither of the patients were taking JINARC at the time of delivery.

10.4.2.2 Prescriber Compliance

Prescriber adherence to the recommendations of the SmPC was monitored. Of the 2091 patients in the safety analysis population, prescribers for 122 (5.8%) patients did not adhere to the recommendations of the SmPC, predominantly due to a CKD stage of 5 (75 patients) (CT-6.1.5). A total of 19 patients were on strong and moderate CYP3A4 inhibitors at starting dose (ST-3). Sixteen of these patients (16/19; 84.2%) that were on strong and moderate CYP3A4 inhibitors started JINARC at 45/15 mg. However, per the JINARC SmPC, patients on moderate CYP3A inhibitor should have been started at a split 15 mg and 15 mg dose, and those on strong CYP3A inhibitor should have been started at 15 mg per day.[2]

Of the 80 patients with confirmed elevated ALT or AST ($\geq 3 \times$ ULN), review of the individual cases showed 86 events in total (CT-10.2.1 and CT-10.2.2). JINARC was discontinued in 39 events, interrupted in 26 events, and dose reduced in 3 events, indicating prescriber compliance in 79.1% (68 out of 86). Action taken was not reported for 3 events. In 15 events (13 events $> 3 \times$ ULN and 2 events $> 5 \times$ ULN) treatment was not changed with a severity of mild to moderate in majority of events (n = 8) or not reported (n = 6). There were 4 events considered unrelated and 5 where causality was not reported.

Dose initiation as recommended in the SmPC was also monitored. The majority of patients (1963/2091; 93.9%) initiated therapy at a starting dose of 60 mg as recommended in the SmPC (ST-20).

Prescriber adherence was further demonstrated by monitoring the exposure during the study, adjusting the treatment needs of each patient. The overall mean (SD) duration of exposure in the PASS was 976.0 (677.0) days, with the minimum duration of exposure at 1 day, maximum at 2319 days, and the median at 978.0 days (ST-12). There was a total of 428 (20.5%) down titrations, with the majority of those patients (321/428) only being down titrated once. Reasons for down titration included tolerability (194 patients), "other" (194 patients), abnormal liver function tests (38 patients), and on CYP3A inhibitors and missing for 1 patient each, respectively (ST-14.1 and ST-14.2).

The majority of events resulting in noncompliance of exposure were either due to elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment or volume depletion (40 [1.9%] and 23 [1.1%] patients, respectively; ST-15).

10.4.3 Patterns of JINARC Use

10.4.3.1 Use in Patients ≥ 50 Years

Use and potential risks of JINARC in patients over the age of 50 years was monitored in the study. The majority of patients (1601 [76.6%]) were ≤ 50 years of age, 444 (21.2%) patients were > 50 to 64 years, and 45 (2.2%) patients were ≥ 65 years of age (CT-6.1.4).

A total of 575 (26.9%) of the patients in the PASS were ≥ 50 years (Table 10.2-1). The majority baseline CKD stage for patients > 50 years was Stage 3b (197 [9.4%] patients), followed by Stage 3a (120 [5.7%] patients), and Stage 2 (64 [3.1%] patients) (ST-1).

Incidence of potentially drug-related TEAEs occurred at a similar ratio for patients ≥ 50 years (362/562, 64.4%) to that of patients < 50 years (1012/1529, 66.2%; ST-16.1).

The most frequently reported serious TEAEs by PT in patients ≥ 50 years was acute kidney injury with 11 events, renal cyst infection and pyelonephritis with 9 events each, and renal pain with 6 events (ST-16.2). No differences were noted in the type of TEAEs experienced by patients who were ≥ 50 years old, and the experience was comparable to patients who were < 50 years old.

10.4.3.2 Long-term Use

The overall mean (SD) duration of exposure in the PASS was 976.0 (677.0) days ranging from 1 to 2319 days (ST-12).

A total of 1839 (87.9%) patients experienced TEAEs during the study; the majority (1533/2091; 73.3%) experienced TEAEs within < 6 months of treatment exposure. Incidence of TEAEs was 49.1% (829 patients) from 6 to 12 months, 56.1% (859 patients) from 12 to 24 months, 49.5% (639 patients) from 24 to 36 months, and 60.4% (550 patients) from > 36 months of treatment exposure (ST-17.1).

The most frequently reported TEAEs by PT that occurred at < 6 months of treatment duration were polyuria in 704 patients, nocturia in 530 patients, thirst in 249 patients, and polydipsia in 219 patients. These events decreased at 6 to 12 months of exposure and occurred in 42, 37, 10, and 5 patients, respectively for each PT at 6 to 12 months of exposure (ST-17.1).

Similarly, incidence of ALT or AST ≥ 3 × ULN decreased with length of exposure and occurred most frequently at < 6 months and 6 to 12 months of treatment duration, decreasing from 12 to 18 months, and further from 18 to 24 months (ST-22).

The incidence of serious TEAEs gradually increased over time with highest incidence occurring most frequently at 12 to 24 months (127 [8.3%] patients), 24 to 36 months (107 [8.3%] patients), and > 36 months (110 [12.1%] patients) of treatment exposure (ST-17.2). The most frequent serious TEAEs reported between 12 to 24 months were renal pain (11 [0.7%] patients), renal cyst infection (9 [0.6%] patients), and renal cyst haemorrhage (8 [0.5%] patients) (ST-17.2). The most frequent serious TEAEs reported between 24 to 36 months were renal cyst infection (8 [0.6%] patients), renal cyst haemorrhage (6 [0.5%] patients), and pyelonephritis (6 [0.5%] patients) (ST-17.2).

10.5 Other Analyses

10.5.1 Progression of Chronic Kidney Disease During the Trial

10.5.1.1 Chronic Kidney Disease Progression by Stage

The frequency of patient progression from one CKD stage to the next was monitored. At baseline, majority of the patients (n = 549; 29.3%) were Stage 2. As of the final CKD stage recorded, 349 of these patients remained Stage 2, and the majority patients were Stage 3a and 3b (n = 340 and n = 448, respectively) (ST-13.1 and ST-13.2).

The number of patients in early and late Stage 4 CKD was also monitored. At baseline, 83 patients were Stage 4a and 30 patients were Stage 4b. As of the final CKD stage recorded, the number of patients in early Stage 4a was 141 and 283 in late Stage 4b (ST-13.1). A summary of the shift in CKD progression by stage is presented in Table 10.5.1.1-1.

Table 10.5.1.1-1 Summary of Shift in CKD Stage

		FINAL CKD STAGE						
Baseline[a] CKD Stage	# of Subjects at Baseline	Stage 1	Stage 2	Stage 3a	Stage 3b	Stage 4a	Stage 4b	Stage 5
Stage 1	297	167	112	14	2	0	1	1
Stage 2	549	21	216	198	85	9	19	1
Stage 3a	455	1	17	115	210	42	60	10
Stage 3b	459	0	3	10	144	80	148	74
Stage 4a	83	0	1	1	6	10	43	22
Stage 4b	30	0	0	2	1	0	12	15
Stage 5	2	0	0	0	0	0	0	2

[a]Baseline = last pre-dose evaluation.
Source: ST-13.2.

10.5.1.2 CKD Stage Progression by Age

The frequency of patient progression from one CKD stage to the next stratified by age group was also monitored. At baseline, majority of patients < 40 years were Stage 1 (n = 249), 40 to 50 years were Stage 2 (n = 239), and >50 years were Stage 3b (n = 197). The majority remained at the same stage or progressed to the next stage in each age group at the last CKD stage recorded. A summary of CKD stage progression in patients < 40 years, 40 to 50 years, and > 50 years are presented in Table 10.5.1.2-1, Table 10.5.1.2-2, and Table 10.5.1.2-3, respectively.

Table 10.5.1.2-1 Summary of Shift in CKD Stage in Patients < 40 Years

CKD Stage	# of Patients at Baseline	Stage 1	Stage 2	Stage 3a	Stage 3b	Stage 4a	Stage 4b	Stage 5
Stage 1	249	153	86	7	1	0	1	1
Stage 2	246	19	113	70	27	7	9	1
Stage 3a	112	1	4	28	50	11	16	2
Stage 3b	72	0	1	3	24	11	21	12
Stage 4a	11	0	0	0	2	2	4	3
Stage 4b	8	0	0	1	0	0	5	2
Stage 5	0	0	0	0	0	0	0	0

Baseline = Last Pre-Dose Evaluation.
Follow-up time = Last Assessment Date of Serum Creatinine - First Date of IMP + 1.
Source: ST-13.4.

Table 10.5.1.2-2 Summary of Shift in CKD Stage in Patients 40 to 50 Years

CKD Stage	# of Patients at Baseline	Stage 1	Stage 2	Stage 3a	Stage 3b	Stage 4a	Stage 4b	Stage 5
Stage 1	44	13	24	6	1	0	0	0
Stage 2	239	2	84	99	42	2	10	0
Stage 3a	223	0	10	58	96	22	33	4
Stage 3b	190	0	1	2	62	32	60	33
Stage 4a	30	0	0	1	1	3	15	10
Stage 4b	11	0	0	1	0	0	5	5
Stage 5	0	0	0	0	0	0	0	0

Baseline = Last Pre-Dose Evaluation.
Follow-up time = Last Assessment Date of Serum Creatinine - First Date of IMP + 1.
Source: ST-13.3.

Table 10.5.1.2-3 Summary of Shift in CKD Stage in Patients > 50 Years

CKD Stage	# of Patients at Baseline	Stage 1	Stage 2	Stage 3a	Stage 3b	Stage 4a	Stage 4b	Stage 5
Stage 1	4	1	2	1	0	0	0	0
Stage 2	64	0	19	29	16	0	0	0
Stage 3a	120	0	3	29	64	9	11	4
Stage 3b	197	0	1	5	58	37	67	29
Stage 4a	42	0	1	0	3	5	24	9
Stage 4b	11	0	0	0	1	0	2	8
Stage 5	2	0	0	0	0	0	0	2

Baseline = Last Pre-Dose Evaluation.
Follow-up time = Last Assessment Date of Serum Creatinine - First Date of IMP + 1.
Source: ST-13.5.

10.5.2 Results of Liver Function Tests Following Discontinuation of JINARC

The initial incidence of elevated ALT or AST (≥ 3 × ULN) was stratified by treatment dosage; 12 patients experienced ALT or AST levels ≥ 3 × ULN at 60 mg, 14 at 90 mg, and 40 at 120 mg (ST-21).

Review of the data showed that all patients had been exposed to JINARC prior to ALT/AST increase. The data presents the dosage information for a whole (monthly) analysis period, reflecting the status at the end of period only. For cases in which the prescriber interrupted or discontinued treatment in the beginning of the analysis period, dosage taken from the data base shows 0 mg (ST-21). This has been acknowledged and updated data is presented in Section 10.4.1.

10.5.3 Tolerability of JINARC at High Doses

The majority of patients (1963/2091, 93.9%) initiated therapy at the recommended starting dose of 60 mg (ST-20). However, 33 (1.6%) patients initiated JINARC therapy at higher than recommended doses, and 95 (4.5%) patients initiated JINARC at lower than recommended doses.

Qualitatively, no differences were identified between the dose groups during the first 10 days of JINARC treatment, with aquaretic effects (PTs: polyuria, thirst, nocturia, polydipsia, and dry mouth) being amongst the most common events reported in all 3 dose groups. TEAEs related to aquaretic effects were generally reported more frequently in patients that started treatment at the recommended dose of 60 mg, including higher incidence of polyuria, nocturia, and polydipsia compared with both the higher and lower than recommended dose. No meaningful differences were noted in the other TEAEs reported in these groups (ST-27).

10.5.4 Co-administration of CYP3A4 Inhibitors

A total of 124 patients received JINARC co-administration with one or more CYP3A4 inhibitors. Sixteen of these patients received strong CYP3A4 inhibitors (amiodarone hydrochloride, clarithromycin, ketoconazole, and ritonavir) (Table 10.5.4-1).

Table 10.5.4-1 Summary of JINARC Co-administration with CYP3A4 Inhibitors	
	Jinarc (N=2136)
CYP3A4 Inhibitors[a]	**n (%)**
Amiodarone Hydrochloride	1 (0.05)
Cimetidine	1 (0.05)
Ciprofloxacin	76 (3.56)
Ciprofloxacin Hydrochloride;hydrocortisone	1 (0.05)
Clarithromycin	12 (0.56)
Diltiazem	4 (0.19)
Diltiazem Hydrochloride	11 (0.51)
Erythromycin	3 (0.14)
Erythromycin Ethylsuccinate;sulfafurazole	1 (0.05)
Fluconazole	5 (0.23)
Ketoconazole	2 (0.09)
Miconazole	1 (0.05)
Ritonavir	1 (0.05)
Verapamil	5 (0.23)

Note: Percentages are based on the number of subjects enrolled.

[a]Medications are coded using the WHO drug dictionary (WHODRUG B3G MAR 2022).
Source: CT-4.2.

Of the 80 patients with ALT or AST levels ≥ 3 × ULN, only 3 (3.8%) patients were on strong CYP3A4 inhibitors; however, transaminase increase was not associated with concomitant medication (ST-23).

A total of 252 patients discontinued JINARC treatment due to tolerability (ST-24). Of these 252 patients, 5 (2.0%) patients were receiving one or more CYP3A4 inhibitors at the time of treatment discontinuation (ST-24). One of these patients was on strong CYP3A4 inhibitors while the remaining 4 patients were on moderate CYP3A4 inhibitors.

10.5.5 Incidence of Renal Impairment

A total of 98 (4.7%) patients experienced TEAEs with a PT of renal impairment (CT-8.2.1). Eleven (0.5%) of the events resulted in treatment discontinuation (CT-8.6.2.1).

Of the 98 TEAEs of renal impairment reported, 13 events in 11 patients were assessed as serious and only 1 of these serious events was considered by the investigator to be related to study drug; however, treatment was stopped due to progression of underlying disease (CT-8.9.1, CT-8.9.2, PDATA-8). Severity of the serious TEAEs was assessed as mild in 2 patients, moderate in 4 patients, and severe in 5 patients (CT-8.5.3).

Specific information regarding the nature of renal impairment or additional information supporting new diagnosis of renal impairment is lacking in the majority of patients

precluding final assessment. No significant new safety information was identified from review of these cases.

10.5.6 Incidence and Timing of Patient Progression to Renal Replacement (Renal Transplantation or Dialysis)

The incidence and timing of patient progression to renal transplant or dialysis was monitored in the study. In total, 29 patients have been identified with progression to end-stage renal disease requiring dialysis or renal transplant (CT-6.2.4). The majority of these patients (16/29) had a baseline CKD Stage 3b with a mean onset of 44.3 months (range: 9 to 60). One patient had a baseline CKD Stage 3a and had progressed to transplant or dialysis at 47 months into the study. Of the 7 patients who had a baseline CKD Stage 4a, the mean onset was 42.3 months (range: 27 to 55), and 2 patients that began with a baseline CKD Stage 4b had a mean onset of 21.5 months (range: 20 to 23). In 3 patients the baseline CKD stage was unknown. A summary of duration of progression to dialysis or transplant by baseline CKD stage is presented in ST-29.

10.5.7 Incidence of Liver Transplantation

One patient in this study received a liver transplant (CT-9.2). The patient was a PPD-year-old PPD, with a medical history of congenital cystic kidney disease. PPD who started JINARC treatment on PPD at a dose of 45 mg/30 mg orally.

The patient's liver function test results were within normal range throughout treatment with JINARC. The patient's baseline values and at screening on PPD were alkaline phosphatase: 64 IU/l (normal range: 30-130), ALT: 16 IU/l (normal range: 11 to 55), AST: 20 IU/L (normal range: 13 to 42), and bilirubin: 0.41 mg/dL (normal range: 0 to 1.23). On PPD, ALT was 12 IU/L, AST was 17 IU/L, and bilirubin was 0.35 mg/dL.

On PPD, the patient underwent elective liver transplant due to existing polycystic liver disease. The procedure occurred 278 days after initiating JINARC treatment. Following the event, JINARC was discontinued. The investigator assessed the event as not related to JINARC and likely related to the patient's underlying condition. The event was considered resolved.

10.6 Adverse Events/Adverse Reactions

10.6.1 Treatment-emergent Adverse Events

Treatment-emergent AEs were experienced by 1839 (87.9%) patients, who reported a total of 10167 events. A total of 412 (19.7%) patients experienced serious TEAEs, and

389 (18.6%) discontinued JINARC due to AEs (CT-8.1.1). The majority of patients (1533/2091; 73.3%) experienced TEAEs within the first 6 months of treatment exposure (ST-17.1). Events were equally distributed between age groups, < 50 years of age (1346/1528, 88.1%), ≥ 50 and < 65 years of age (450/517, 87.0%), and ≥ 65 years of age (42/45, 93.3%) (ST-19).

The SOCs in which the greatest number of patients reported TEAEs were renal and urinary disorders (1282 [61.3%] patients), infections and infestations (760 [36.6%] patients), general disorders and administration site conditions (738 [35.3%] patients), gastrointestinal disorders (685 [32.8%] patients), and metabolism and nutrition disorders (561 [26.8%] patients) (CT-8.2.1).

The most frequently reported TEAEs by PT (incidence ≥ 10% of all patients) were polyuria (743 [35.5%] patients), nocturia (595 [28.5%] patients), renal pain (321 [15.4%] patients), thirst (268 [12.8%] patients), fatigue (262 [12.5%] patients), COVID-19 (238 [11.4%] patients), polydipsia (228 [10.9%] patients), hypertension (223 [10.7%] patients), and headache (217 [10.4%] patients) (CT-8.7.2). Analysis of the incidence of TEAEs by treatment dosage did not identify a trend (ST-18.1). A summary of all AEs and incidence of TEAEs by SOC, MedDRA PT, and severity can be found in CT-8.1.1 and CT-8.2.3, respectively. A summary of incidence of TEAEs by duration of exposure and treatment dosage can be found in ST-17.1 and ST-18.1, respectively.

10.6.2 Potentially Related Treatment-emergent Adverse Events

A total of 1374 (65.7%) patients experienced TEAEs that were assessed to be potentially drug-related by the investigator (CT-8.3.1). The incidence of potentially drug-related TEAEs was similar between patients who were < 50 years of age (1012/1529 patients; 66.2%) and patients who were ≥ 50 years of age (362/562 patients, 64.4%) (ST-16.1). The most frequently reported potentially related TEAEs by PT were polyuria (738 [35.3%] patients), nocturia (585 [28.0%] patients), thirst (264 [12.6%] patients), and polydipsia (226 [10.8%] patients) (CT-8.3.2). The majority of the events were mild (990/1374), and majority of those mild events (728) occurred in patients < 50 years of age (ST-16.1).

A summary of incidence of potentially drug-related TEAEs by SOC, MedDRA PT, severity, and age group can be found in ST-16.1.

10.6.3 Serious Treatment-emergent Adverse Events

Serious TEAEs were experienced by 412 (19.7%) patients, who reported a total of 747 events (CT-8.9.1). Of those 412 patients, 254 (16.6%) were < 50 years of age compared with 158 (28.1%) patients who were ≥ 50 years of age (ST-16.2).

The SOCs in which the greatest number of patients reported serious TEAEs were infections and infestations (137 patients, 197 events), renal and urinary disorders (94 patients, 142 events), and gastrointestinal disorders (56 patients, 66 events) (CT-8.9.1).

The most frequently reported serious TEAEs by PT (incidence ≥ 1.0% of all patients) were renal cyst infection (37 [1.8%] patients), renal pain (24 [1.1%] patients), pyelonephritis (23 [1.1%] patients), and renal cyst haemorrhage (21 [1.0%] patients) (CT-8.9.1). Analysis of the incidence of serious events and treatment dosage did not identify a trend (ST-18.2). By duration of exposure, the incidence of serious TEAEs gradually increased over time: 4.9% (< 6 months), 4.5% (6 - 12 months), 8.3% (12 - 24 months), 8.3% (24 - 36 months), and 12.1% (> 36 months) (ST-17.2).

A summary of incidence of serious TEAEs by SOC, MedDRA PT, severity, and age group; by duration of exposure, and by treatment dosage can be found in ST-16.2, ST-17.2, and ST-18.2, respectively.

10.6.4 Discontinuations

A total of 551 (25.8%) patients discontinued the study. Of these discontinuations, 120 (5.6%) were due to loss to follow-up, 105 (4.9%) were due to withdrawal by subject, 92 (4.3%) were due to AEs, and 53 (2.5%) were due to physician decision. A total of 141 (6.6%) patients discontinued due to "other" nonspecified reasons. A summary of all reasons for discontinuation reported by the investigator is presented in Table 10.6.4-1.

Table 10.6.4-1 Reported Reasons for Discontinuation

	Jinarc (N=2136)
Number of Subjects	**n (%)**
Enrolled	2136 (100.0)
Completed	1564 (73.2)
Discontinued	551 (25.8)
Adverse event	92 (4.3)
Lost to follow-up	120 (5.6)
Non-compliance with study drug	14 (0.7)
Physician decision	53 (2.5)
Pregnancy	4 (0.2)
Study terminated by sponsor	22 (1.0)
Withdrawal by subject	105 (4.9)
Other	141 (6.6)

Note: Percentages are based on the number of subjects enrolled.
Note: Reasons for discontinuation as reported by the investigator in the case report form.
Note: Discontinuations of "study terminated by sponsor" are characterised as patients who had inconsistent information reported by the investigator in the case report form.
Source: CT-2.1.

10.6.5 Fatal Treatment-emergent Adverse Events

Treatment-emergent AEs with a fatal outcome were experienced by 22 (1.1%) patients (CT-8.1.1). A summary of patient IDs and TEAEs with a fatal outcome is presented in Table 10.6.5-1. All fatal TEAEs were assessed as not related to JINARC.

Incidence of fatal TEAEs was slightly higher in males than females (13 males, 9 females) and a majority (16/22; 72.7%) of patients with fatal TEAEs were ≥ 50 years (CT-9.1).

A listing of deaths outcome by individual patient can be found in CT-9.1.

Table 10.6.5-1 Summary of TEAEs Resulting in a Fatal Outcome

Subject ID	Treatment-emergent Adverse Event
PPD	

Note: No additional information is available for TEAEs of death resulting in fatal outcome.
Source: CT-9.1.

11 Discussion

11.1 Key Results

This was a 7.5-year, multicentre, non-interventional, PASS for patients prescribed JINARC for ADPKD. The primary objective of this PASS was to characterise and quantify the identified risk of idiosyncratic liver injury in JINARC treated patients with ADPKD in routine clinical practice.

Two thousand one hundred and thirty-six patients were enrolled into the study. Of these, 2091 (97.9%) patients received at least one dose of study medication and are included in the safety analysis. A total of 1564 (73.2%) patients completed the study.

The overall mean age of patients in the PASS was 43.0 years (SD: 10.4 years) (range: 18 to 79 years). At treatment initiation, the majority of patients (1601; 76.6%) were ≤ 50 years of age, 444 (21.2%) patients were > 50 to 64 years, and 45 (2.2%) patients were ≥ 65 years of age. There were slightly more male than female patients (1096 vs 1038).

A total of 258 patients with elevation of hepatic transaminases and/or hepatic events potentially associated with the risk of liver injury have been identified.

Elevated ALT or AST levels (≥ 3 × ULN) was identified in 80 (4.0%) patients in the clinical database. Action taken (drug withdrawal and interruption) was in line with SmPC in 79.1% of all events. In cases where no action was reported, the majority of events were mild or moderate in nature and considered not related to treatment by the investigator. The initial incidence of elevated ALT or AST (≥ 3 × ULN) was stratified by treatment dosage; 12 patients experienced ALT or AST ≥ 3 × ULN at 60 mg, 14 at 90 mg, and 40 at 120 mg.

In addition, 49 patients had ALT or AST > 5 × ULN, 15 patients had ALT or AST > 10 × ULN, and 5 patients had ALT or AST > 20 × ULN. A total of 27 (1.4%) patients experienced > 2 × ULN BT; no patient met Hy's Law laboratory criteria.

One patient received a liver transplant during the study. The patient had a medical history of polycystic liver disease and underwent elective liver transplant. The transplant was not related to JINARC, and treatment was discontinued after the event.

A total of 244 hepatic AEs were reported with discontinuation of JINARC in response to the hepatic AEs occurring in 65 (3.1%) patients.

Of the 2091 patients in the safety analysis population, prescribers for 122 (5.8%) patients did not adhere to the recommendations of the SmPC, predominantly including patients

with a CKD stage of 5 (75 patients); a total of 19 patients were on strong and moderate CYP3A4 inhibitors at starting dose. Sixteen of these patients (16/19; 84.2%) started JINARC at 45/15 mg. Per the JINARC SmPC, patients on moderate CYP3A inhibitor should have been started at a split 15 mg and 15 mg dose, and those on strong CYP3A inhibitor should have been started at 15 mg per day.

The majority of patients (1963; 93.9%) initiated therapy at a starting dose of 60 mg. The overall mean (SD) duration of exposure in the PASS was 976.0 (677.0) days, with the minimum duration of exposure at 1 day, and maximum at 2319 days.

Baseline CKD stages were Stage 1 (297; 14.2%), Stage 2 (549; 26.3%), Stage 3a (455; 21.8%), Stage 3b (459; 22.0%), Stage 4a (83; 4.0%), Stage 4b (30; 1.4%), and Stage 5 (2; 0.1%). The majority baseline CKD stage for patients > 50 years was Stage 3b (197 patients; 9.4%), followed by Stage 3a (120 patients; 5.7%), and Stage 2 (64 patients; 3.1%). As of the final CKD stage recorded, stages were Stage 1 (189; 9.0%), Stage 2 (349; 16.7%), Stage 3a (340; 16.3%), Stage 3b (448; 21.4%), Stage 4a (141; 6.7%), Stage 4b (283; 13.5%), and Stage 5 (125; 6.0%). No trend was identified when CKD stage shifts were evaluated by age group.

In the 36 patients who initiated treatment at doses higher than 60 mg, the most frequently reported TEAEs within 10 days of treatment initiation were polyuria (6 [16.7%] patients), and thirst and nocturia (3 [8.3%] patients, each). The frequency of these events was comparable or higher in patients who initiated treatment at 60 mg compared with patients in the higher dose group.

Of the 1014 female patients in the safety sample, 607 (59.9%) met the criteria of childbearing potential. A total of 168 (16.6%) female patients received a pregnancy test, with 21 (2.1%) positive test results. An additional 10 pregnancies were identified from a review of all safety data resulting in a total of 31 cases of pregnancy identified. Individual case review of the 31 pregnancies showed that in 13 cases no maternal exposure was reported (planned pregnancies). In 12 cases maternal exposure was identified, 6 of which discontinued treatment the same day pregnancy was detected. Four cases reported pregnancy of partner, 3 cases had exposure up to 3 months, and in 2 cases insufficient information was provided to assess maternal exposure.

Two patients had premature babies; one experienced neonatal disorder, and neither patient was taking JINARC at the time of delivery.

Majority of patients (1533/2091; 73.3%) experienced TEAEs within < 6 months of treatment exposure. Incidence of TEAEs was 49.1% (829 patients) from 6 to 12 months, 56.1% (859 patients) from 12 to 24 months, 49.5% (639 patients) from 24 to 36 months,

and 60.4% (550 patients) from 36 months of treatment exposure. Analysis of the incidence of TEAEs by treatment dosage did not identify a trend.

Treatment-emergent AEs were experienced by 1839 (87.9%) patients who reported a total of 10167 events. Treatment-emergent AEs were equally distributed between age groups, < 50 years of age (1346/1528, 88.1%), ≥ 50 and < 65 years of age (450/517, 87.0%), and ≥ 65 years of age (42/45, 93.3%). The most frequently reported TEAEs by PT were polyuria (743 [35.5%] patients), nocturia (595 [28.5%] patients), renal pain (321 [15.4%] patients), thirst (268 [12.8%] patients), fatigue (262 [12.5%] patients), COVID19 (238 [11.4%] patients), polydipsia (228 [10.9%] patients), hypertension (223 [10.7%] patients), and headache (217 [10.4%] patients). Adverse events observed in this PASS are in line with known safety profile of JINARC and underlying condition in ADPKD population.

A total of 1374 (65.7%) patients experienced TEAEs that were assessed to be potentially drug-related by the investigator. The incidence of potentially related TEAEs was similar between patients who were < 50 years of age (1012/1529 patients; 66.2%) and patients who were ≥ 50 years of age (362/562 patients; 64.4%). The most frequently reported TEAEs by PT were polyuria (738 [35.3%] patients), nocturia (585 [28.0%] patients), thirst (264 [12.6%] patients), and polydipsia (226 [10.8%] patients). Most of the events were mild (990/1374) and majority of the mild events (728) occurred in patients < 50 years of age. The majority of frequently reported TEAEs are expected ADRs in line with the pharmacology of JINARC.

Serious TEAEs were experienced by 412 (19.7%) patients who reported a total of 747 events. Of those 412 patients, 254 were < 50 years of age, and the remaining 158 were ≥ 50 years of age. The most frequently reported serious TEAEs by PT were renal cyst infection (37 [1.8%] patients), renal pain (24 [1.1%] patients), pyelonephritis (23 [1.1%] patients), and renal cyst haemorrhage (21 [1.0%] patients). A trend was not identified between serious events and treatment dosage. The majority (127/412) of serious events occurred at 12 to 24 months of treatment exposure.

A total of 551 (25.8%) patients discontinued the study. Of these discontinuations, 120 (5.6%) were due to loss to follow-up, 105 (4.9%) were due to withdrawal by patient, 92 (4.3%) were due to AEs, 53 (2.5%) were due to physician decision, and 14 (0.7%) were due to noncompliance with the study drug. A total of 141 (6.6%) patients discontinued due to “other” nonspecified reasons. Review of cases showed that in 110 cases study was terminated within 2 weeks, of which the majority of patients never were exposed to treatment.

Treatment-emergent AEs with a fatal outcome were experienced by 22 (1.1%) patients. All fatal events were not related to JINARC.

11.2 Limitations

There were considerable issues with enrolment in this study, with patient accrual falling considerably behind the initial projections. This was mostly due to much slower commercial uptake than was anticipated and a slower rate of new countries achieving commercial launch from which patients for the study are necessarily drawn. In addition, in 2018 the General Data Protection Regulation was implemented resulting in the requirement of Ethics Committee approvals, thus delaying recruiting. The impact of COVID-19 and site fatigue were also factors. The release of generic tolvaptan in 2021 also resulted in a large number of patients discontinuing participation from the study. Measures were taken to maximize opportunities for enrolment but remained below targets for the duration of the study. To address this limitation, the study protocol was amended (Amendment 4) to reduce the sample size from 3000 to 2100, and the study follow-up duration from 3 to 2 years.

11.3 Interpretation

The benefit-risk of JINARC remains unchanged. Based on the data, patients ≥ 50 years of age do not appear to be at greater risk for developing TEAEs.

Data show that risk minimisation measures implemented for JINARC have proven effective. As JINARC has been on the market for more than 9 years in Europe, benefit-risk are well understood, and appropriate treatment is well established in clinical practice.

No new safety information has been identified with the analysis of study data.

11.4 Generalisability

As this was a real-world study conducted in patients prescribed JINARC in a standard clinic setting, the results should be generalisable to the use of tolvaptan in Europe and maybe beyond. The only bias that may affect this is that the prescribers who agreed to be investigators (and probably also the patients recruited) may have been more likely to be motivated to comply with the safety recommendations, possibly leading to slightly favorable results.

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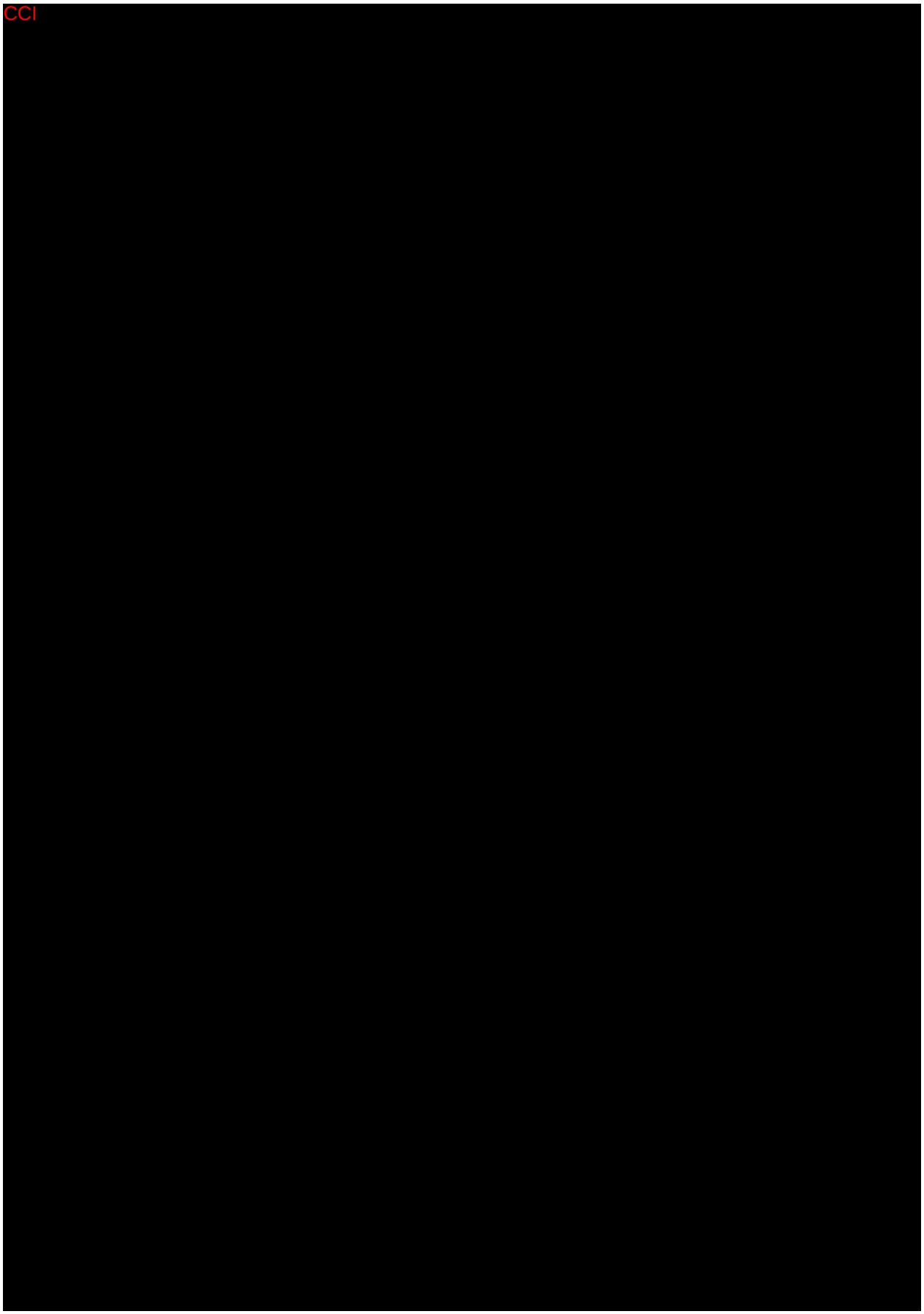
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13 Conclusion

This study was intended to explore the safety profile and usage of JINARC when used in the real-world setting in Europe, particularly with relation to the risk of liver injury that was identified in the interventional pre-registrational studies.

The data presented in this report indicate that the risk mitigation methods are adequate to identify patients who develop hepatotoxicity and demonstrates the adequacy of the suggested liver monitoring for such events and of the suggested steps for the prescriber to take to protect the patient. The data also suggest that these recommended steps were followed, and patients were thus protected from progression to liver injury. Results show adequate clinical assessment of laboratory values where action was taken (drug withdrawal and interruption) in 79.1% of events. The remaining events the majority were considered mild or moderate and not related or recovered with continuous treatment.

Of the 80 patients with ALT or AST levels ≥ 3 × ULN, only 3 (3.8%) patients were on strong CYP3A4 inhibitors; however, transaminase increase was not associated with concomitant medication. Additionally, only 5 out of 252 (2.0%) patients that ended treatment due to tolerability were also on CYP3A4 inhibitors at the time of treatment discontinuation. One of these patients was on strong CYP3A4 inhibitors while the other 4 patients were on moderate CYP3A4 inhibitors. No patient met Hy's Law laboratory criteria, and no significant safety information was identified from the review of the data in 80 patients with confirmed ALT or AST levels ≥ 3 × ULN.

Of the 2091 patients in the safety analysis population, prescribers for 122 (5.8%) patients did not adhere to the recommendations of the SmPC, predominantly including patients with a CKD stage of 5. The majority of patients (93.9%) initiated therapy at a starting dose of 60 mg as recommended in the SmPC.

A total of 31 cases of pregnancy were identified over the duration of the study. No trends were observed in the use of JINARC in pregnant women.

The average age at initiation was 43.0 years (range: 18 to 79 years), which is very similar to the ages in the interventional studies. Overall, 26.9% of the patients were over 50 years of age at initiation of JINARC in this study. This is important as the first phase 3 study (TEMPO 3:4) limited patients to below 50 years. Thus, the examination of the safety in this group is of particular interest. No differences were noted in the type and incidence of TEAEs experienced by patients who were ≥ 50 years old, and the experience was

comparable to patients who were < 50 years old; including the incidence of potential liver injury.

The 22 deaths reported in the study are unrelated to JINARC and at least 3 events (subarachnoid haemorrhage) are known complications of ADPKD.

The additional risk minimisation measures implemented for JINARC have proven effective in mitigating the risk of liver injury. These, combined with the subsequent patient management and adherence to the SMPC, have resulted in no deaths related to liver injury.

Overall, no new safety concerns have been identified.

14 References

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