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Efficacy and safety of onzotrigine, a selective $Na_V1.8$ inhibitor, in patients with moderate to severe pain after abdominoplasty

Neil Singla[1], Ben Vaughn[1], Timothy Rogier[1], Todd Bertoch[2], Harold Minkowitz[3], Mallory Loflin[1], Ada Kumar[1], Nathaniel Katz[4]

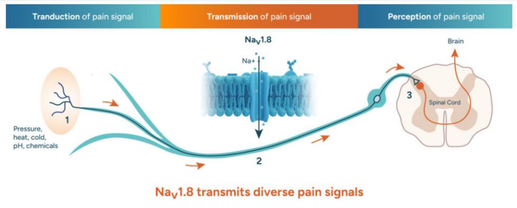
[1]Latigo Biotherapeutics, Thousand Oaks, CA; [2]CenExcel; [3]Evolution Research Group, University of Texas M.D. Anderson Cancer Center; [4]Ein Sof Innovations, Vital Clinical Solutions



INTRODUCTION

- $Na_V1.8$ is a voltage-gated sodium ion channel expressed in the dorsal root ganglion neurons that plays a key role in the transmission of pain signals (Figure 1).
- 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.[1,2]
- Abdominoplasty is an established, soft-tissue postoperative pain model which results in moderate to severe acute pain that is usually treated with a multimodal regimen involving opioids, NSAIDs and/or acetaminophen.[3]

Figure 1: $Na_V1.8$ and the transmission of pain

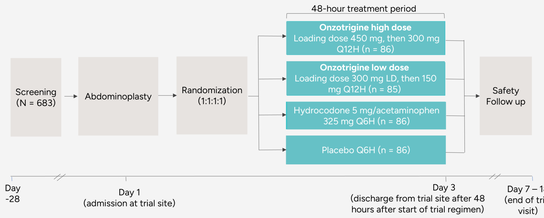


$Na_V1.8$ transmits diverse pain signals

METHODS

- A Phase 2b, randomized, double-blind, placebo- and active-controlled, dose-ranging trial was conducted to evaluate the efficacy and safety of low and high doses of onzotrigine*, a $Na_V1.8$ inhibitor, compared to placebo and an opioid reference in treating acute pain in healthy adults undergoing partial abdominoplasty (Figure 2 and Table 1).
- Data related to this research has previously been published[4]; here we present the results of additional exploratory endpoints to demonstrate other indicators of efficacy of onzotrigine as well as additional safety data.
- Since the onzotrigine high dose regimen was selected to advance in future trials, only the results from the high-dose group are reported.

Figure 2: Study design



Adapted from Singla N, et al. *N Engl J Med* 2026
Oxycodone 5mg Q6H was permitted as rescue.

ASSESSMENTS[4]

- NPRS is a validated, patient-reported measure to assess pain intensity where patients rate their pain from 0 (no pain) to 10 (worst possible pain).
- SPID is a time-weighted sum of pain intensity differences from baseline, measured using NPRS.
- PGA is a 5-level, patient reported assessment of pain control: poor, fair, good, very good or excellent; favorable refers to good, very good or excellent.
- PID from baseline, measured using NPRS scores.

STUDY ENDPOINTS[4]

Primary Endpoint

- SPID from 0 – 48 hours (SPID48)

Secondary Endpoints

- Total opioid rescue consumption over 48 hours, in MME
- Proportion of participants requiring no opioid rescue over 48 hours
- Median time to ≥2 or ≥1 reduction in NPRS from baseline
- Incidence of nausea or vomiting over the treatment period
- PID at 60 minutes using NPRS
- SPID from 0 – 24 hours (SPID24)
- Proportion of participants with favorable PGA (good, very good and excellent) at the end of treatment

Exploratory Endpoints (other exploratory endpoints not reported here)

- Participants with ≥30%, ≥50% and ≥70% reduction in NPRS at 24 hours

KEY INCLUSION CRITERIA

- Age 18 to 65 years.
- Underwent a lower abdominoplasty with rectus plication without other collateral procedures.
- Did not have any medical complications during surgery.
- Within 4 hours after completion of surgery, reported moderate or severe pain on the VRS and a pain score ≥5 on the NPRS, at rest.

KEY EXCLUSION CRITERIA

- Current or long-term opioid use.
- History of chronic pain conditions, depression, anxiety or other psychiatric disorders not clinically stable for at least 90 days before surgery, intra-abdominal and/or pelvic surgery that resulted in any complications or cardiovascular disease.
- Chronic use of analgesics or benzodiazepines.

RESULTS

- Key baseline characteristics were similar between the groups (Table 2). All results are with the full analysis set.
- The least squares mean difference in SPID48 between onzotrigine and placebo was significant at 62.08 (95% CI 36.95 – 87.21), approximately 50% larger than the effect of the opioid reference vs. placebo at 40.86 (95% CI 15.71 – 66.01) (Figure 3). [4]
- Figure 4 shows the placebo-adjusted 48-hour effect for high-dose onzotrigine and other analgesics studied in the abdominoplasty model.**
- 52% of patients receiving onzotrigine remained opioid-free, vs. 22% for placebo (Figure 5).[4]
- Median time to meaningful pain relief (≥2-point NPRS reduction) was 52 minutes with onzotrigine vs. 88 minutes for placebo and 83 minutes for the opioid reference (Figure 5).
- Proportion of participants with ≥30%, ≥50%, and ≥70% NPRS reduction at 24 hours after first dose of study drug was 76%, 60%, 36% for onzotrigine; 67%, 51%, 24% for the opioid reference; and 56%, 34%, 13% for placebo (Figure 6).

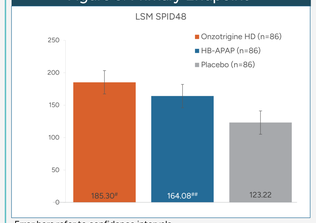
Table 2: Baseline Characteristics

	Onzotrigine HD (n = 86)	HB-APAP (n = 86)	Placebo (n = 86)
Age, years (mean ± SD)	40.3 ± 8.6	41.2 ± 8.9	39.9 ± 9.1
Female sex, n (%)	85 (99)	85 (99)	85 (99)
Race, n (%)			
White	60 (70)	55 (64)	60 (70)
Black	18 (21)	27 (31)	21 (24)
Asian	6 (7)	1 (1)	0
Other	2 (2)	3 (3)	5 (6)
BMI, kg/m^2 (mean ± SD)	27.1 ± 4.2	27.4 ± 3.8	26.7 ± 3.7
VRS category[¥], n (%)			
Moderate	41 (48)	50 (58)	37 (43)
Severe	45 (52)	36 (42)	49 (57)
NPRS score	7.5 ± 1.2	7.3 ± 1.2	7.4 ± 1.3

Adapted from Singla N, et al. *N Engl J Med* 2026
[¥]VRS is a 4-point scale ranging from no pain to severe pain

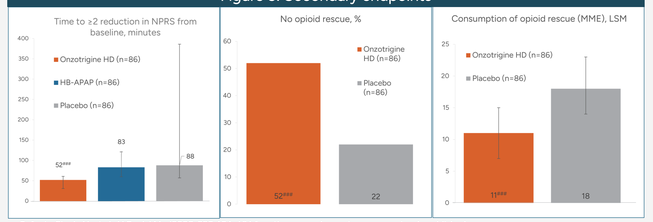
*Onzotrigine (formerly LTG-001) is an investigational drug; its efficacy and safety have not been evaluated by any regulatory agency.
**These data are derived from different clinical trials, with differences in trial design and patient population. As a result, cross-trial comparisons cannot be made,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

Figure 3: Primary Endpoint[4]



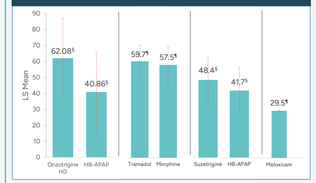
Error bars refer to confidence intervals
#p<0.001 versus placebo;
##p<0.05 versus placebo

Figure 5: Secondary endpoints



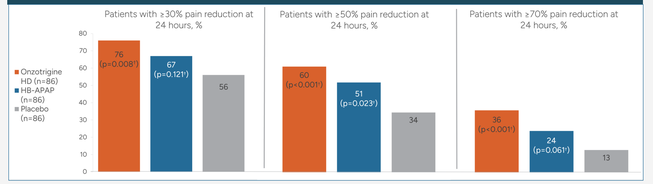
Refer to Singla N, et al. *N Engl J Med* 2026; 395:454-464 for other secondary outcomes, previously published.
Error bars refer to confidence intervals.
###p<0.05 versus placebo

Figure 4: SPID48 in abdominoplasty trials‡[4-9]



The doses of the medications depicted above are as follows: tramadol IV 50mg, morphine IV 4 mg, suzetrigine PO at the FDA approved dose, HB-APAP PO 5 mg/325mg, meloxicam IV 30 mg and onzotrigine PO high dose group.
‡Outcomes are from different trials and are presented for information only.
§ Error bars refer to the confidence intervals
¶ Error bars refer to the standard error.

Figure 6: Exploratory Endpoints



†nominal p values versus placebo

SAFETY[4]

- The percentage of patients who had at least 1 TEAE was lowest in the onzotrigine HD group (Table 3).
- The majority of TEAEs were rated as mild or moderate in severity.
- One serious TEAE occurred in each group. None of these were deemed trial-related.
- TEAEs leading to discontinuation of study drug/trial occurred only in the hydrocodone bitartrate-acetaminophen group.
- Additionally, no clinically relevant QTc prolongation nor hepatic injury were observed.

Table 3: Treatment-Emergent Adverse Events

Adverse events	Onzotrigine HD, n=86	HB-APAP, n=86	Placebo, n=86
Any AE	43 (50)	54 (63)	56 (65)
Any severe AE (grade≥3)	3 (3)	6 (7)	3 (3)
≥5 % of patients			
Nausea	17 (20)	28 (33)	32 (37)
Headache	15 (17)	16 (19)	20 (23)
Dizziness	5 (6)	9 (10)	9 (10)
Constipation	2 (2)	5 (6)	8 (9)
Vomiting	1 (1)	6 (7)	5 (6)
Pyrexia	6 (7)	1 (1)	2 (2)
Syncope	1 (1)	4 (5)	3 (3)
Presyncope	5 (6)	1 (1)	1 (1)

Adapted from Singla N, et al. *N Engl J Med* 2026.

CONCLUSIONS AND FUTURE DIRECTION

- Onzotrigine led to significant reductions in moderate to severe pain over 48 hours compared to placebo.
- The percentage of patients who received no opioid rescue medication was over twice as high with onzotrigine than with placebo; onzotrigine significantly reduced the use of opioid rescue medication.
- Meaningful pain relief occurred in significantly more patients with onzotrigine compared to placebo, with a shorter time to pain relief.
- Onzotrigine demonstrated a favorable safety and tolerability profile.
- Further studies are needed to confirm the efficacy and safety profile of onzotrigine in additional models of pain.
- Latigo Biotherapeutics plans to conduct a placebo-controlled Phase 3 trial to evaluate the efficacy and safety of onzotrigine in participants with acute, moderate to severe pain after bunionectomy and an open-label Phase 3 safety trial.

LIMITATIONS[4]

- In this trial, onzotrigine was evaluated as a monotherapy which is not reflective of clinical practice where acute pain is typically managed multimodally.
- The trial population was comprised mostly of women as the majority of abdominoplasties are performed in women.

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Abbreviations: TEAE, treatment-emergent adverse event; BL, baseline; BMI, body mass index; CI, confidence interval; EOT, end of treatment; FDA, Food and Drug Administration; HB-APAP, hydrocodone bitartrate – acetaminophen; HD, high dose; IV, intravenous; PO, oral; LD, low dose; LSM, least-squared mean; Q12H, every 12 hours; Q6H, every 6 hours; MME, morphine milligram equivalents; NPRS, numeric pain rating scale; NSAID, non-steroidal anti-inflammatory drugs; PID, Pain intensity difference; PGA, Patient global assessment; SD, standard deviation; SPID, Summed pain intensity difference; VRS, verbal rating scale; vs., versus

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