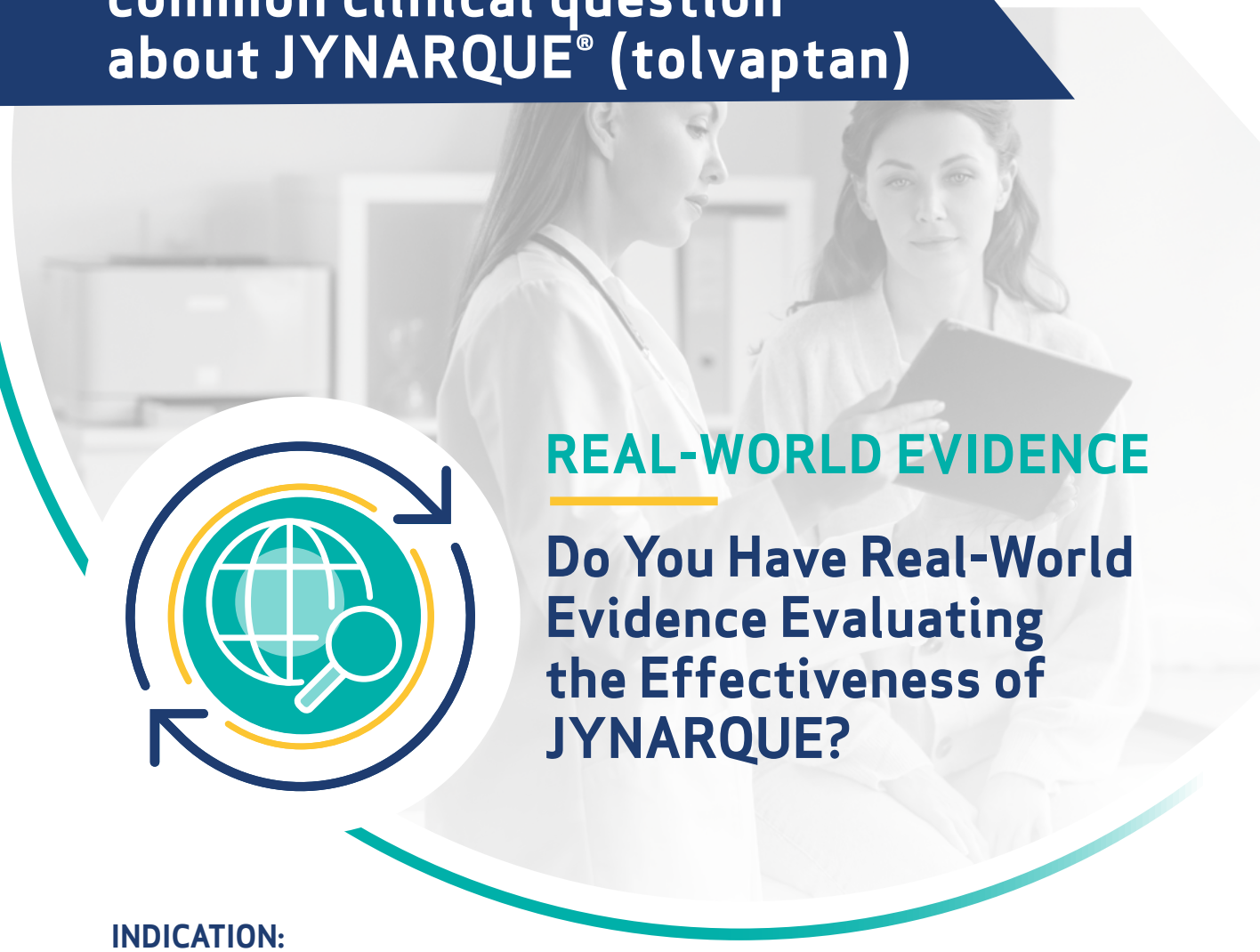
An evidence-based answer to a

common clinical question about JYNARQUE® (tolvaptan)



REAL-WORLD EVIDENCE

Do You Have Real-World Evidence Evaluating the Effectiveness of JYNARQUE?

INDICATION:

JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

WARNING: RISK OF SERIOUS LIVER INJURY

- **JYNARQUE® (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported**
- **Measure transaminases (ALT, AST) and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for the first 18 months and every 3 months thereafter. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity**
- **Because of the risks of serious liver injury, JYNARQUE is available only through a Risk Evaluation and Mitigation Strategy program called the JYNARQUE REMS Program**

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

Please see **IMPORTANT SAFETY INFORMATION** on pages 10–11.

JYNARQUE®
(tolvaptan)
15, 30, 45, 60, 90 mg tablets

JYNARQUE® (tolvaptan) has demonstrated effectiveness in slowing kidney function decline in the 2 largest clinical trials of more than 2800 patients with ADPKD across CKD stages 1–4[1-4]

TEMPO 3:4 Trial[1]

A 36-month trial of patients with CKD stages 1, 2, and 3

The primary endpoint was the annual rate of change in the total kidney volume. The third endpoint was the rate of kidney function decline (slope of eGFR) during treatment

REPRISE Trial[2]

A 12-month trial of patients with CKD late stage 2 to early stage 4

The primary endpoint was the treatment difference in the change in eGFR from pretreatment baseline to posttreatment follow-up, annualized by dividing each participant's treatment duration

Patients treated with JYNARQUE by CKD stage[1,2,4]

CKD stage GFR (mL/min/1.73 m²)	Stage 1 ≥90	Stage 2 89-60	Stage 3a 59-45	Stage 3b 44-30	Stage 4 29-15
TEMPO 3:4 36-month trial, n=961	35%	48%	14%	3%	
REPRISE 12-month trial, n=681		5%	31%	44%	20%

Please see clinical trial efficacy and safety data on pages 8–9.

SELECT IMPORTANT SAFETY INFORMATION:

CONTRAINDICATIONS:

- History, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
- Taking strong CYP3A inhibitors
- With uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia
- Hypersensitivity (e.g., anaphylaxis, rash) to JYNARQUE or any component of the product
- Uncorrected urinary outflow obstruction
- Anuria

CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; GFR=glomerular filtration rate; REPRISE=Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy; TEMPO=Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes.

Please see **IMPORTANT SAFETY INFORMATION** on pages 10–11.

Rationale

While the efficacy of JYNARQUE® (tolvaptan) in clinical trials setting is well established, little is known about its effectiveness in real-world clinical practice.[5]

Objectives

To evaluate the real-world effectiveness of JYNARQUE by comparing annual rate of change in kidney function, as measured by eGFR, in adult patients (aged ≥18 years) with ADPKD treated with and without JYNARQUE.[5]

Study Overview

- A retrospective, non-interventional chart review study was conducted to evaluate the clinical impact of JYNARQUE in a real-world setting[5]
  - Nephrologists (N=57) were recruited through a web-based survey to provide data from medical records of JYNARQUE-treated patients under their care (cases: N=149)[5]
  - The study period of chart review spanned from May 2019 to September 2022[5]
  - Historical controls (patients not treated with JYNARQUE; N=959) were selected from the CRISP I and II, HALT-PKD Study A, and OVERTURE studies in the pooled ADPKD database[5,6]
- eGFR was calculated using the CKD-EPI equation based on serum creatinine[7]
- Matched analysis–Set 1: cases and controls were matched 1:1 on baseline age (±2 years), gender, and CKD stage (1, 2, 3a, 3b, 4, 5)[5]
  - The comparison between cases and controls in the matched analysis used a mixed model with eGFR as the response variable
- Matched analysis–Set 2: additional analyses were performed wherein cases and controls were matched on baseline age (±2 years), gender, and eGFR (±5 mL/min/1.73 m²)[5]

Study Limitations[5]

- Nephrologists were selected via convenience sampling, potentially limiting the generalizability of the results
- The medical records chosen may be from memorable patients or patients seen more recently; therefore, the selected patients may not be representative of the general ADPKD population
- Patient data such as diagnoses and laboratory measurements collected from medical records may contain inaccuracies

CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CRISP=Consortium for Radiologic Imaging Studies of PKD; HALT-PKD=HALT Progression of PKD; OVERTURE=Observational Study in Patients With Autosomal Dominant Polycystic Kidney Disease; PKD=polycystic kidney disease.

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STUDY POPULATION

US NEPHROLOGISTS were recruited to provide data on JYNARQUE® (tolvaptan)–treated ADPKD patients under their care

57 NEPHROLOGISTS treating **149** PATIENTS

JYNARQUE Treated Patients (n=110)	Historical controls: JYNARQUE Not-Treated Patients (n=110)
Inclusion criteria	
✓ Patients were required to have JYNARQUE continuously (ie, interruptions no longer than 60 days) for ≥2 years beginning after April 2018 (when JYNARQUE was approved for ADPKD in the US)	✓ Patients were required to be in MIC 1C to 1E. The intention was to include patients at risk of rapid progression in compliance with the recommendation for JYNARQUE treatment
Exclusion criteria	
✗ Patients who had previously participated in JYNARQUE clinical trials; had a kidney transplant, dialysis, or renal malignancies before being treated with JYNARQUE; or had ever been treated with JYNARQUE for hyponatremia	✗ Patients who used JYNARQUE in CRISP, who were randomized to low-blood-pressure control arms in HALT-PKD Study A, and who were enrolled in OVERTURE in Japan

Study Limitations[5]

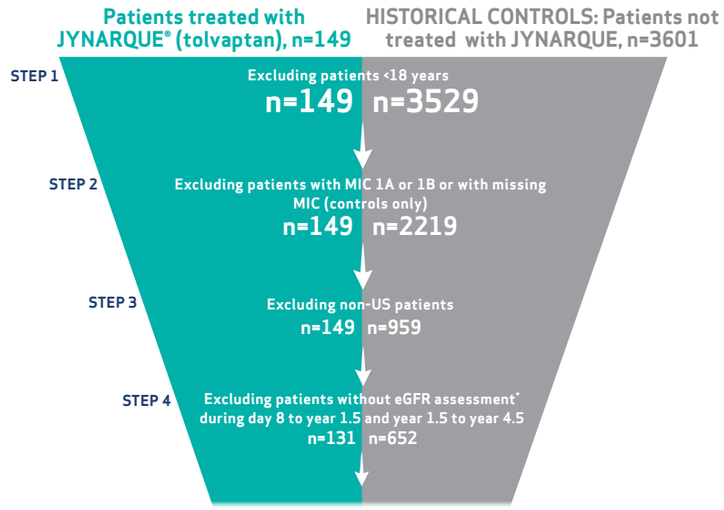
- Although historical controls were matched to cases on key patient characteristics to control for confounding, the potential for residual confounding still exists
- Some cases in the full set were not matched with a control. This may further limit generalizability and reduce statistical power. However, only the distribution of CKD stage was slightly different from that in the full set
- Using historical controls could introduce non-contemporaneous bias

SELECT IMPORTANT SAFETY INFORMATION:

Serious Liver Injury: JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) can reduce the risk of severe hepatotoxicity. To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin prior to initiating JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter.

MIC=Mayo imaging classification.

Patient Selection



SET 1: MATCHED ON AGE, GENDER, CKD STAGE

n=110 n=110

84.0% (n=110) were matched to historical controls

SET 2: MATCHED ON AGE, GENDER, eGFR

n=98 n=98

74.8% (n=98) were matched to historical controls

Baseline Characteristics

Matched analysis set 1 (n=220)

CKD Stages	
JYNARQUE Treated Patients (n=110)	Historical controls: JYNARQUE Not-Treated Patients (n=110)
1: 13% 2: 31% 3a: 33% 3b: 16% 4: 7%	1: 13% 2: 31% 3a: 33% 3b: 16% 4: 7%

Matched analysis set 2 (n=196)

CKD Stages	
JYNARQUE Treated Patients (n=98)	Historical controls: JYNARQUE Not-Treated Patients (n=98)
1: 10% 2: 28% 3a: 37% 3b: 18% 4: 7%	1: 10% 2: 36% 3a: 20% 3b: 26% 4: 7% 5: 1%

- For both sets:
  - There was a majority of males (≥60%) and the mean age was ≈43 years old
  - The majority of subjects were white (≥65%)
  - The majority of subjects were CKD stage 3a or less (≥66%)
- Mean eGFR was:
  - Set 1 – tolvaptan: 60.4 mL/min/1.73 m^2; and historical controls: 63.2 mL/min/1.73 m^2
  - Set 2 – for both tolvaptan and historical controls: 57.9 mL/min/1.73 m^2

*In the historical controls cohort, eGFR assessment >4.5 years, eGFR assessments from the HALT-PKD low-blood-pressure control group for patients initiating in CRISP , and eGFR assessments collected after surgical or invasive radiological procedures were excluded.

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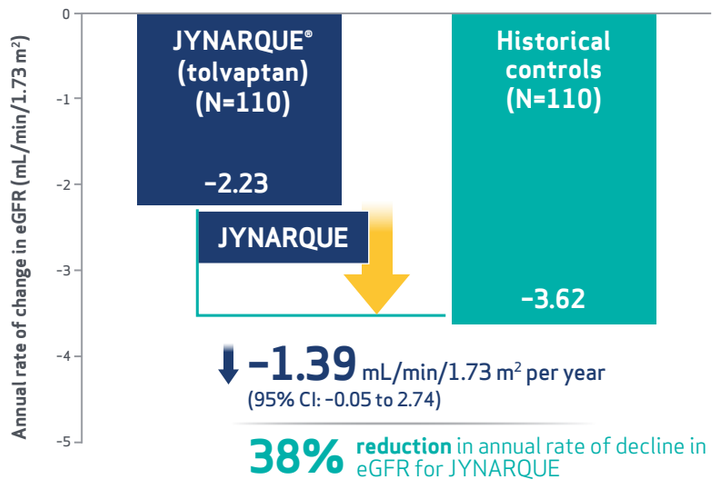
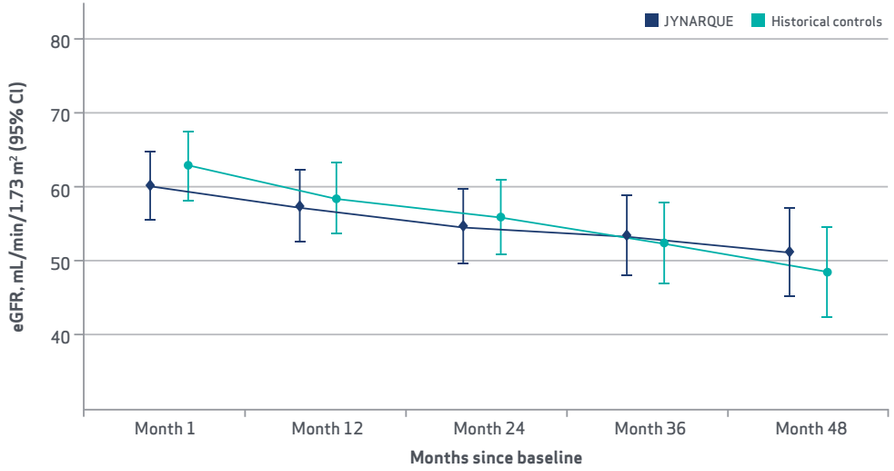
Estimated annual rate of change in eGFR by treatment in the matched analysis



Estimated eGFR over time



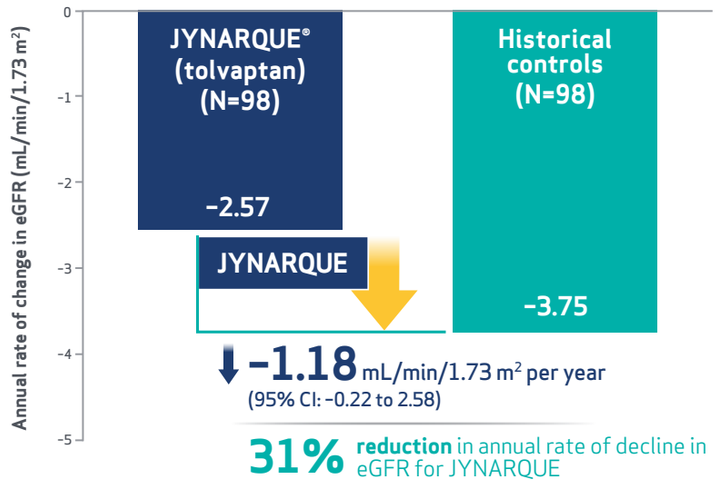
	Month 1	Month 12	Month 24	Month 36	Month 48
JYNARQUE	60.0 (55.2-64.9)	58.0 (53.2-62.8)	55.8 (50.9-60.6)	53.5 (48.4-58.7)	51.3 (45.8-56.8)
Historical controls	63.2 (58.4-68.1)	59.9 (55.1-64.7)	56.3 (51.4-61.2)	52.7 (47.5-57.9)	49.0 (43.4-54.7)

SELECT IMPORTANT SAFETY INFORMATION:

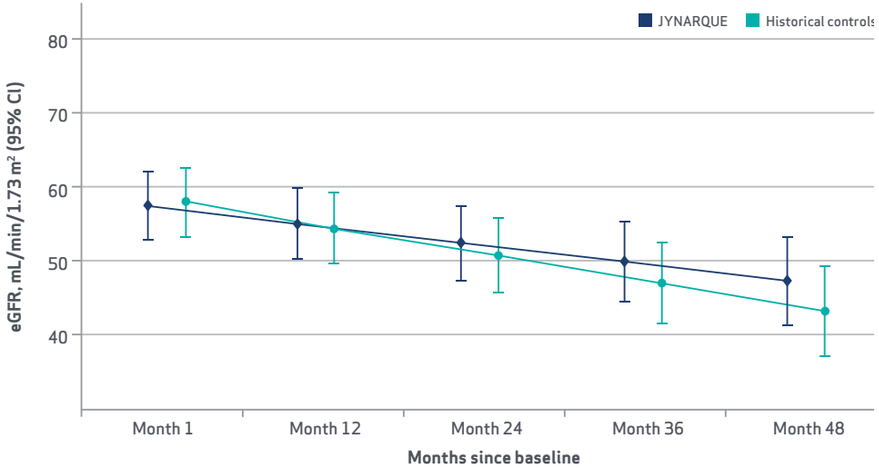
Hypernatremia, Dehydration and Hypovolemia: JYNARQUE therapy increases free water clearance which can lead to dehydration, hypovolemia and hypernatremia. Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because they may signal dehydration. Ensure abnormalities in sodium concentrations are corrected before initiating therapy. If serum sodium increases above normal or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, suspend JYNARQUE until serum sodium, hydration status and volume status parameters are within the normal range.

Please see **IMPORTANT SAFETY INFORMATION** on pages 10–11.

Estimated annual rate of change in eGFR by treatment in the matched analysis



Estimated eGFR over time



	Month 1	Month 12	Month 24	Month 36	Month 48
JYNARQUE	57.5 (53.0-62.0)	55.1 (50.6-59.7)	52.6 (47.8-57.4)	50.0 (44.8-55.2)	47.4 (42.7-53.2)
Historical controls	58.0 (53.5-62.5)	54.6 (50.0-59.1)	50.9 (46.0-55.7)	47.1 (41.8-52.4)	43.4 (37.5-49.2)

Conclusions

- In this pooled analysis evaluating the real-world use of JYNARQUE in adult patients with ADPKD in the US, JYNARQUE slowed the annual rate of decline in eGFR compared with matched historical controls
- These results are consistent with findings from clinical trials of JYNARQUE and expand the body of evidence supporting the effect of JYNARQUE in preserving kidney function in patients with ADPKD

JYNARQUE® (tolvaptan)
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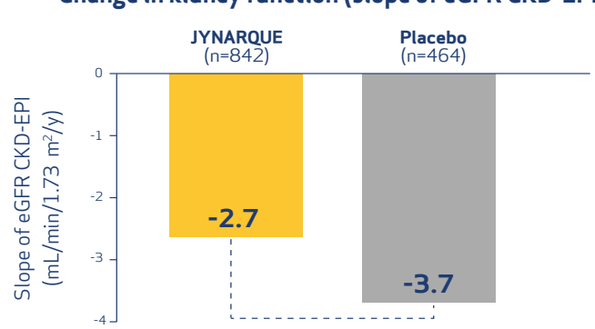
The TEMPO 3:4 and REPRISE trials showed JYNARQUE effectiveness in slowing kidney function decline in ADPKD over a broad range of CKD stages[1,2]

TEMPO 3:4 Trial[1]
A 36-month trial of patients with CKD stages 1, 2, and 3

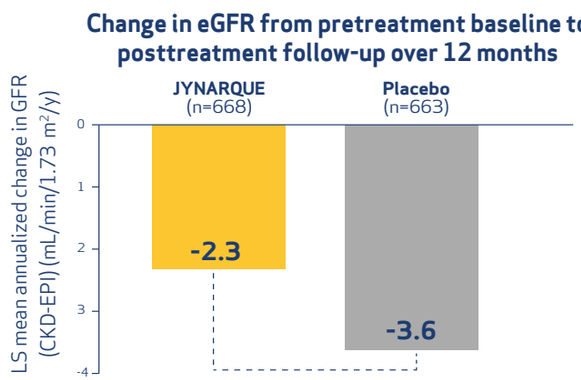


26%
reduction in decline of kidney function[8]

Treatment effect:
1.0 mL/min/1.73 m^2/y (95% CI, 0.6 to 1.4, *P*<0.0001)

TEMPO 3:4 met its prespecified primary endpoint of 3-year change in TKV (*P*<0.0001). The difference in TKV between treatment groups mostly developed within the first year, at the earliest assessment, with little further difference seen in years 2 and 3. In years 4 and 5 during the TEMPO 3:4 extension trial, both groups received JYNARQUE and the difference between the groups in TKV was not maintained. JYNARQUE has little effect on kidney size beyond what accrues during the first year of treatment.

REPRISE Trial[2]
A 12-month trial of patients with CKD late stage 2 to early stage 4



35%
reduction in decline of kidney function[9]

Treatment effect:
1.3 mL/min/1.73 m^2/y (95% CI, 0.86 to 1.68, *P*<0.0001)

LS=least squares; TKV=total kidney volume.

Please see **IMPORTANT SAFETY INFORMATION** on pages 10–11.

Clinical safety profile of JYNARQUE

TEMPO 3:4—Treatment-emergent adverse reactions in ≥3% of JYNARQUE-treated patients with risk difference ≥1.5%, randomized period

Adverse reaction	Percentage of patients reporting reaction	
	JYNARQUE (n=961)	Placebo (n=483)
Increased urination*	69.5	28.0
Thirst*	63.7	23.4
Dry mouth	16.0	12.4
Fatigue	13.6	9.7
Diarrhea	13.3	11.0
Dizziness	11.3	8.7
Dyspepsia	7.9	3.3
Decreased appetite	7.2	1.0
Abdominal distension	4.9	3.3
Dry skin	4.9	1.7
Rash	4.2	1.9
Hyperuricemia	3.9	1.9
Palpitations	3.5	1.2

Most common observed adverse reactions with JYNARQUE (incidence >10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria and polydipsia.

- The REPRISE trial employed a 5-week single-blind titration and run-in period for JYNARQUE prior to the randomized, double-blind period. During the JYNARQUE titration and run-in period, 126 (8.4%) of the 1496 patients discontinued the study; 52 (3.5%) were due to aquaretic effects and 10 (0.7%) were due to liver test findings. Because of this run-in design, the adverse reaction rates observed during the randomized period are not described
- In the 2 double-blind, placebo-controlled trials, ALT elevations >3 times ULN were observed at an increased frequency with JYNARQUE compared with placebo (4.9% [80/1637] vs 1.1% [13/1166], respectively) within the first 18 months after initiating treatment and increases usually resolved within 1 to 4 months after discontinuing the drug

INDICATION and IMPORTANT SAFETY INFORMATION for JYNARQUE® (tolvaptan)

INDICATION

JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS LIVER INJURY

- **JYNARQUE® (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported**
- **Measure transaminases (ALT, AST) and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for the first 18 months and every 3 months thereafter. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity**
- **Because of the risks of serious liver injury, JYNARQUE is available only through a Risk Evaluation and Mitigation Strategy program called the JYNARQUE REMS Program**

CONTRAINDICATIONS:

- History, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
- Taking strong CYP3A inhibitors
- With uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia
- Hypersensitivity (e.g., anaphylaxis, rash) to JYNARQUE or any component of the product
- Uncorrected urinary outflow obstruction
- Anuria

Serious Liver Injury: JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) can reduce the risk of severe hepatotoxicity. To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin prior to initiating JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter.

IMPORTANT SAFETY INFORMATION (CONT'D)

Hypernatremia, Dehydration and Hypovolemia: JYNARQUE therapy increases free water clearance which can lead to dehydration, hypovolemia and hypernatremia. Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because they may signal dehydration. Ensure abnormalities in sodium concentrations are corrected before initiating therapy. If serum sodium increases above normal or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, suspend JYNARQUE until serum sodium, hydration status and volume status parameters are within the normal range.

Inhibitors of CYP3A: Concomitant use of JYNARQUE with drugs that are moderate or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and conivaptan) increases JYNARQUE exposure. Use with strong CYP3A inhibitors is contraindicated; dose reduction of JYNARQUE is recommended for patients taking moderate CYP3A inhibitors. Patients should avoid grapefruit juice beverages while taking JYNARQUE.

Adverse Reactions: Most common observed adverse reactions with JYNARQUE (incidence >10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria and polydipsia.

Other Drug Interactions:

- **Strong CYP3A Inducers:** Co-administration with strong CYP3A inducers reduces exposure to JYNARQUE. Avoid concomitant use of JYNARQUE with strong CYP3A inducers
- **V_2-Receptor Agonist:** JYNARQUE interferes with the V_2-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V_2-agonist

Pregnancy and Lactation: Based on animal data, JYNARQUE may cause fetal harm. In general, JYNARQUE should be discontinued during pregnancy. Advise women not to breastfeed during treatment with JYNARQUE.

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

Please see FULL PRESCRIBING INFORMATION, including **BOXED WARNING**.

Real-World Evidence of JYNARQUE® (tolvaptan) Effectiveness in Patients With ADPKD

JYNARQUE slowed eGFR decline in ADPKD subjects in trials,[1,2] but knowledge about its real-world effectiveness is limited.

The clinical impact of JYNARQUE in the real-world setting was assessed in a retrospective chart analysis.[5]

- JYNARQUE slowed eGFR decline compared with historical controls[5]
  - The estimated annual rate of change in eGFR was −1.39 mL/min/1.73 m^2 per year or 38% reduction in decline (95% CI: −0.05 to 2.74) and −1.18 mL/min/1.73 m^2 per year or 31% reduction in decline (95% CI: −0.22 to 2.58) for JYNARQUE compared with historical controls in the matched analysis sets 1 and 2, respectively
- This retrospective study has some limitations[5]
  - Nephrologists' patient selection may be biased due to convenience sampling and recall bias, limiting the study's generalizability
  - Patient medical records may contain mistakes or inconsistencies when it comes to diagnoses, tests, treatments, or other clinical details

This study has shown the clinical impact of JYNARQUE on preserving the kidney function of patients with ADPKD in real-world clinical practice.[5]

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References: 1. Torres VE, Chapman AB, Devuyst O, et al; for the TEMPO 3:4 Trial Investigators. *N Engl J Med*. 2012;367(25):2407-2418. **2.** Torres VE, Chapman AB, Devuyst O, et al; for the REPRISE Trial Investigators. *N Engl J Med*. 2017;377(20):1930-1942. **3.** Data on file. TOL-008. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **4.** Torres VE, Higashihara E, Devuyst O, et al; for the TEMPO 3:4 Trial Investigators. *Clin Am Soc Nephrol*. 2016;11(5):803-811. **5.** Perrone RD, Nunna S, Gandhi HK, et al. Poster presented at: ASN Kidney Week; November 1-5, 2023; Philadelphia, PA. **6.** Zhou X, Davenport E, Ouyang J, et al. *Kidney Int Rep*. 2022;7(5):1037-1048. **7.** Irazabal MV, Rangel JL, Bergstralh EJ, et al. *J Am Soc Nephrol*. 2015;26(1):160-172. **8.** Data on file. JYN-011. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **9.** Data on file. JYN-012. Otsuka America Pharmaceutical, Inc.; Rockville, MD.

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