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Treatment with URAT1 Inhibitor Pozdeutinurad (AR882) in a Phase 3, Double-Blind, Randomized Study Lowers Serum Urate Levels in Participants with Gout

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ACR Convergence
Where Rheumatology Meets

URAT1, uric acid transporter-1.

Disclosures

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- Consultant: Sobi, Amgen
- Grant/research: Arthrosi, Crystalys

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- Investigator: Arthrosi
- Consultant: Amgen, Sobi
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- Individual stocks and stock options: Selecta Biosciences Inc
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- Speaker: AbbVie, AstraZeneca, BMS, Chugai, Eisai, Eli Lily, Janssen, Pfizer
- Researcher: AbbVie, Amgen, BMS, Eli Lily, Gilead, GSK, Janssen, Novartis, Pfizer, SUN Pharma, UCB Pharma

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Learning objectives

- Summarize the efficacy and safety data from the REDUCE-2 phase 3 trial
- Detail the potential of pozdeutinurad as a highly-selective URAT1 inhibitor for patients with gout

Burden of gout



Gout is a **systemic inflammatory disease** that is **suboptimally treated**, with high economic and healthcare utilization costs when uncontrolled[1,2]



A **"treat-to-target" strategy** is vital to **maintain serum urate (SU) <6 mg/dL**, **decrease uric acid deposits** and **reduce the number of gout flares**[1,3]



There is an **unmet need** for **effective oral urate-lowering therapies (ULTs)** that help patients **achieve this target**[4,5]

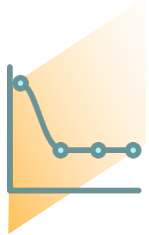
SU, serum urate; ULT, urate-lowering therapy.

1. Khanna P, et al. *J Clin Med.* 2020;9:3204. **2.** Flores N M, et al. *J Med Econ.* 2019:22:1–6. **3.** FitzGerald JD, et al. *Arthritis Care Res.* 2020;72:744–760. **4.** Pou MA, et al. *Br J Gen Pract.* 2026; 76:e624–633. **5.** Singh JA, et al. *J Rheumatol.* 2020;47:449–460.

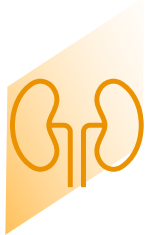
Pozdeutinurad



A next-generation, highly-selective uric acid transporter-1 (URAT1) inhibitor, which blocks uric acid reabsorption



Demonstrated SU lowering up to 18 months and no known cross-reactivity with xanthine oxidase inhibitors in phase 2 studies[1–5]



Initial data indicate potential use in renal-impaired patients[1,6]

SU, serum urate; URAT1, uric acid transporter-1.

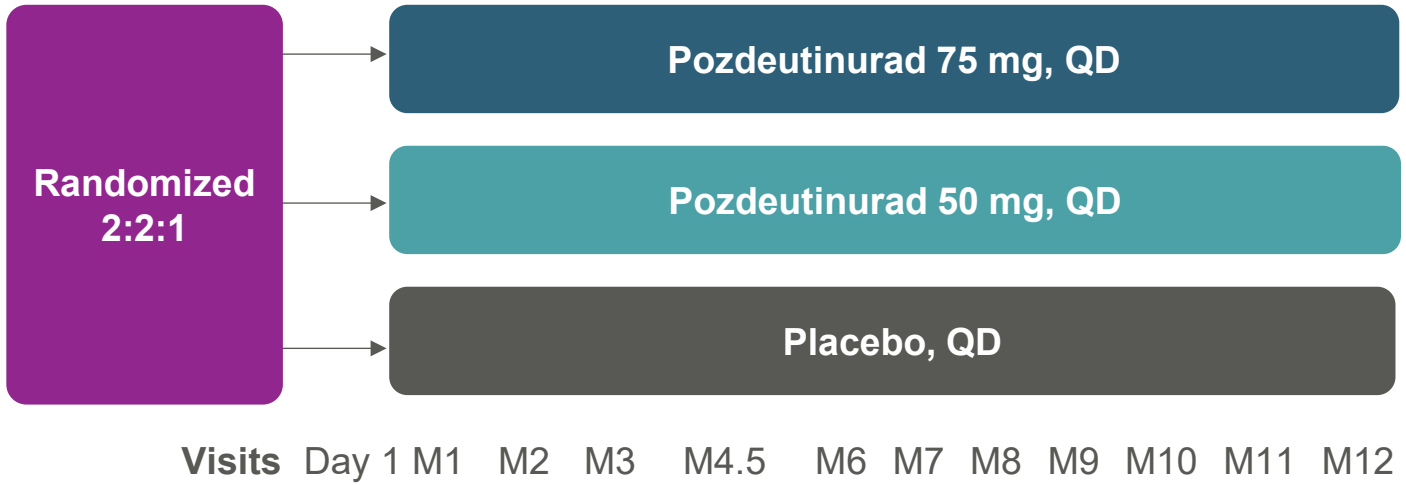
1. Shen Z, et al. *Ann Rheum Dis.* 2021;80:844. **2.** Wei J, et al. *Arthritis Rheumatol.* 2023;75. **3.** Keenan R, et al. *Ann Rheum Dis.* 2025;77. **4.** Shen Z, et al. *Ann Rheum Dis.* 2021;80:843. **5.** Yeh LT, et al. *Arthritis Rheumatol.* 2020;72. **6.** Shen Z, et al. *Ann Rheum Dis.* 2021;73.

REDUCE-2 study design

REDUCE-2 (NCT06439602) **was a global, double-blind, randomized, placebo-controlled phase 3 study across ~80 sites** in Australia, Hong Kong, New Zealand, Taiwan and the USA

Key inclusion criteria:

- ✓ Adults (18–85 years)
- ✓ Diagnosed with gout based on the 2015 ACR/EULAR Classification Criteria
- ✓ ≥2 self-reported gout flares in the previous 12 months
- ✓ ULT-naïve/not currently receiving ULT with SU ≥7 mg/dL or receiving ULT with SU >6 mg/dL and willing to undergo a >10-day washout before Day 1 dosing



Participant randomization was stratified across treatment groups by renal impairment[a], nephrolithiasis history and presence of tophi[b]

[a]Functional (estimated creatinine clearance [eCL_{cr}] ≥60 mL/min) or impaired (≥30 to <60 mL/min). [b]In the bilateral hands, wrists, feet or ankles.
ACR, American College of Rheumatology; eCL_{cr}, estimated creatinine clearance; EULAR, European Alliance of Associations for Rheumatology; M, month; QD, once daily; SU, serum urate; ULT, urate-lowering therapy.

REDUCE-2 study endpoints



Primary endpoint

Proportion of patients with SU <6 mg/dL at Month 6



Key secondary and exploratory endpoints[a]

- Safety and tolerability
- SU levels
  - Change from baseline at Months 6 and 12
  - Proportion of patients with SU <5 mg/dL, <4 mg/dL, and <3 mg/dL at Months 6, 9, and 12

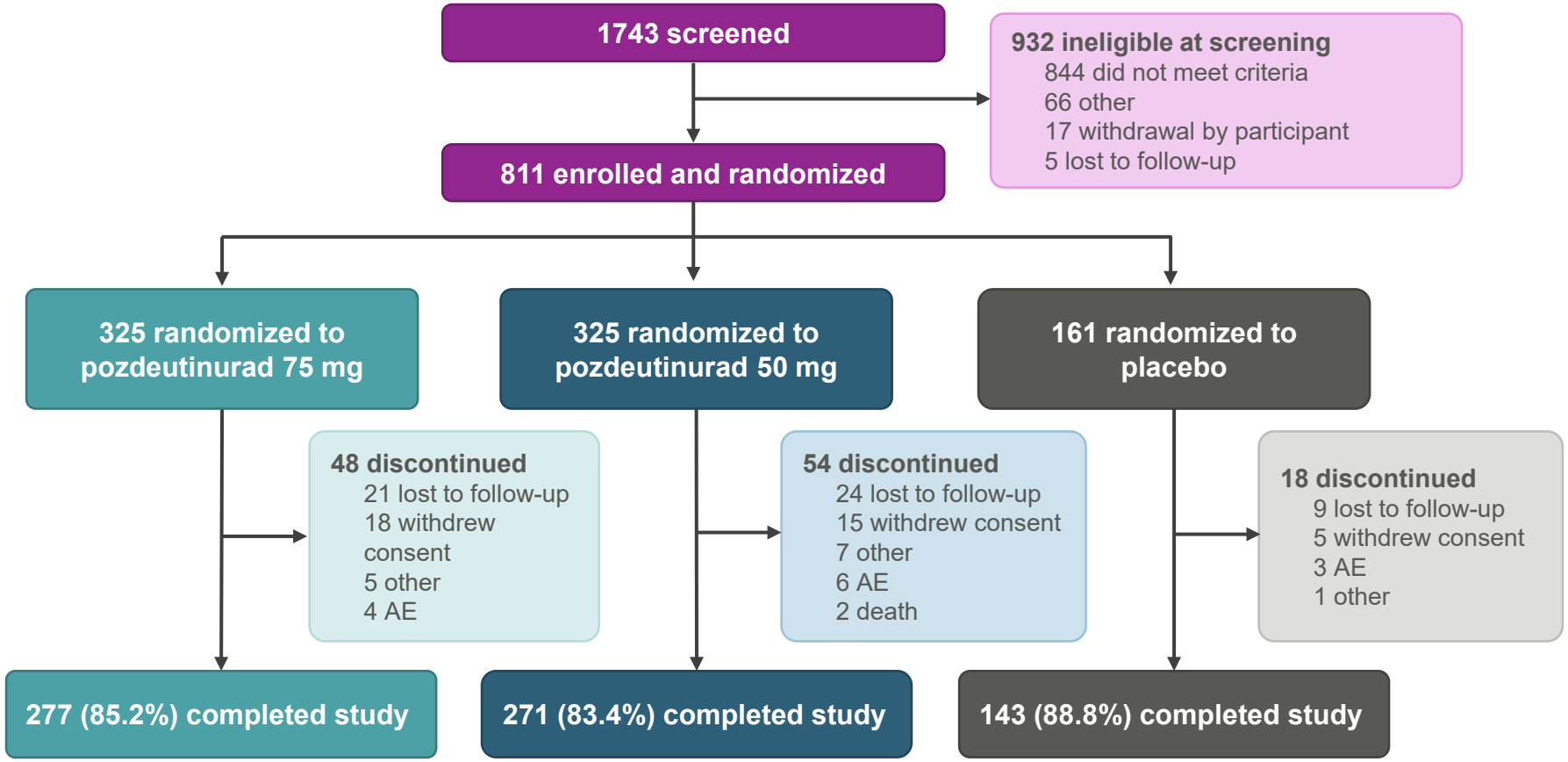


Analysis populations

- Efficacy was analyzed in the intent-to-treat (ITT)[b] and per-protocol (PP)[c] populations
- Safety was analyzed in all patients who received ≥1 dose of treatment

[a]A subset of selected secondary and exploratory endpoints are shown for presentation purposes and do not represent the full set of prespecified endpoints. [b]All randomized patients.
[c]All randomized patients completing 6 months of treatment without important protocol deviations.
ITT, intent-to-treat; PP, per-protocol; SU, serum urate.

>85% of patients completed the study



'Completed study' is based on the End of Study CRF and does not reflect completion of the full study treatment.
AE, adverse event; CRF, case report form.

Baseline patient characteristics

Patient characteristics	75 mg n=325	50 mg n=325	Placebo n=161	Overall n=811
Age, years, mean (SD)	56.0 (12.0)	56.1 (12.4)	55.5 (11.5)	55.9 (12.0)
BMI, kg/m^2, mean (SD)	32.4 (5.4)	32.1 (5.4)	32.5 (5.7)	32.3 (5.4)
Male, n (%)	302 (92.9)	300 (92.3)	148 (91.9)	750 (92.5)
Race, n (%)				
White	184 (56.6)	184 (56.6)	96 (59.6)	464 (57.2)
Black or African American	71 (21.8)	66 (20.3)	35 (21.7)	172 (21.2)
Asian	47 (14.5)	56 (17.2)	24 (14.9)	127 (15.7)
Key comorbidities, n (%)				
Hypertension	172 (52.9)	167 (51.4)	91 (56.5)	430 (53.0)
Type 2 diabetes	47 (14.5)	53 (16.3)	21 (13.0)	121 (14.9)
Chronic kidney disease (CKD)	19 (5.8)	19 (5.8)	10 (6.2)	48 (5.9)
Coronary artery disease	8 (2.5)	11 (3.4)	8 (5.0)	27 (3.3)

Patients were evenly distributed across treatment groups and generally representative of the gout population[1]

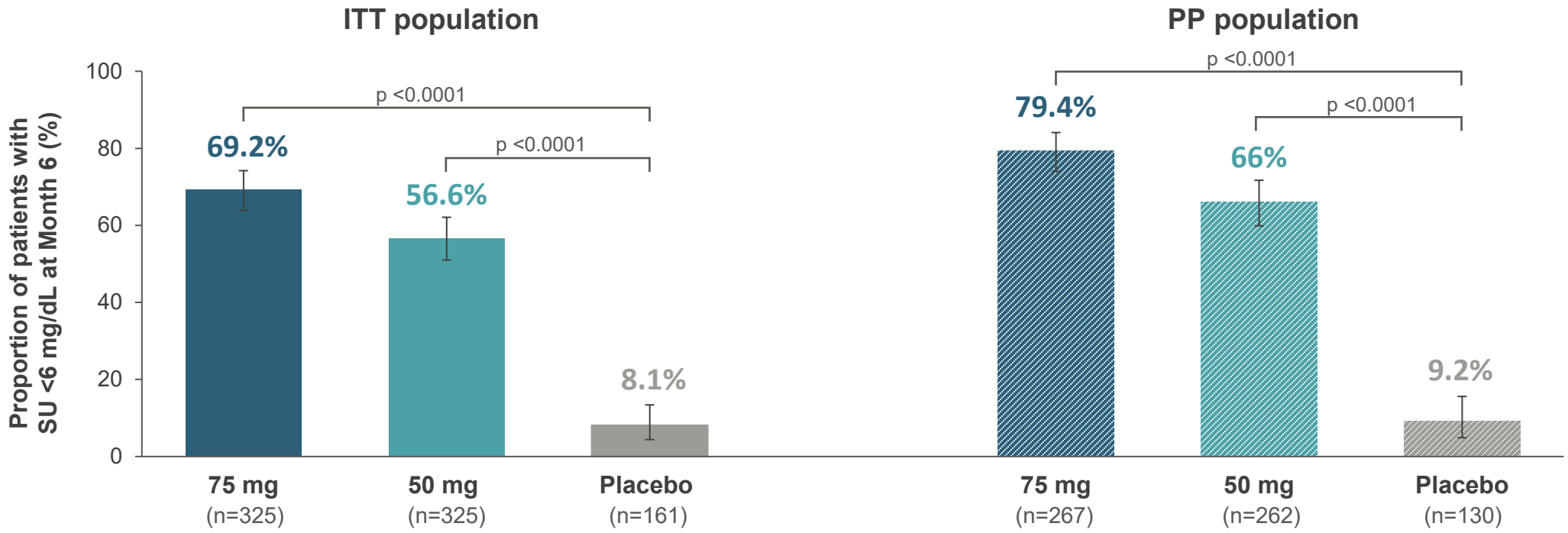
Results shown for the ITT population.
BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; SD, standard deviation.
1. Asghari KM, et al. *BMC Musculoskelet Disord.* 2024;25:1047.

Baseline disease characteristics

Disease characteristics	75 mg n=325	50 mg n=325	Placebo n=161	Overall n=811
SU, mg/dL, mean (SD)	8.42 (1.5)	8.36 (1.5)	8.32 (1.4)	8.38 (1.5)
Patients with tophi,[a] n (%)	82 (25.2)	87 (26.8)	48 (29.8)	217 (26.8)
Flares in prior 12 months, mean (SD)	5.4 (6.6)	4.5 (4.3)	4.9 (3.9)	4.9 (5.3)
eCL_{cr}, mL/min, mean (SD)	110.4 (41.2)	111.0 (41.4)	109.8 (40.6)	110.5 (41.1)
<60 mL/min, n (%)	23 (7.1)	30 (9.2)	11 (6.8)	64 (7.9)
≥60 mL/min, n (%)	302 (92.9)	295 (90.8)	150 (93.2)	747 (92.1)
Patients with history of nephrolithiasis, n (%)	31 (9.5)	30 (9.2)	15 (9.3)	76 (9.4)

Results shown for the ITT population. [a]Per principal investigator baseline assessment.
eCL_{cr}, estimated creatinine clearance; ITT, intent-to-treat; SD, standard deviation; SU, serum urate.

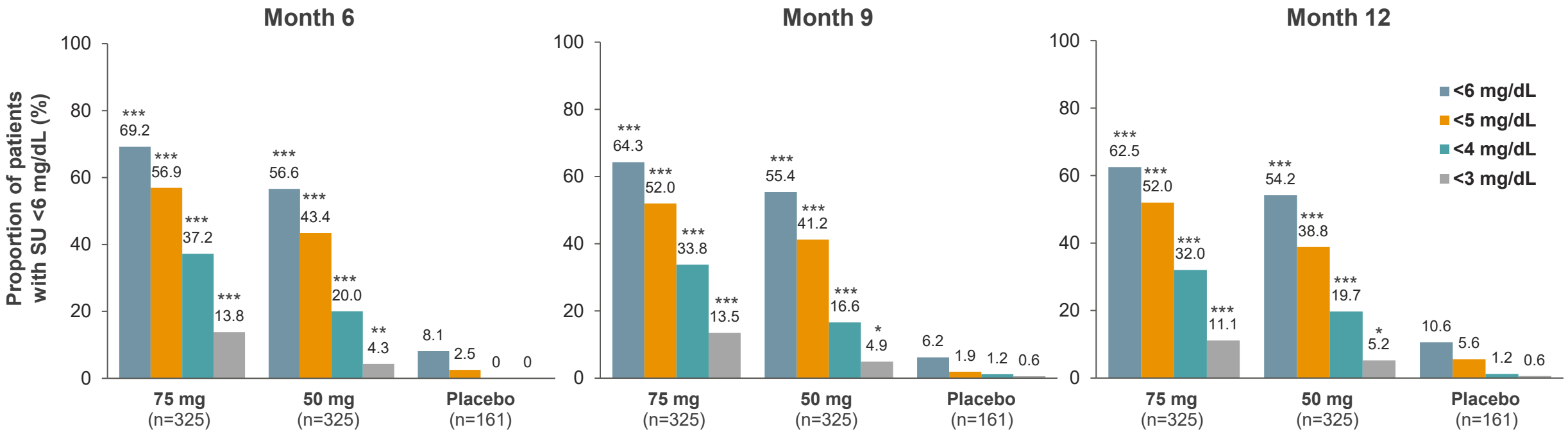
Pozdeutinurad resulted in reduction of SU levels to <6 mg/dL at Month 6



Statistically significant number of treated patients reached target SU levels at Month 6, with a clear dose-response relationship to pozdeutinurad

Participants missing data at Month 6 are considered non-responders. Participants who used prohibited medications (i.e., ULT) that potentially impacted efficacy interpretation, taken within 14 days prior to the SU assessment at Month 6 or discontinued study drug early prior to Month 6, are considered non-responders (i.e., composite variable strategy). P-values for pairwise comparisons of treatment groups are based on a CMH chi-square test, stratified by renal function (last eCL_{cr} prior to randomization ≥30 to <60 mL/min vs ≥60 mL/min), tophus status and history of nephrolithiasis. Error bars represent 95% CI (two-sided 95% Clopper-Pearson exact CI).
CI, confidence interval; eCL_{cr}, estimated creatinine clearance; CMH, Cochran-Mantel-Haenszel; ITT, intent-to-treat; PP, per-protocol; SU, serum urate; ULT, urate-lowering therapy.

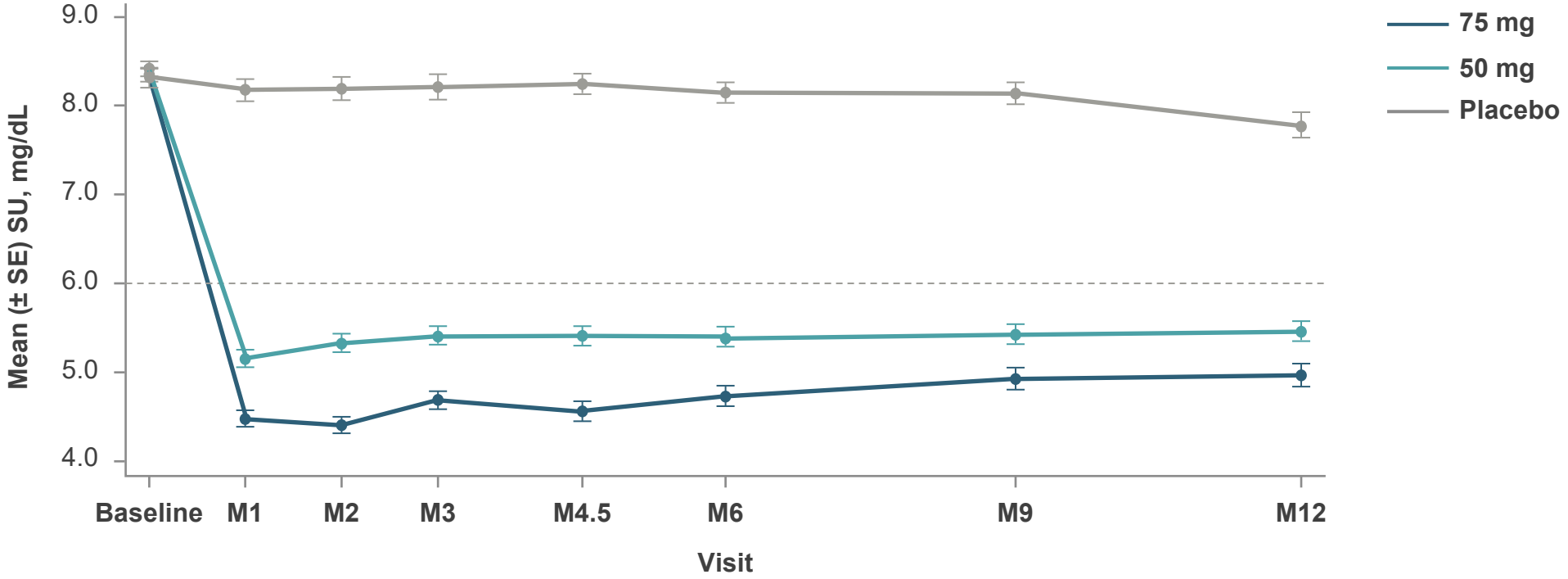
Sustained achievement of SU <5, <4, and <3 mg/dL at Months 6, 9 and 12



At all time points, significantly higher proportions of pozdeutinurad-treated patients achieved SU levels of <5, <4, and <3 mg/dL vs placebo

Results shown for the ITT population. Patients with missing data at each visit are considered non-responders. P-values for pairwise comparisons of treatment groups are based on a CMH chi-square test, stratified by renal function (last eCL_{cr} prior to randomization ≥30 to <60 mL/min vs ≥60 mL/min), tophus status and history of nephrolithiasis.
Statistically significant difference to placebo (*P<0.05; **P≤0.01; ***P≤0.001).
eCL_{cr}, estimated creatinine clearance; CMH, Cochran-Mantel-Haenszel; ITT, intent-to-treat; SU, serum urate.

Clinically meaningful and enduring SU reductions were observed as early as Month 1 through Month 12



Patients, n	Baseline	M1	M2	M3	M4.5	M6	M9	M12
75 mg	325	316	310	311	276	294	287	280
50 mg	325	313	308	306	277	289	279	273
Placebo	161	157	153	156	142	150	145	144

Results shown for the ITT population, including only patients with data available at each respective visit. Dotted line represents ACR guideline target SU level of 6 mg/dL.
ACR, American College of Rheumatology; ITT, intent-to-treat; M, month; SE, standard error; SU, serum urate.

Pozdeutinurad safety profile was comparable to placebo

Event, n (%)	75 mg n=326	50 mg n=324	Placebo n=161
≥1 TEAE	**198 (60.7)**	**200 (61.7)**	**98 (60.9)**
≥1 treatment-related TEAE[a,b]	42 (12.9)	31 (9.6)	19 (11.8)
≥1 TESAE	**18 (5.5)**	**15 (4.6)**	**13 (8.1)**
≥1 treatment-related TESAE[a]	1 (0.3)[c]	0	0
TEAE leading to discontinuation of study drug	**18 (5.5)**	**18 (5.6)**	**10 (6.2)**

[a]Related events include those reported as "possibly related" or "related" to study treatment. [b]Treatment-related TEAEs in ≥1% of any treatment group included: blood creatine increased, diarrhea, headache (all groups); blood creatine phosphokinase increased (placebo and pozdeutinurad 50 mg only); nausea (placebo and pozdeutinurad 75 mg group only); nephrolithiasis (pozdeutinurad 75 mg and 50 mg only).
[c]One treatment-related SAE was gouty attack leading to hospitalization.
TEAE, treatment-emergent adverse event; TESEA, treatment-emergent serious adverse event.

Renal TEAEs were infrequent and similar across all treatment groups

Event, n (%)	75 mg n=326	50 mg n=324	Placebo n=161
Treatment-related TEAEs			
Renal and urinary disorders	**6 (1.8)**	**7 (2.2)**	**2 (1.2)**
Renal stones[a]	3 (0.9)*	6 (1.9)*[b]	1 (0.6)
Acute renal injury	0	1 (0.3)	1 (0.6)
Hematuria	2 (0.6)	0	0
Renal impairment	1 (0.3)	1 (0.3)*	0
CKD worsening	0	1 (0.3)[c]	0
Renal colic	1 (0.3)*	0	0

*Individual participants with multiple renal TEAEs represented.
[a]Includes nephrolithiasis, calculus urinary and ureterolithiasis. [b]One patient is represented twice by two separate reported TEAEs (nephrolithiasis and ureterolithiasis). [c]Patient was diagnosed with CKD before the study and had marked pre-existing albuminuria. CKD worsening was reported on basis of elevated urine albumin-creatinine ratio; serum creatinine remained stable.
CKD, chronic kidney disease; TEAE, treatment-emergent adverse event.

Key takeaways

Pozdeutinurad treatment resulted in:

- Significant reductions in SU <6 mg/dL at Month 6
- Large percentage of patients with SU <5 mg/dL and lower
- Early SU reductions achieved and maintained through 12 months

Pozdeutinurad was generally well tolerated with a low incidence of renal AEs

Pozdeutinurad is a potent oral uricosuric agent with potential to address the unmet needs in patients living with gout

AE, adverse event; SU, serum urate.

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