

Pilavapadin in Neuropathic Pain

October 14, 2025

Forward-Looking Statements

- This presentation, including any oral presentation accompanying it, contains “forward-looking statements,” including statements about Lexicon’s strategy and operating performance and events or developments that we expect or anticipate will occur in the future, such as projections of our future results of operations or of our financial condition, the potential therapeutic and commercial potential of pilavapadin (LX9211), LX9851, sotagliflozin and our other drug programs, the success of our commercialization efforts with respect to INPEFA[®] (sotagliflozin) and any other approved products, the results of and expected timing of the completion of ongoing and future clinical trials, the expected timing and outcome of discussions with regulatory authorities regarding such trials and any applications for approval based on such trials, our other research and development efforts, and the anticipated trends in our business.
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- Information identifying such important factors is contained in our most recent annual report on Form 10-K and quarterly reports on Form 10-Q, including the sections entitled “Risk Factors,” as well as our current reports on Form 8-K, in each case filed with the Securities and Exchange Commission.
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Pilavapadin: Summary of Key Conclusions from Pooled Analyses of Phase 2 Studies in DPNP



Analyses support advancement of 10 mg into Phase 3 development based on:

1. **Validated biological activity**, as evidenced by a linear relationship between increased plasma levels of pilavapadin and pain reduction.
2. **Clinically meaningful efficacy** of the 10mg dose, with a 2-point average daily pain score (ADPS) reduction from baseline at 12 weeks.
3. **Acceptable tolerability profile** of the 10mg dose, with placebo-like treatment completion rates.
4. **Acceptable safety profile** in line with standard of care, further bolstered by subsequent studies showing no prolonged QTc interval with pilavapadin treatment and no significant impact on the pharmacokinetics (PK) of pilavapadin from mild to moderately impaired renal function.



Next steps underway:

- Request for end-of-Phase 2 meeting has been accepted by U.S. FDA; anticipate potential for meeting by year-end
- Optimized Phase 3 protocol to reduce variability
- Partnership discussions progressing

Pilavapadin in Neuropathic Pain

Pain Therapeutics Summit - October 14, 2025

Suma Gopinathan, Ph.D.

AGENDA



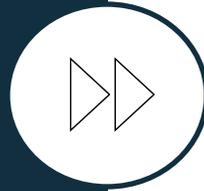
Background

Key facts on DPNP and MOA



Phase 2 Program in DPNP

RELIEF-DPN 1
PROGRESS
Pooled Analysis



Advancing Pilavapadin

Thorough QTc study
Renal Impairment Study

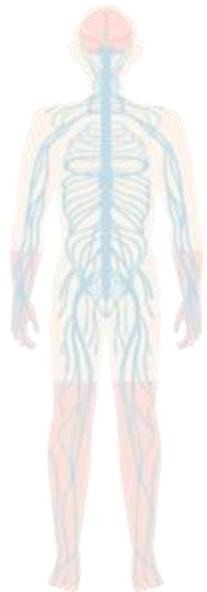


Q&A

Diabetic Peripheral Neuropathic Pain: A highly prevalent chronic condition with significant unmet needs

9M

1 in 4 people living with diabetes suffer from diabetic peripheral neuropathic pain (DPNP). By 2035, there will be 13M people with DPNP in the US^{1,2,3}



70%

of individuals with neuropathic pain do not achieve meaningful pain management⁴

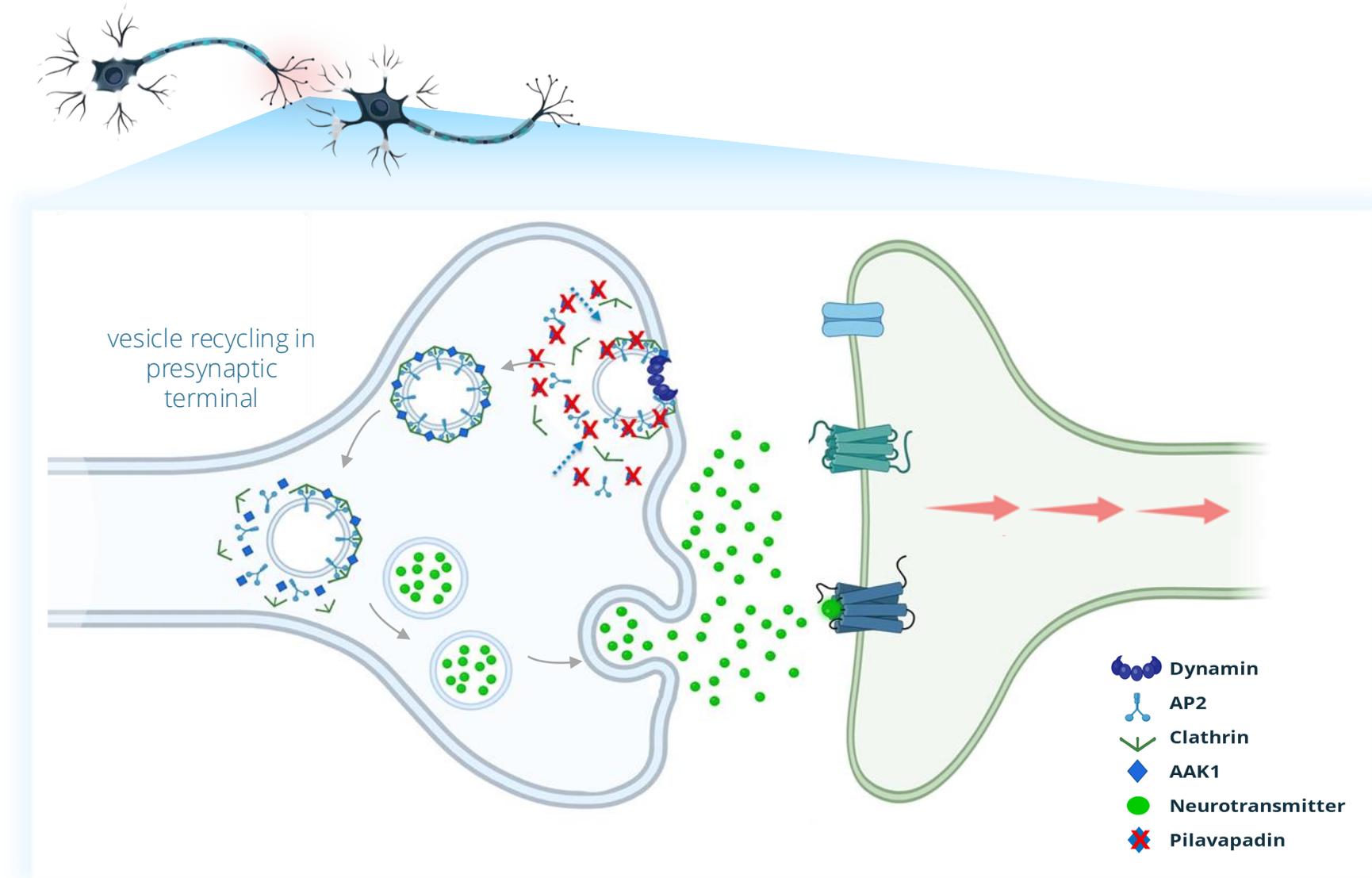
60%

of treated patients will discontinue, switch or add on therapies⁵. Most are stuck in a cycle of trial and failure with available treatments

1. CDC National Diabetes Statistics Report 2024. Source: prevalence rate of DPNP in diabetics is based on primary and secondary research; Source: Clearview Analysis; 2. Braffet BH et al. Diabetes Care. 2024 Sept; 47(9): 1559-1567; doi.org/10.2337/dc23-1749; 3. GRADE Research Group, NEJM. 2022 Sept; 387(12): 1075-1088; DOI: 10.1056/NEJMoa2200436; 4. Rosenberger DC, et al. J Neural Transm (Vienna). 2020 Apr;127(4):589-624. doi: 10.1007/s00702-020-02145-7. Epub 2020 Feb 8.; 5. Veeva Compass data; based on internal Lexicon claims analysis

Opioid-independent MOA | Pilavapadin inhibits AAK1, dampening pain signaling

- 1** In neuropathic pain, there is sustained synaptic transmission in nociceptive circuits. This depends on synaptic vesicle exocytosis and endocytosis in presynaptic terminals.
- 2** Clathrin-mediated endocytosis is important in synaptic vesicle recycling. **AAK1 enhances the affinity of AP-2 to bind to clathrin, mediating endocytosis**
- 3** **Pilavapadin inhibits AAK1, disrupting the recycling of SV, depleting release of neurotransmitters**, dampening synaptic transmission, reducing pain signaling.



Phase 2 Program in DPNP

**Proof of Concept
Study**

RELIEF-DPN 1

**Dose-finding
Study**

PROGRESS



**Assess
Safety and
Efficacy**



**Evaluate
Pragmatic
Study
Design**



**Determine
Optimal
Dose for
Phase 3**

RELIEF-DPN 1 | POC study schema

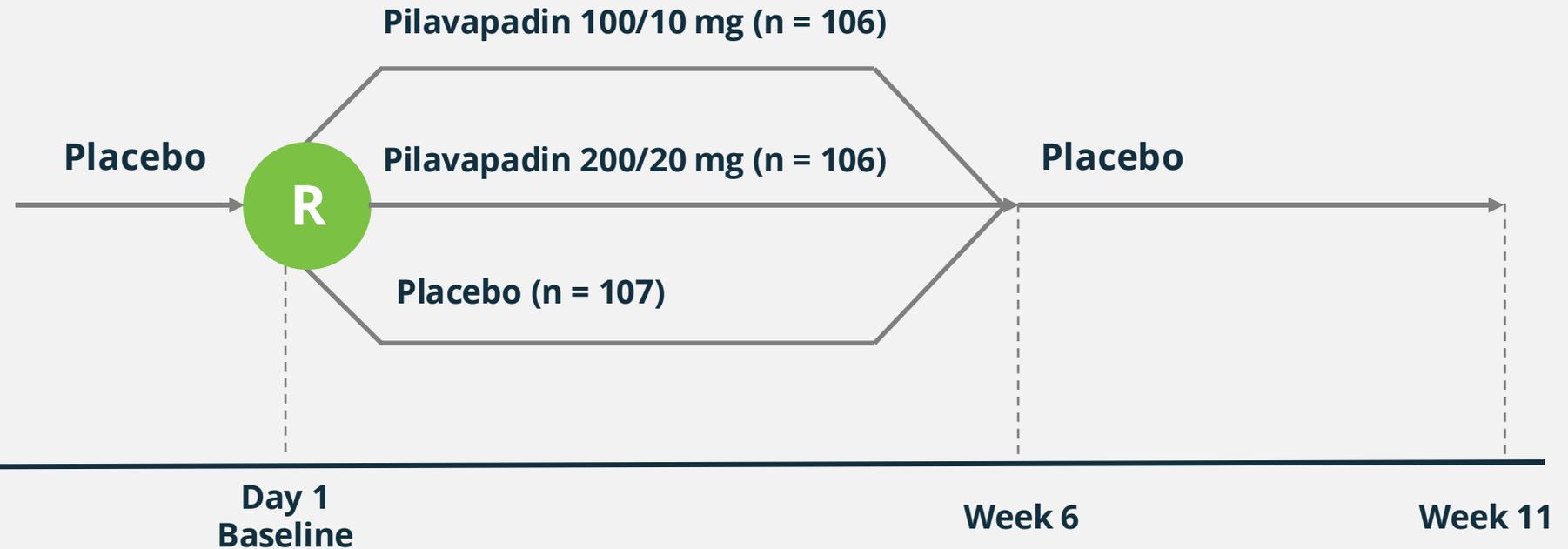
Patient Population

Run in period
2-week

Double-Blind Treatment Period
6-week

Safety Follow-up
5-week

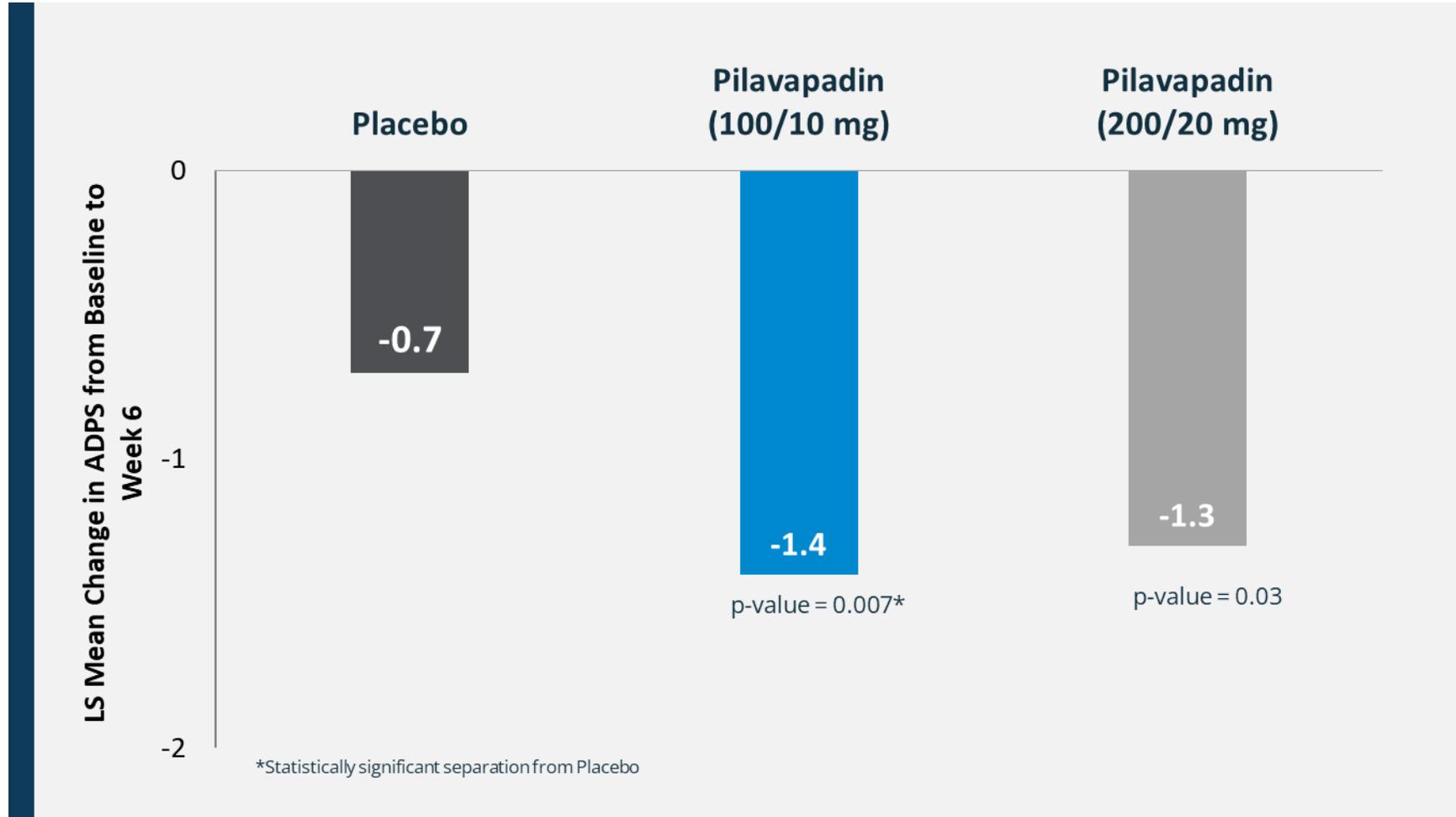
- Individuals with T1DM or T2DM
- Moderate to severe pain
- **Allowed to remain on background standard of care treatment**



DPNP: diabetic peripheral neuropathic pain
Pop-Busui et al, Diabetes Care 2024, 47(8):1325-1332

10x loading dose on Day 1, followed by maintenance dose

RELIEF-DPN 1 | Primary endpoint: Statistically significant reduction in ADPS in the low-dose arm



ADPS: average daily pain score
Pop-Busui et al, Diabetes Care 2024, 47(8):1325-1332

RELIEF-DPN 1 | Treatment emergent adverse events during double-blind treatment period primarily driven by 10x loading dose

Treatment emergent adverse event (preferred term)	Placebo (N = 107) n (%)	Pilavapadin 100 mg/10 mg (N = 106) n (%)	Pilavapadin 200 mg/20 mg (N = 106) n (%)
Dizziness	2 (1.9)	16 (15.1)	29 (27.4)
Headache	4 (3.7)	9 (8.5)	10 (9.4)
Nausea	3 (2.8)	9 (8.5)	12 (11.3)

Pop-Busui et al, Diabetes Care 2024, 47(8):1325-1332

PROGRESS | Dose-finding study to improve tolerability and maintain efficacy

Goals for PROGRESS



To **demonstrate efficacy** without loading dose

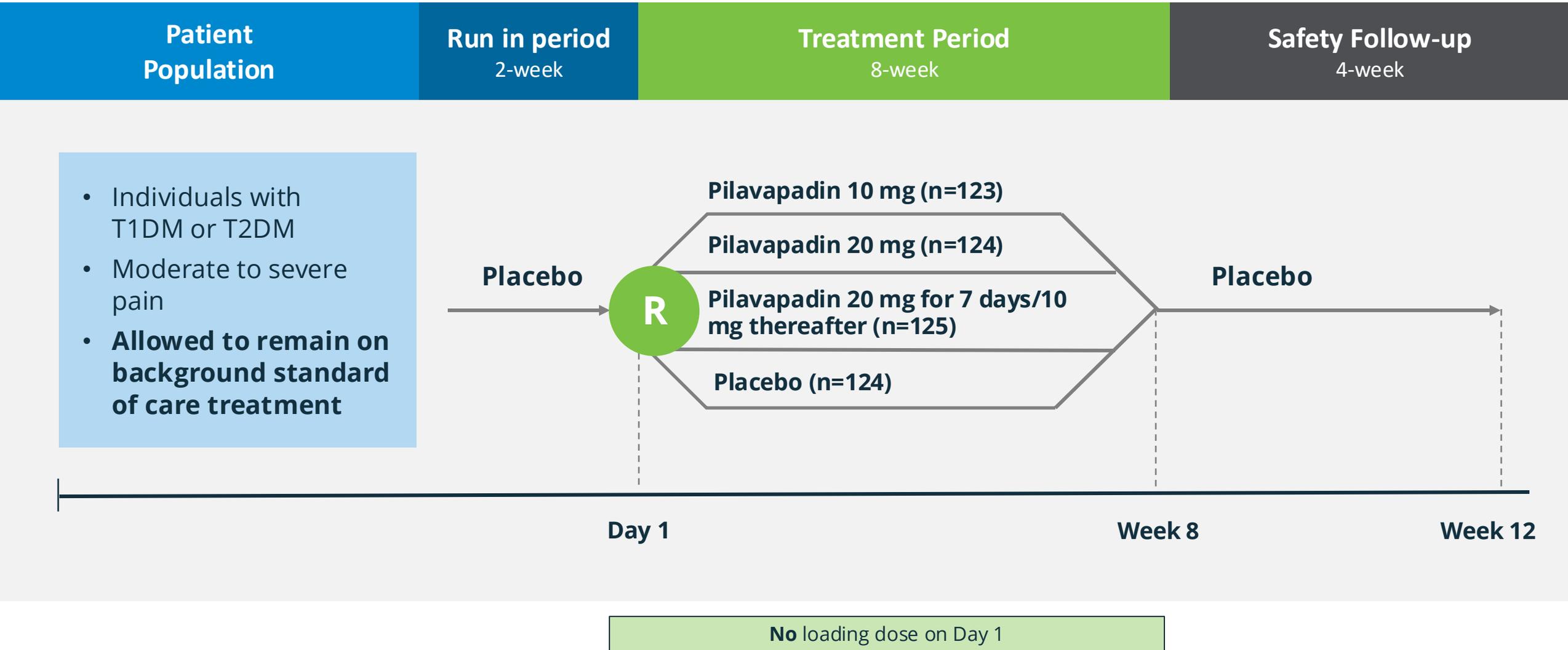


To **improve tolerability** without loading dose



Identify an **effective and tolerable dose** to advance to Phase 3

PROGRESS | Phase 2b study schema



PROGRESS | Key demographics and baseline characteristics

	Placebo (N =124)	10 mg (N =123)	20 mg/10 mg* (N =124)	20 mg (N =125)	TOTAL (N =496)
AGE (YEARS)					
Mean (SD)	61.2 (10.02)	62.2 (9.45)	59.8 (11.29)	62.6 (9.93)	61.5 (10.22)
SEX, n (%)					
Male	71 (57.3)	76 (61.8)	72 (58.1)	73 (58.4)	292 (58.9)
Female	53 (42.7)	47 (38.2)	52 (41.9)	52 (41.6)	204 (41.1)
RACE, n (%)					
White	70 (56.5)	78 (63.4)	80 (64.5)	81 (64.8)	309 (62.3)
Black or African American	44 (35.5)	34 (27.6)	40 (32.3)	38 (30.4)	156 (31.5)
Other	10 (8.1)	11 (8.9)	4 (3.2)	6 (4.8)	31 (6.3)

*20mg QD x 7 days; then 10mg QD thereafter

PROGRESS | Key demographics and baseline characteristics (continued)

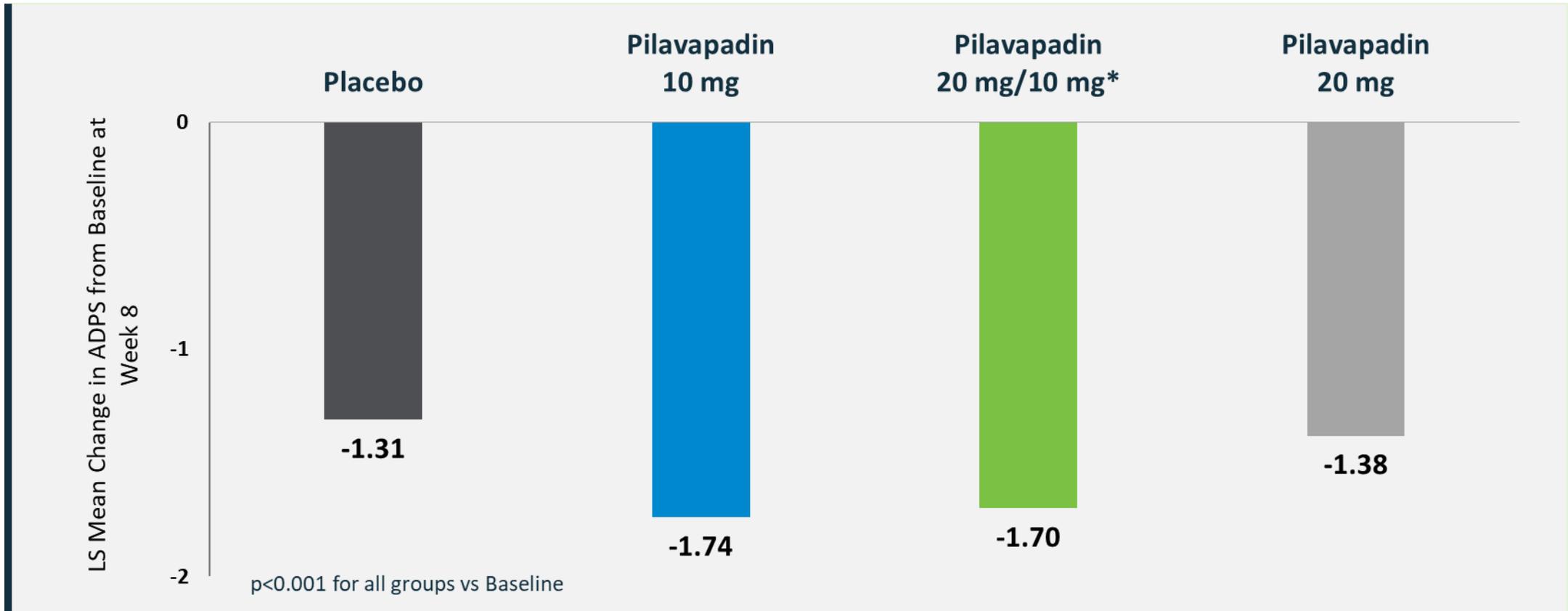
	Placebo (N =124)	10 mg (N =123)	20 mg/10 mg* (N =124)	20 mg (N =125)	TOTAL (N =496)
PAIN SEVERITY AT RANDOMIZATION, n (%)					
Moderate [ADPS 5-7]	82 (66.1)	83 (67.5)	83 (66.9)	83 (66.4)	331 (66.7)
Severe [ADPS 8-9]	42 (33.9)	40 (32.5)	41 (33.1)	42 (33.6)	165 (33.3)
CONCOMITANT DPNP DRUG USE, n (%)					
Yes ¹	39 (31.5)	37 (30.1)	35 (28.2)	41 (32.8)	152 (30.6)
No	85 (68.5)	86 (69.9)	89 (71.8)	84 (67.2)	344 (69.4)

*20mg QD x 7 days; then 10mg QD thereafter

ADPS = average daily pain score; DPNP = Diabetic Peripheral Neuropathic Pain

¹Most frequent medications for DPNP were gabapentin (22%), pregabalin (4%), duloxetine

PROGRESS | 10 mg dose demonstrates clinically meaningful reduction in ADPS from Baseline

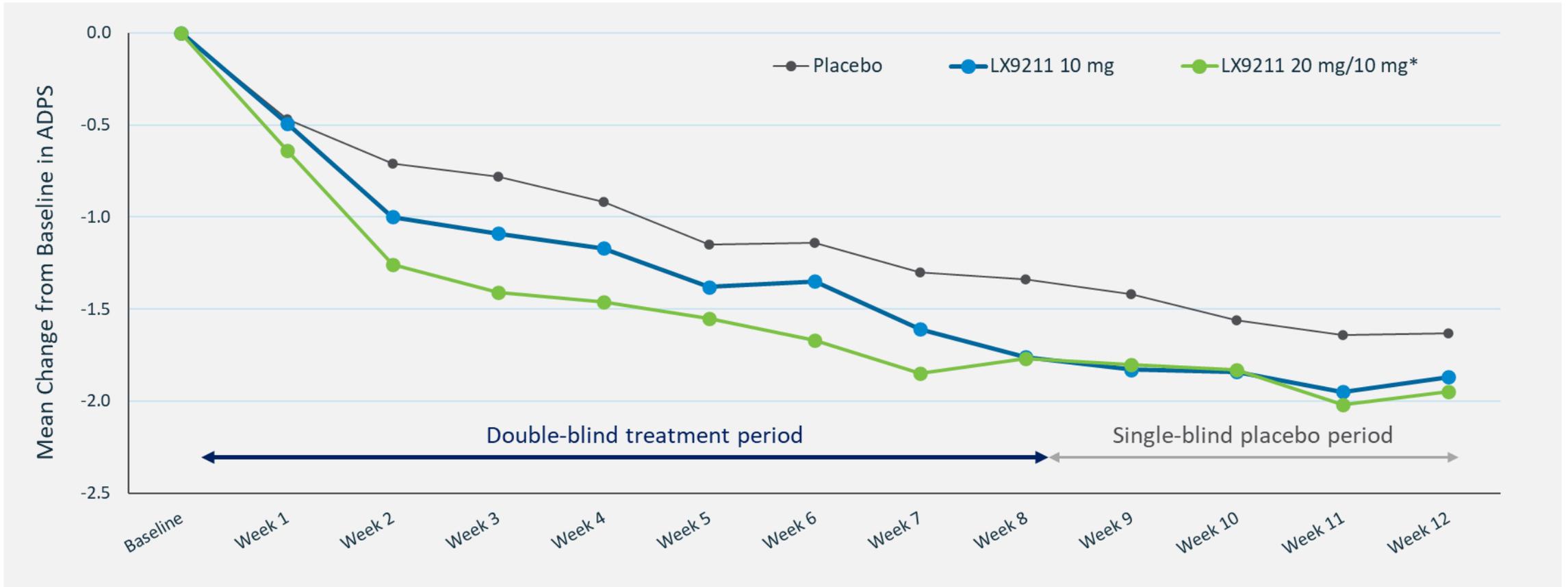


Missed primary endpoint due to lack of dose response in 20 mg arm; post-hoc analysis showed nominally significant reduction in ADPS in 10 mg arms

*Pilavapadin 20 mg for 7 days and then 10 mg thereafter
ADPS = average daily pain score

PROGRESS | 10 mg dose delivered clinically meaningful 2-point ADPS reduction from baseline by weeks 11 - 12

Mean ADPS – 10 mg Time course (Change from Baseline to Week 12)



ADPS = average daily pain score

PROGRESS | Improved tolerability profile compared to RELIEF-DPN-1

Most frequent treatment-emergent adverse events during double-blind treatment period

Treatment emergent adverse event (preferred term)	Placebo (N = 123) n (%)	Pilavapadin 10 mg (N = 122) n (%)	Pilavapadin 20 mg/10 mg (N = 123) n (%)	Pilavapadin 20 mg (N = 124) N (%)
Dizziness	2 (1.6)	9 (7.4)	6 (4.9)	18 (14.5)
Nausea	0	11 (9.0)	7 (5.7)	10 (8.1)
Constipation	0	7 (5.7)	5 (4.1)	5 (4.0)

*Safety population: includes all patients who received study drug; excludes four patients (one in each study arm) who were randomized but never received study drug

PROGRESS | Placebo-like completion rate in the 10 mg arm

Number of participants	Placebo (N = 124) n (%)	Pilavapadin 10 mg (N = 123) n (%)	Pilavapadin 20 mg/10 mg (N = 124) n (%)	Pilavapadin 20 mg (N = 125) n (%)	Total (N = 496)* n (%)
Completed	109 (87.9)	108 (87.8)	103 (83.1)	96 (76.8)	416 (83.9)
Discontinued	15 (12.1)	15 (12.2)	21 (16.9)	29 (23.2)	80 (16.1)

*Intent-to-treat (ITT) population includes four patients (one in each study arm) who were randomized but never received study drug

Pooled Phase 2 Analysis | Advancing to Phase 3



**Investigate
exposure-response
relationship across
two large Phase 2
studies**

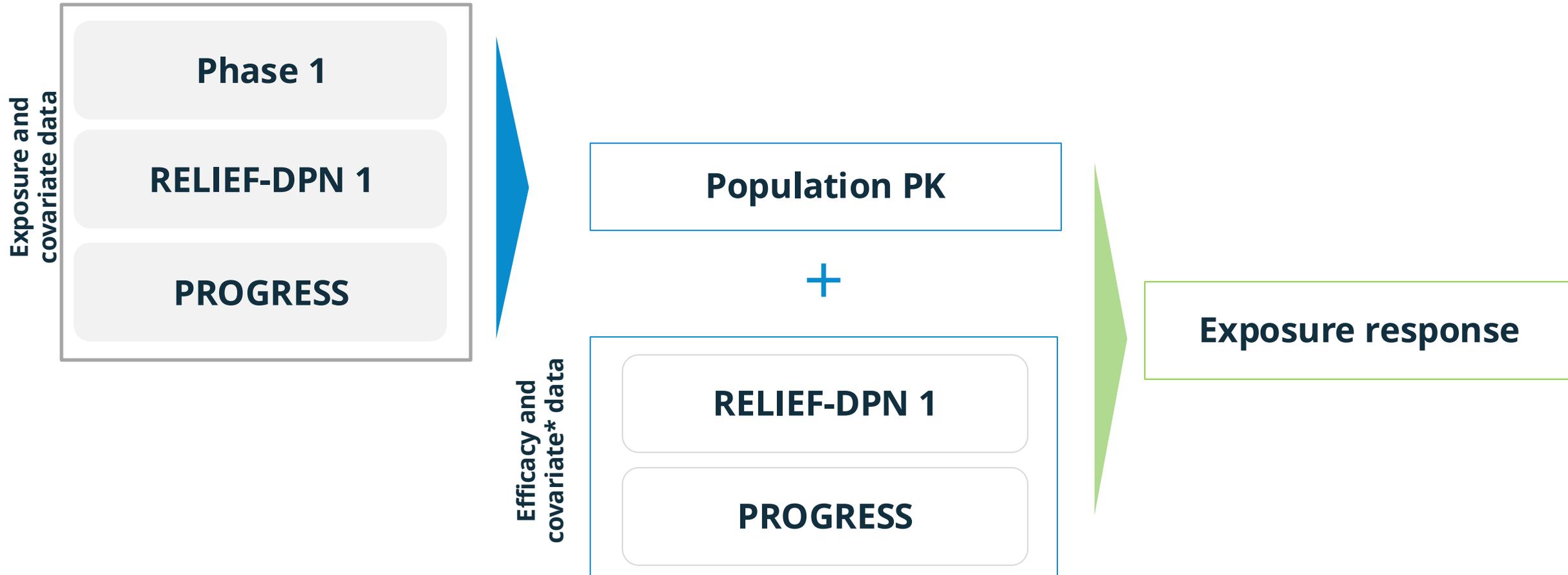


**Investigate lack of
efficacy in
PROGRESS 20 mg
arm**



**Confirm the
robustness of the
10 mg dose**

Pooled Phase 2 Analysis | Methodology



*Covariates: body weight, BMI, age, sex, race, concomitant DPNP medication, rescue medication and baseline ADPS on both the slope and intercept parameters

Pooled Phase 2 Analysis | Results support advancing 10 mg dose to Phase 3

Key Findings:



Linear exposure-response relationship

↑ exposure (C_{min}) → ↓ ADPS (change from baseline)

Baseline pain score was the only significant covariate



Participants in the PROGRESS 20 mg arm were less adherent

- Potentially driven by increased adverse events in 20 mg arm

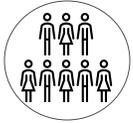


10 mg dose strikes balance between safety and efficacy

- High doses increases tolerability and adherence risks
- Lower doses lack adequate exposure for efficacy

Advancing Pilavapadin | Absence of relevant QTc prolongation & renal function impact ($CR_{CL} \geq 30$ mL/min) on PK → inclusion of broader patient population in Phase 3

Thorough QTc study



Population:

- Healthy volunteers



Dose Levels:

- Therapeutic and supratherapeutic



Results:

- Pilavapadin did not cause a relevant prolongation of the QTc interval

Renal Impairment study



Population:

- Participants with varying degrees of kidney function



Dose Level:

- Therapeutic



Results:

- Renal Function ($CR_{CL} \geq 30$ mL/min) had no significant impact on the PK of Pilavapadin

Advancing Pilavapadin | 10 mg dose is Phase 3 ready with protocol optimized to reduce variability

Phase 3 Design Features



Larger sample size

Potential for reduced variability



Longer treatment duration

Potential for greater improvement in ADPS with longer treatment duration



Two treatment arms

Lower placebo response anticipated

Thank You