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The Cold Pressor Test as a Predictive Pharmacodynamic Biomarker for Na_V 1.8 inhibitor Development

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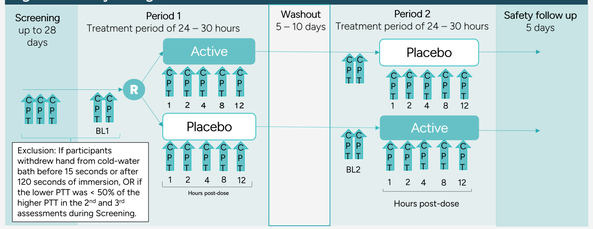
INTRODUCTION

- Analgesic drug development remains a high societal priority, yet the field has been marked by repeated late-stage failures, partly due to the limited ability of preclinical models to predict clinical analgesia.
- The cold pressor test (CPT) is an established pain model where an extremity is immersed in extremely cold water to produce tonic pain.
- The CPT has limitations, including:
  - Sensitive to some classes of analgesics, such as opioids, but relatively insensitive to others, e.g. non-steroidal anti-inflammatory drugs (NSAIDs).
  - Variations in methodology of administering CPT can have significant impact on reproducibility of study results.[1]
- A negative result can be difficult to interpret, because it may reflect either an inactive compound, a suboptimal method, or a compound from a class that is effective in clinical pain yet ineffective in CPT.
- Selective Na_V1.8 inhibition is a novel non-opioid analgesic mechanism which blocks the transmission of pain signals in peripheral sensory neurons without central nervous system effects including the risk of addiction.[2,3]
- Some evidence suggest that CPT can register the effects of Na_V1.8 antagonists.[4,5]
- The objective of this analysis was to evaluate the application of cold pressor test as a pharmacodynamic biomarker for Na_V1.8 inhibitor analgesic development.

*Onzotrigine (formerly known as LTG-001) is an investigational drug; its efficacy and safety have not been evaluated by any regulatory agency
**LTG-305 development program has been discontinued.
*** These data are derived from different clinical trials at different points in time, with differences in trial design and patient population. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.

METHODS

Figure 1. Study Design



All consecutive CPT tests were performed at least 30 minutes apart. Randomization and study drug administration occurred within 60 minutes of the second BL (Day 1) pre-dose CPT.

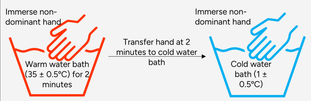
Table 1. Cold pressor series comprising 9 cohorts from 5 trials

Study No. (NCT #)	Drug class	CPT cohort	Dosing regimen	Assessment window	Washout period	No. of participants randomized
LTG-OBS-102 (NCT06600607)	Gabapentinoid	Pregabalin 300 mg vs PBO	Single dose	0–12 h	5 days	20
LTG-001-001 (NCT06049095)	Na_V1.8 inhibitor	Onzotrigine* 100 mg vs PBO	Single dose	0–12 h	6 days	20
		Onzotrigine* 300 mg vs PBO	Single dose	0–12 h	6 days	20
		Onzotrigine* 600 mg vs PBO	Single dose	0–12 h	6 days	21
LTG-305-001 (NCT06554574)	Na_V1.8 inhibitor	LTG-305 480 mg vs PBO	Single dose	0–30 h	6 days	20
		LTG-305 480 mg vs PBO	Daily dosing, 5 d	0–24 h, post day 1 and day 5 dose	10 days	20
LTG-OBS-103 (NCT06972212)	Na_V1.8 inhibitor	Suzetrigine 100 mg vs PBO	Single dose	0–24 h	6 days	20
LTG-321-013 (NCT07110610)	Na_V1.8 inhibitor	LTG-321 90 mg vs PBO	Single dose	0–24 h	6 days	20
		LTG-321 270 mg vs PBO	Single dose	0–24 h	6 days	20

- A total of 9 independent cold pressor cohorts from 5 separate studies were included in this cross-cohort analysis, evaluating four Na_V1.8 inhibitors (onzotrigine*, LTG-305**, LTG-321 and suzetrigine) with pregabalin as a positive control.
- All 5 studies had similar methodologies with differences noted in Table 1:
  - All were randomized, double-blind, placebo-controlled, 2-period crossover studies conducted in healthy male adults (Figure 1).
  - All used the same CPT procedure (Figure 2).
- In this cross-cohort analysis, the primary measure was AUC_{0-12}, which is the time-weighted average of placebo-adjusted change from baseline in Pain Tolerance Threshold (PTT) from 0-12 hours.
- CPT results were compared with clinical post-abdominoplasty pain results from published studies using SPID12.[6,7]

Figure 2. Procedure for Cold Pressor Test

Instructions to participants:
- **Immerse hand ~ 8 to 10 cm into each water bath**
- **Separate fingers, avoid clenching the hand and keep the hand still**
- **Keep the hand immersed in the cold water as long as tolerable**

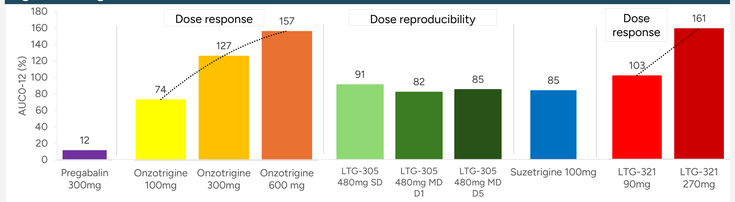


Note: Maximum duration of cold-water immersion is 180 seconds
Pain tolerance threshold (PTT) is the time to hand withdrawal when the cold can no longer be tolerated
PTT was assessed just prior to dosing (baseline) and at 1, 2, 4, 8 and 12 hours post-dose.

RESULTS

- The CPT test:
  - Demonstrated dose response (Figure 3).
  - Demonstrated downside (CPT could distinguish active drug from placebo) and upside sensitivity (CPT could distinguish among active treatments as proportion of CPTs that reached the 180-second ceiling increased with the size of the effect) (Table 2).
  - Were substantially consistent with the clinical effects in abdominoplasty in magnitude and rank order (Figure 4)
    - Relative to suzetrigine 100 mg, onzotrigine produced larger effects in both settings (Figure 4 and Table 3).***
    - The time course of the effect corresponded between the two settings, each curve normalized to its own peak (Figure 5).
    - In both CPT and abdominoplasty, the effect appeared within about 1–2 hours, peaked early (near 2 hours in the CPT and about 4 hours in abdominoplasty), and was maintained through 12 hours.
  - Demonstrated study reproducibility
    - Placebo response was stable across all 5 studies; AUC_{0-12} ranged from -8% to +7% in the placebo groups.
    - Evidence supporting active-dose reproducibility (Figure 3)
      - There was minimal accumulation with repeat dosing of LTG-305**, with Day 5 plasma AUC only 14% higher than Day 1 AUC.
      - LTG-305** 480 mg produced similar CPT effects on Day 1 and Day 5 of the multi-dose arms, and in the single dose arm.

Figure 3. Drug effect as assessed with CPT



Each post-dose PTT was expressed as a multiple of that participant's own pre-dose baseline (e.g. 50 seconds against a 40 second baseline was 1.25 X baseline; multiples were analyzed on a log scale so that participants with different baseline times share a common scale). Because each participant received drug in 1 period and placebo in the other, the drug effect is the drug's multiple divided by placebo's multiple in the same participants (e.g. 1.25 ÷ 1.04 = 1.20, a 20% increase over placebo).

Table 2. Sensitivity

Drug and dose	Responder analysis: proportion reaching the 180 s immersion ceiling		CPT cohort efficacy
	% participants reaching 180 s ceiling (≥1 assessment)	% assessments reaching 180 s ceiling	CFB in PTT 2 hours post-dose, LS ratio
LTG-321 270 mg	60	34	2.61
LTG-321 90 mg	35	20	2.03
Onzotrigine 600 mg	55	39	2.95
Onzotrigine 300 mg	40	31	2.52
Onzotrigine 100 mg	30	22	1.76
LTG-305[¥] 480 SD	35	23	2.01
LTG-305[¥] 480 mg MD D1			2.89
LTG-305[¥] 480 mg MD D5			1.94
Suzetrigine 100 mg	40	27	1.84
Placebo (all studies)[§]	4	3	NA
Pregabalin 300 mg	0	0	0.98

[¥]LTG-305 responder value is across its cohorts
[§]Placebo responder value is across all cohorts

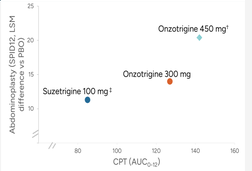
RESULTS

Table 3. Benchmarking: cold pressor versus abdominoplasty (relative to suzetrigine)

Drug and dose	Cold pressor effect vs suzetrigine	Abdominoplasty SPID $_{0-12}$ (LSM diff vs placebo)	Abdominoplasty effect vs suzetrigine
Suzetrigine 100 mg	reference	11.3	reference
Onzotrigine 300 mg	+49%	14	+24%
Onzotrigine 450 mg[†]	+67%	20.4	+81%

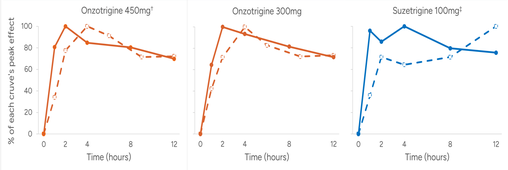
Cross-cohort/cross-program comparison. Cold pressor effect = AUC 0–12. Abdominoplasty effect = SPID over the matched 0–12 h window (SPID12, LSM difference vs placebo); suzetrigine's published 0–48h primary was SPID48 = 48.4.[7]
[†]Onzotrigine 450 mg was not studied in the CPT; its cold pressor value is interpolated as the mean of the 300 mg (127%) and 600 mg (157%) results = 142% (Figure 4).

Figure 4. Predictive validity: CPT vs abdominoplasty



[†]The CPT result for onzotrigine 450 mg was interpolated
[‡]The suzetrigine CPT results were from the Latigo program and its abdominoplasty effect was from the published literature.

Figure 5. Time course of effect: CPT versus abdominoplasty



[†]The CPT result for onzotrigine 450 mg was interpolated
[‡]Suzetrigine abdominoplasty values were estimated from Reference 7.
Solid line represents CPT results; Dotted line represents abdominoplasty results
Each curve is normalized to its own peak

CONCLUSION

- We believe the CPT can function as a pharmacodynamic biomarker for Na_V1.8 antagonists in acute postoperative pain – reproducible, dose-responsive and predictive of doses that proved effective clinically.
- The set of model attributes used here (assay sensitivity, dynamic range, reproducibility, dose-responsiveness and predictive validity) can be used to evaluate a human experimental pain model to support drug development decisions.

LIMITATIONS

- The cross-program comparisons between the CPT and abdominoplasty were between different studies.
- The 180-second immersion ceiling can still censor the strongest responders and compress the top of the scale.
- Evidence for active drug reproducibility came from a single drug and dose (LTG-305 480 mg).
- The CPT studies were conducted in healthy young men and may not be generalizable to women or older adults.

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Abbreviations: BL, baseline; CPT, cold pressor test; d, daily; h, hours; LSM, least squares mean; MD, multi-dose; PBO, placebo; PO, orally; PTT, Pain tolerance threshold; R, randomization; SPID48, sum of pain-intensity difference over 48 hours of treatment; SPID12, sum of pain-intensity difference over 12 hours of treatment; AUC_{0-12}, time-weighted average of placebo-adjusted change in PTT

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DISCLOSURES: Neil Singla, Timothy Rogier, Ben Vaughn, Holly Carlisle, Mallory Loflin, Kyra Wade and Ada Kumar are employees of and own shares in Latigo Biotherapeutics. Neil Singla also owns shares in Evolution Research Group, which performed clinical trial services for the Vertex and Latigo abdominoplasty studies. Nathaniel Katz is a paid clinical and scientific consultant to Latigo Biotherapeutics, as well as consultant/scientific advisory board member for multiple other sponsors of analgesics. Chris Wynne is an employee of and holds shares in NZCR.

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