An evidence-based answer to a common clinical question about JYNARQUE® (tolvaptan)

Are there any data that support the ability of JYNARQUE in delaying time to end-stage kidney disease (ESKD) in patients with ADPKD?

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**

Please see **IMPORTANT SAFETY INFORMATION** on pages 12–13.

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 over 2800 patients with ADPKD across CKD stages 1–4[1-3]

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 of eGFR from pretreatment baseline to posttreatment follow-up, annualized by dividing by 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 pages 10–11 for additional information on pivotal trials.

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

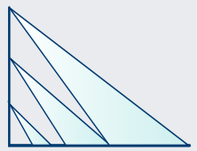
GFR=glomerular filtration rate; REPRISE=Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy; TEMPO=Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes.

Please see **IMPORTANT SAFETY INFORMATION** on pages 12–13.

In the absence of clinical data, the expected but still unproven benefit of JYNARQUE® (tolvaptan) to delay ESKD has been modeled by several investigators

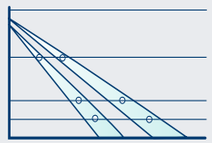
- An open-label study (TEMPO 4:4) and a small single-center retrospective analysis suggest that tolvaptan's slowing of the rate of estimated GFR (eGFR) decline is sustained and cumulative (approximately 1 mL/min/1.73 m² per year of treatment) over time[5,6]
- To date, no outcomes-driven clinical trials have been conducted to document the impact of JYNARQUE on time to ESKD

Predicting the impact of JYNARQUE on delaying ESKD



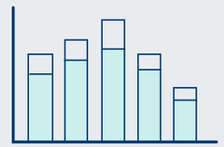
Based on TEMPO 3:4 and REPRISE data[7]

Chebib FT et al.



Based on the ADPKD Outcomes Model[8,9]

Bennett H et al.



Based on TEMPO 3:4 and Mayo subclass[10]

Mader G et al.

PREDICTION MODELS

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Prediction model based on TEMPO 3:4 and REPRISE data[7]

Chebib FT, Perrone RD, Chapman AB, Dahl NK, Harris PC, Mrug M, Mustafa RA, Rastogi A, Watnick T, Yu ASL, and Torres VE

MODEL OVERVIEW

Results of the TEMPO 3:4 and REPRISE trials were extrapolated to estimate the potential benefit of JYNARQUE treatment in delaying the need for renal replacement therapy.

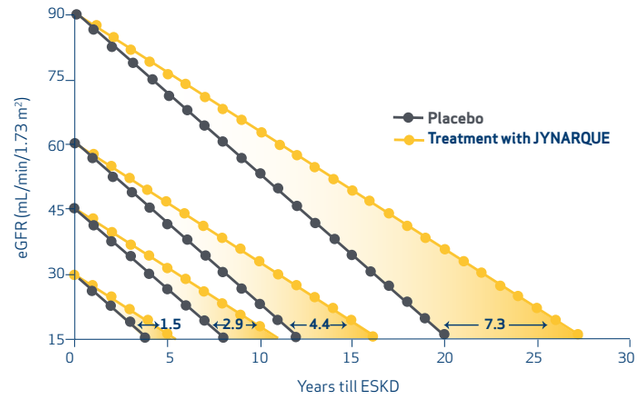
The model assumed that all patients exhibit similar declines in eGFR over time as they progress to ESKD.

Based on available data, the effect of JYNARQUE was predicted to be sustained and cumulative.

JYNARQUE is predicted to delay ESKD by a greater number of years if therapy is initiated in patients with more preserved renal function

Predicted impact of JYNARQUE in delaying ESKD[7]

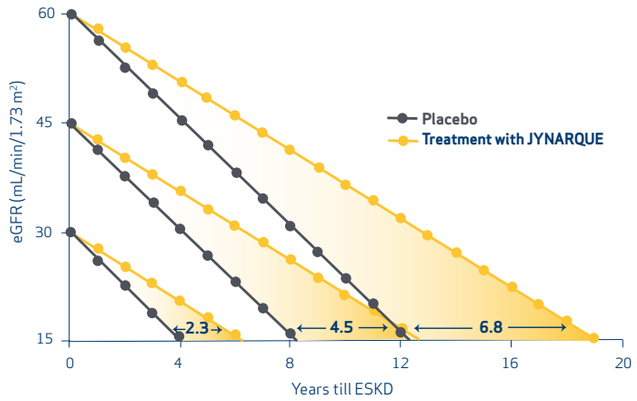
Based on TEMPO 3:4*



Predicted delay in ESKD	eGFR at JYNARQUE initiation
7.3 YEARS	90 ML/MIN
4.4 YEARS	60 ML/MIN
2.9 YEARS	45 ML/MIN
1.5 YEARS	30 ML/MIN

Predictions based on TEMPO 3:4 may underestimate the long-term treatment effect because the impact of therapy on eGFR decline was less than that observed in REPRISE in patients with more advanced disease.

Based on REPRISE†



Predicted delay in ESKD	eGFR at JYNARQUE initiation
6.8 YEARS	60 ML/MIN
4.5 YEARS	45 ML/MIN
2.3 YEARS	30 ML/MIN

*These extrapolations are made using the average decline in eGFR seen with placebo (3.7 mL/min per year) and tolvaptan (2.72 mL/min per year) in the TEMPO 3:4 trial.
†These extrapolations are made using the average decline in eGFR seen with placebo (3.61 mL/min per year) and tolvaptan (2.34 mL/min per year) in the REPRISE trial.

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 12–13.

SELECT IMPORTANT SAFETY INFORMATION:

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 tolvaptan 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.

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Prediction model based on the ADPKD Outcomes Model[8]

Bennett H, McEwan P, Hamilton K, O'Reilly K

MODEL OVERVIEW

The effect of JYNARQUE on ADPKD progression was modeled by applying a constant treatment effect to the rate of renal function decline, consistent with that observed in the TEMPO 3:4 trial.

Following validation, the ADPKD Outcomes Model (ADPKD-OM)* was used to estimate the potential long-term renal benefits of JYNARQUE therapy in hypothetical ADPKD cohorts.

***The ADPKD-OM represents a tool to predict natural disease progression and long-term outcomes in ADPKD patients, based on readily available and/or measurable clinical characteristics.[9]**

The effect of JYNARQUE therapy on ADPKD progression was added to the ADPKD-OM by applying a constant reduction to the rate of renal function (eGFR) decline predicted for an untreated patient.

Consistent with TEMPO 3:4 observations, the natural rate of eGFR decline was reduced by 26.4% when using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

The Mayo Imaging Classification is a simple tool using htTKV and age to identify a patient's risk of ADPKD progression[11,12†]

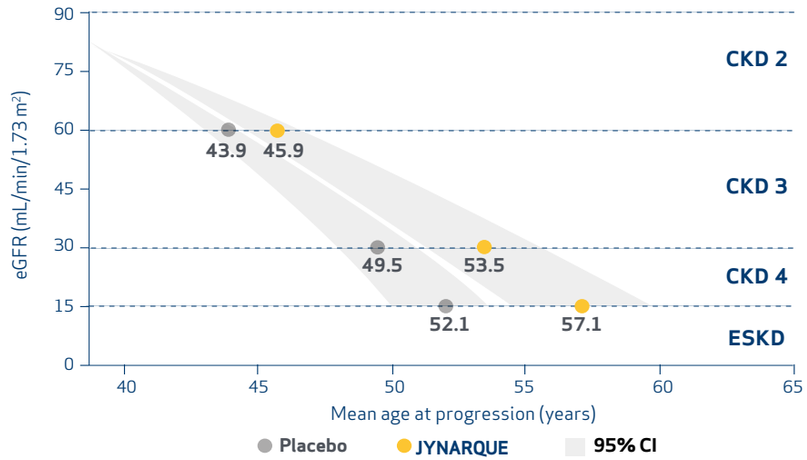
Mayo imaging class	1A	1B	1C	1D	1E
Estimated slope of change in eGFR	−0.23	−1.33	−2.63	−3.48	−4.78
Risk for eGFR decline	Low risk	Intermediate risk	High risk	High risk	High risk

eGFR units=mL/min/1.73 m²/yr.

htTKV=height-adjusted total kidney volume.
†Bilateral and diffuse distribution, with mild, moderate, or severe replacement of kidney tissue by cysts, where all cysts contribute similarly to TKV. Classification only applies to patients with typical morphology of ADPKD as defined by diffuse bilateral cystic involvement of the kidneys.[12]

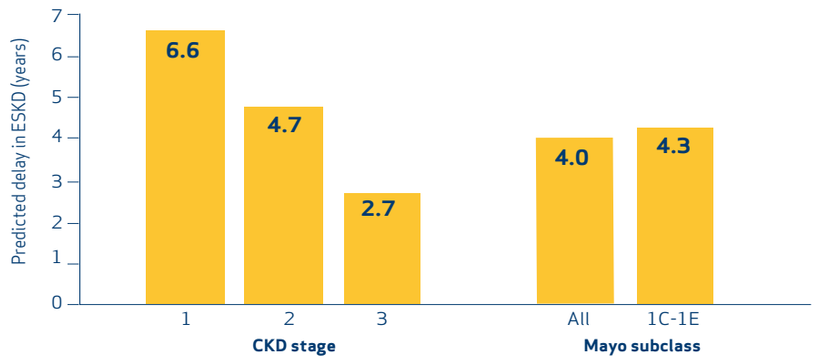
Projected impact of JYNARQUE® (tolvaptan) is greater when introduced in the earlier stages of CKD

Predicted trajectory of CKD progression in modeled ADPKD patients treated with JYNARQUE compared with natural history[8]



+5 YEARS
predicted delay in mean age of ESKD onset with JYNARQUE
compared with natural disease progression (57 years vs 52 years, respectively)

Predicted delay in ESKD based on stage of renal disease



SELECT IMPORTANT SAFETY INFORMATION:

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.

SELECT IMPORTANT SAFETY INFORMATION:

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:** Tolvaptan interferes with the V_2-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V_2-agonist

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Prediction model based on TEMPO 3:4 and the Mayo subclass[10]

Mader G, Purser MF, Mladsi DM

MODEL OVERVIEW

The TEMPO 3:4 treatment effect differentiated by the Mayo subclass level was applied to predict the time to ESKD.

The model applied a constant treatment effect to baseline natural history progression estimates as estimated via the Irazabal equation.

In the base-case analysis, the annual absolute reduction in eGFR decline for JYNARQUE vs placebo of 1.20 mL/min/1.73 m^2 from the TEMPO 3:4 trial was applied to predicted eGFR decline in the absence of treatment.

The model applies the treatment effect for JYNARQUE at the subclass level regardless of CKD stage.

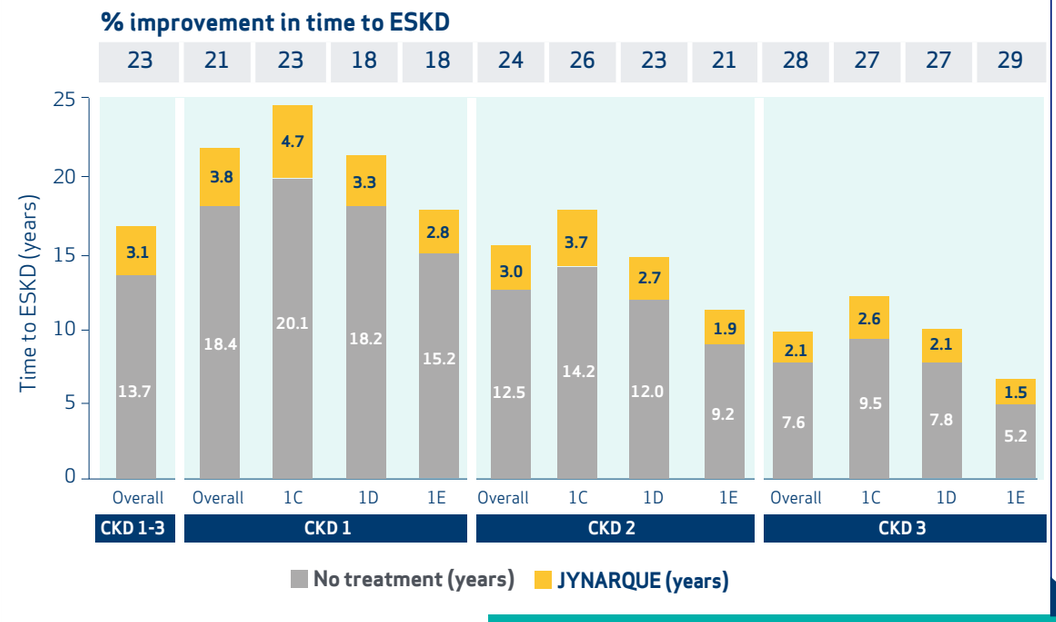
SELECT IMPORTANT SAFETY INFORMATION:

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.

Please see **IMPORTANT SAFETY INFORMATION** on pages 12–13.

JYNARQUE® (tolvaptan)–treated patients predicted to spend more time in earlier CKD and experience later onset of ESKD compared with no treatment

Predicted impact of JYNARQUE by CKD stage and Mayo subclass on time to ESKD



18% to 29% improvement in predicted time to ESKD

in patients beginning JYNARQUE in CKD stages 1–3 compared with patients not treated with JYNARQUE

Results were consistent across CKD stages and Mayo subclasses

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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

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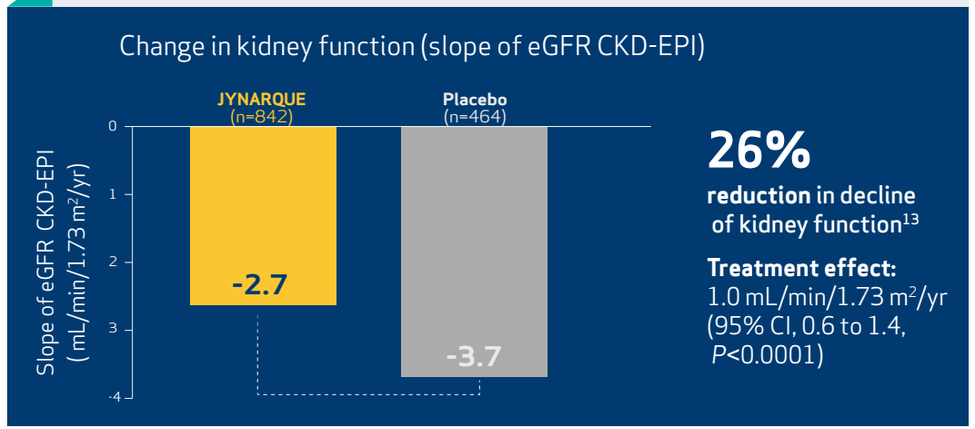
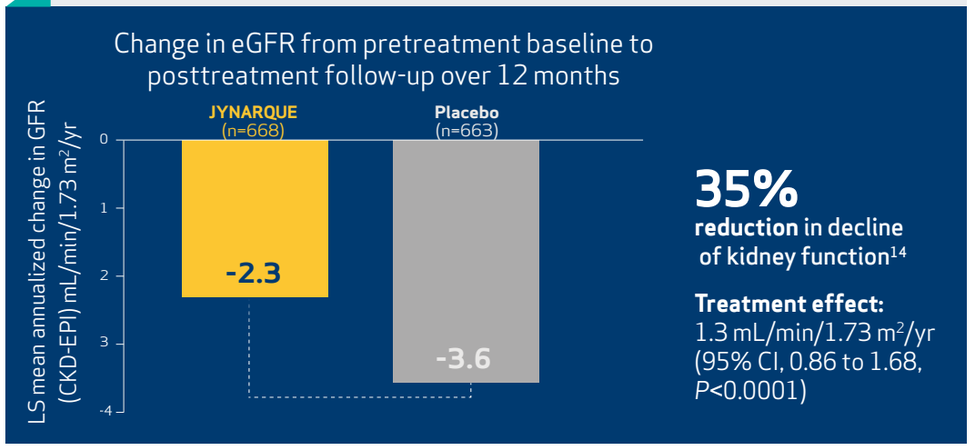
The TEMPO 3:4 and REPRISE trials showed JYNARQUE® (tolvaptan) effectiveness in slowing kidney function decline in ADPKD over a broad range of CKD stages[1,2]

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



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. Tolvaptan 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



CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CI=confidence interval; LS=least squares.

Please see **IMPORTANT SAFETY INFORMATION** on pages 12–13.

Clinical Safety Profile of JYNARQUE® (tolvaptan)

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 two 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

ALT=alanine aminotransferase; ULN=upper limit of normal.
*Increased urination includes micturition urgency, nocturia, pollakiuria, polyuria.
†Thirst includes polydipsia and thirst.

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INDICATION and IMPORTANT SAFETY INFORMATION for JYNARQUE® (tolvaptan)

INDICATION

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- **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**

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IMPORTANT SAFETY INFORMATION (CONT'D)

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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.**

An evidence-based answer to a common clinical question about JYNARQUE® (tolvaptan)

Predicting the impact of JYNARQUE in delaying ESKD

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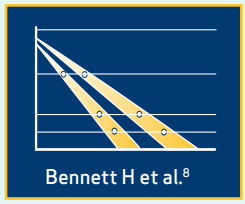

Based on the ADPKD Outcomes Model[8,9]

Based on TEMPO 3:4 and Mayo subclass[10]

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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. TOLV-008. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **4.** Torres VE et al. *Clin J Am Soc Nephrol*. 2016;11(5): 803-811. **5.** Torres VE, Chapman AB, Devuyst O, et al; for the TEMPO 4:4 Trial Investigators. *Nephrol Dial Transplant*. 2017;33(3):477-489. **6.** Edwards ME, Chebib FT, Irazabal MV, et al. *Clin J Am Soc Nephrol*. 2018;13(8):1153-1161. **7.** Chebib FT, Perrone RD, Chapman AB, et al. *J Am Soc Nephrol*. 2018;29(10):2458-2470. **8.** Bennett H, McEwan P, Hamilton K, O'Reilly K. *BMC Nephrol*. 2019;20(1):136. **9.** McEwan P, Bennett Wilton H, Ong ACM, et al. *BMC Nephrol*. 2018;19(1):37. **10.** Mader G, Purser MF, Mladsi DM, et al. Poster presented at Kidney Week 2020 Reimagined; October 22-25, 2020. **11.** Magistroni R, Corsi C, Martí T, Torra R. *Am J Nephrol*. 2018;48:67-78. **12.** Irazabal MV, Rangel LJ, Bergstralh EJ, et al. *J Am Soc Nephrol*. 2015;26(1):160-172. **13.** Data on file. JYN-011. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **14.** Data on file. JYN-012. Otsuka America Pharmaceutical, Inc.; Rockville, MD.

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