

Suzetrigine as Part of Multimodal Therapy Enables Opioid-Free Recovery After Aesthetic and Reconstructive Surgeries

Samuel Lin¹, Jessica McCoun², Daneshvari Solanki³, Jai Mehta⁴, William Bortcosh⁴, Lanju Zhang⁴, Darin Correll⁴, Richard Scranton⁴, Todd Bertoch⁵

¹Beth Israel Deaconess Medical Center, Boston, MA; ²CenExel ACMR Clinical Research, Atlanta, GA; ³HD Research, LLC, Bellaire, TX; ⁴Vertex Pharmaceuticals Incorporated, Boston, MA; ⁵CenExel JBR Clinical Research, Salt Lake City, UT

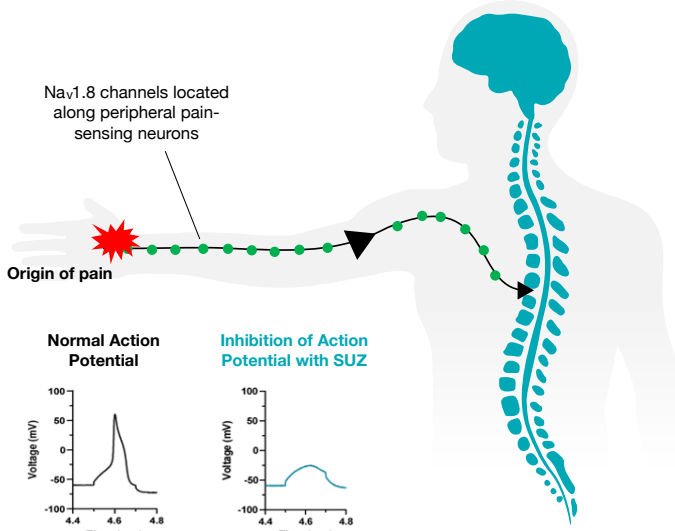


INTRODUCTION

- Multimodal analgesia** is a common approach for managing moderate-to-severe acute pain
- Opioids** are commonly used for pain management, but are associated with tolerability issues (e.g., nausea, vomiting, constipation) and safety concerns (e.g., addiction, opioid use disorder)

Na_v1.8

- Na_v1.8 antagonism inhibits action potentials in peripheral nociceptors and DRG and therefore inhibits propagation of pain signals to the brain
- Selectively expressed on peripheral nociceptors and DRG but not the brain; targeting this channel does not have a risk of addiction¹



Suzetrigine

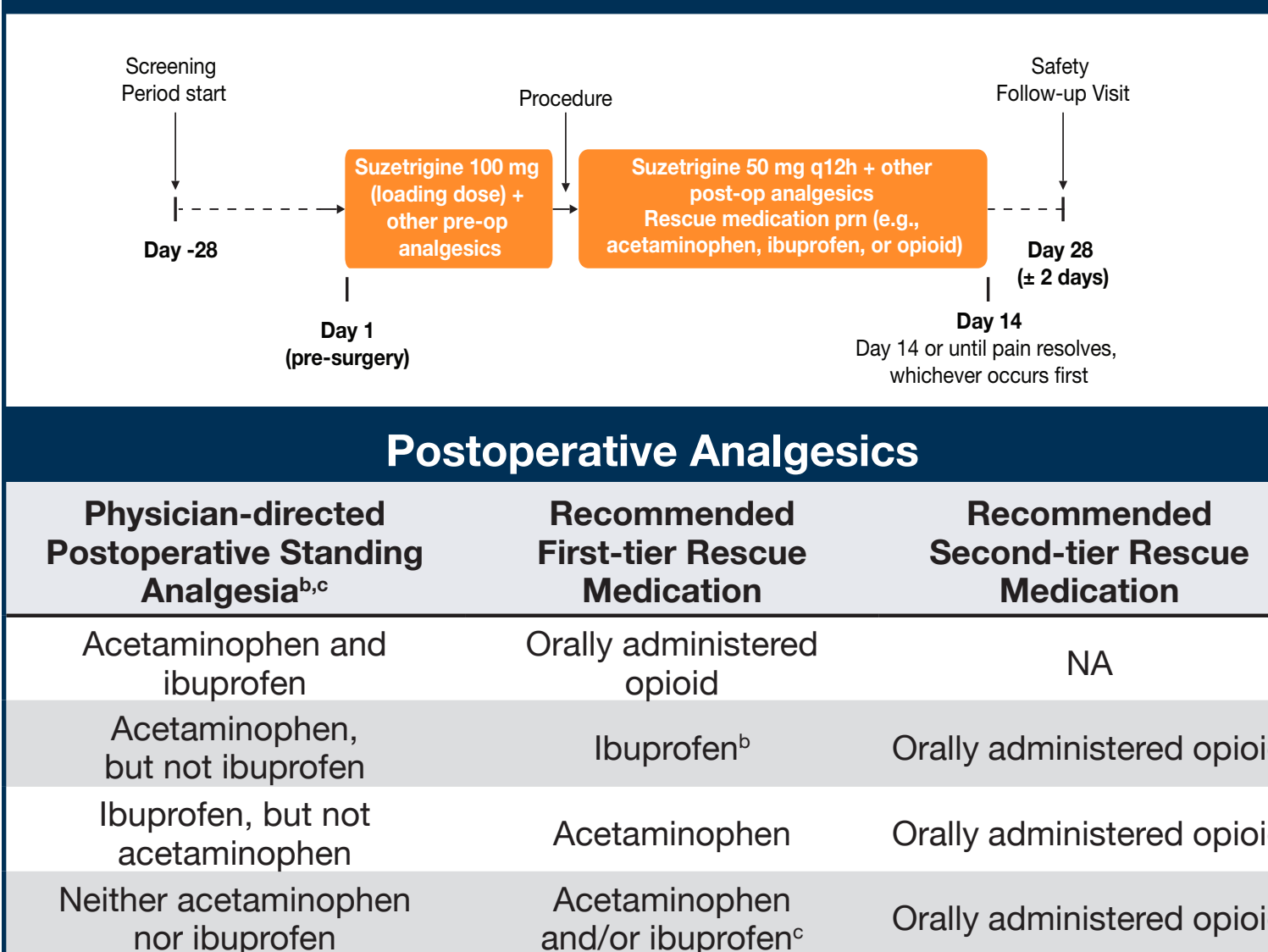
- Oral, small molecule, non-opioid** highly selective for Na_v1.8
- Selective pain signal inhibitor** that is peripherally acting
- Approved in the US to treat moderate-to-severe acute pain in adults
- In phase 3 randomized, controlled studies (abdominoplasty/bunionectomy; N=2191), suzetrigine administered postoperatively had statistically significant and clinically meaningful pain relief compared to placebo as a monotherapy, with efficacy similar to moderate opioid therapy²

KEY OBJECTIVES

- To evaluate the effectiveness of suzetrigine as a part of multimodal therapy in treating acute postoperative pain
- To evaluate opioid use when suzetrigine is included as part of multimodal therapy

METHODS

Figure 1. Study Design



ATC: around the clock; NA: not applicable; NSAID: nonsteroidal anti-inflammatory drug; post-op: postoperative; pre-op: preoperative; prn: as needed; q12h: every 12 hours
Notes: Other preoperative analgesics, if utilized, were administered at approximately the same time as the loading dose of suzetrigine. Pre-, intra-, and postoperative analgesics were administered by the participant's physician based on the standard of care for the surgical procedure (e.g., acetaminophen, NSAIDs, dexamethasone, gabapentin [≤500 mg]). Pre-, intra-, and postoperative analgesics utilized by participants in this study are presented in Table 5.
^aThe recommended postoperative standing analgesics (in addition to suzetrigine) were acetaminophen and ibuprofen (administered together ATC), however, alternative postoperative standing analgesics could be prescribed at the discretion of the participant's physician.
^bFor participants in this scenario for whom ibuprofen is contraindicated, an orally administered opioid could be used as a first-tier rescue medication.
^cA participant for whom ibuprofen is contraindicated could take acetaminophen alone.

- Single-arm study evaluating effectiveness and opioid-sparing potential of suzetrigine (100 mg preoperatively then 50 mg every 12 hours) for treatment of acute pain as part of multimodal therapy in aesthetic or reconstructive surgeries wherein historically opioids are commonly used ≥72 hours postoperatively for pain management.
- Investigators determined the multimodal therapy based on the standard of care for the surgical procedure; acetaminophen and/or ibuprofen were the recommended postoperative standing analgesics in the protocol.

Key Eligibility Criteria

- Age ≥ 18 years
- BMI ≥ 18.0 to ≤ 40.0 kg/m²
- Scheduled to undergo an aesthetic or reconstructive surgical procedure that would typically be treated with opioid therapy for at least 72 hours postoperatively

Study Endpoints

Primary Endpoint (Effectiveness)

- Proportion of participants reporting good, very good, or excellent on a patient global assessment for pain control at the end of treatment^a

Other Endpoints (Effectiveness)

- Proportion of participants reporting good, very good, or excellent on a patient global assessment for pain control over time
- Proportion of participants who remain rescue opioid-free through 72 hours after the end of surgery
- Proportion of participants who remain rescue opioid-free through the end of treatment
- Total opioid rescue medication usage through 72 hours after the end of surgery
- Total opioid rescue medication usage through the end of treatment
- Number of days of opioid rescue medication usage through the end of treatment
- Time to first opioid rescue medication use
- 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9) domain scores at end of treatment
- Incidence of vomiting, nausea, or constipation through the end of treatment

Other Endpoint (Safety)

- Safety and tolerability

^aThis study used a 5-point Likert scale (poor, fair, good, very good, or excellent) for a patient global assessment evaluation.

RESULTS

Table 1. Study Enrolled a Diverse Group of Participants Who Underwent a Broad Range of Aesthetic and Reconstructive Surgical Procedures

	Suzetrigine N=99
Age (years)	
Mean (SD)	41.2 (10.5)
Min, max	18, 66
≥65, n (%)	2 (2.0)
Sex, n (%)	
Female	91 (91.9)
Male	8 (8.1)
Race, n (%)	
White	63 (63.6)
Black or African American	34 (34.3)
Multiracial	2 (2.0)
Ethnicity, n (%)	
Hispanic or Latino	35 (35.4)
Not Hispanic or Latino	63 (63.6)
Not collected per local regulation	1 (1.0)
BMI (kg/m²), mean (SD)	28.39 (4.26)
Surgical procedure, n (%)	
Breast (aesthetic)	33 (33.3)
Abdominoplasty (with liposuction)	28 (28.3)
Breast (reconstructive)	13 (13.1)
Turbinoplasty	13 (13.1)
Liposuction	8 (8.1)
Brachioplasty	3 (3.0)
Skin grafts	1 (1.0)

BMI: body mass index; SD: standard deviation
Note: Table includes participants who received at least one dose of suzetrigine.

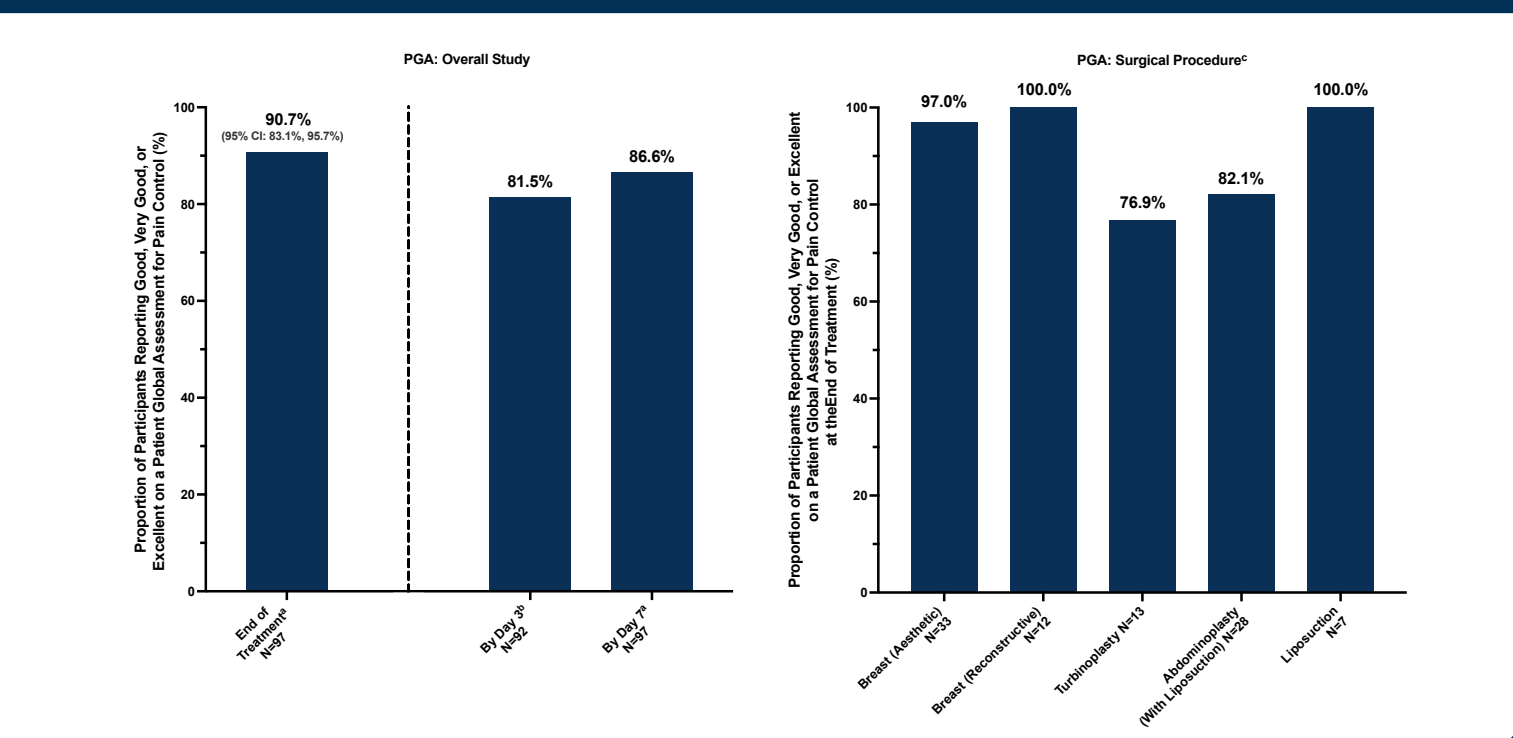
Table 2. Nearly All Participants Completed Treatment With Suzetrigine

	Suzetrigine n (%)
Enrolled	100
Dosed with suzetrigine	99
Completed treatment	97 (98.0)
Reason for completion of treatment	
Pain resolution	67 (67.7)
Completed dosing until Day 14	30 (30.3)
Discontinued treatment	2 (2.0)
Reason for discontinuation of treatment	
Physician decision ^a	1 (1.0)
Other ^b	1 (1.0)

Note: Percentages were calculated relative to the number of participants who received at least one dose of suzetrigine.
^aPhysician decision due to aggressive behavior displayed by participant; this was not considered an adverse event by the investigator.
^bParticipant withdrew consent because unhappy with surgery results.

- Nearly all participants (98.0%) completed treatment with suzetrigine.
- Two participants discontinued suzetrigine; neither were due to adverse events or lack of efficacy.

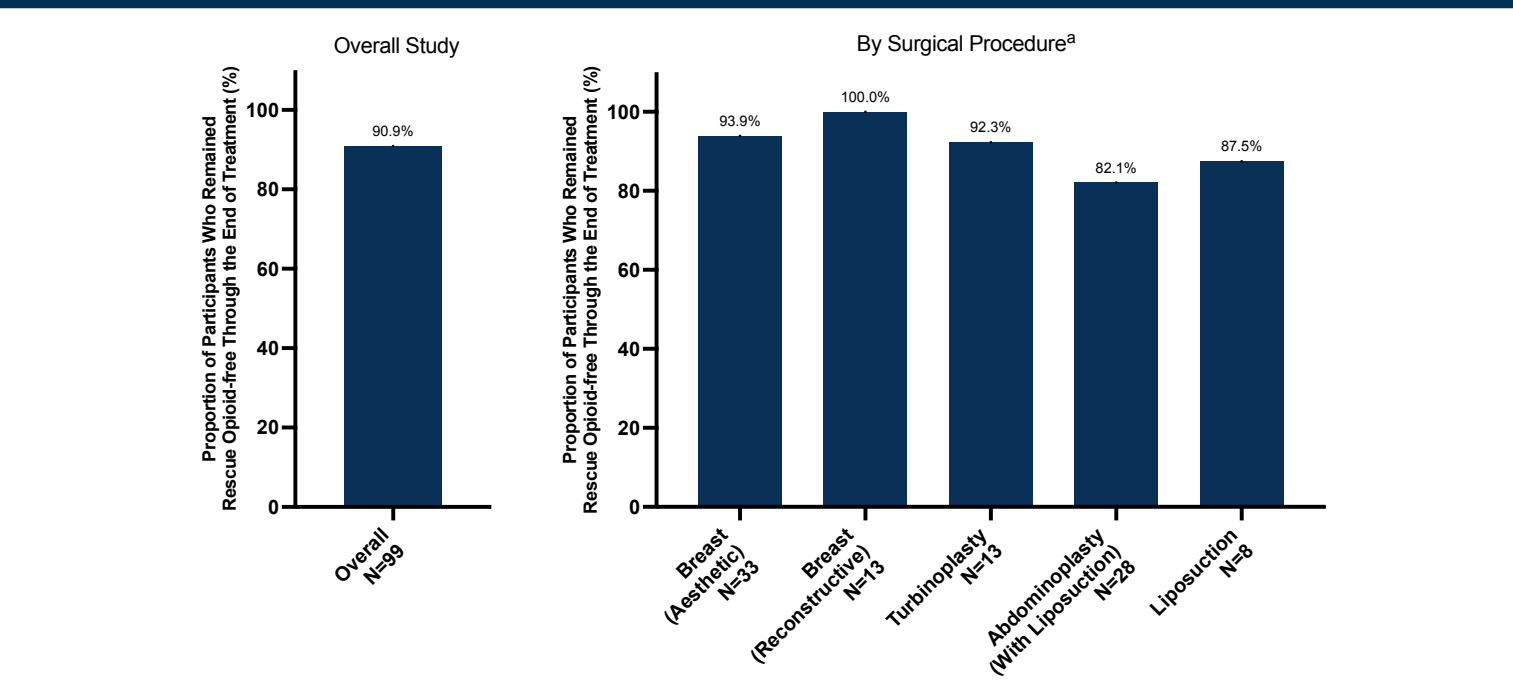
Figure 2. Most Participants (90.7%) Rated the Effectiveness of Suzetrigine as Part of Multimodal Therapy as Good, Very Good, or Excellent on a Patient Global Assessment, Which Was Consistent Across Surgical Procedures



CI: confidence interval; PGA: patient global assessment
^aAt the End of Treatment and Day 7, 2 participants were not included in the analysis because they did not have any patient global assessment in the effectiveness evaluation period.
^bAt Day 3, 7 participants were not included because they did not have any patient global assessment on or before Day 3.
^cOnly procedures with N≥5 are presented.

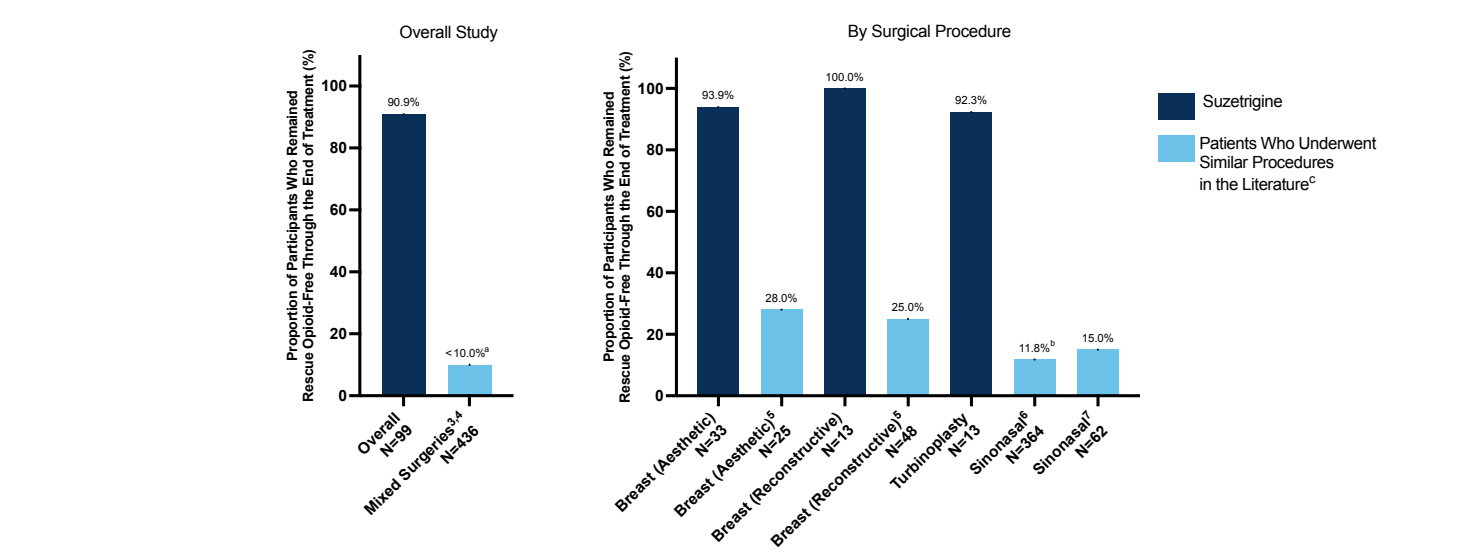
- Most participants (90.7%) rated the effectiveness of suzetrigine as part of multimodal therapy for treating pain on a patient global assessment as good, very good, or excellent at the end of treatment (primary endpoint).
 - 81.5% and 86.6% of participants rated the effectiveness of multimodal therapy including suzetrigine for treating pain on a patient global assessment as good, very good, or excellent by Day 3 and Day 7, respectively.
- Effectiveness was generally consistent across surgical procedures.

Figure 3. Most Participants (90.9%) Were Rescue Opioid-Free Through the End of Treatment; Results Were Generally Consistent Across Surgical Procedures



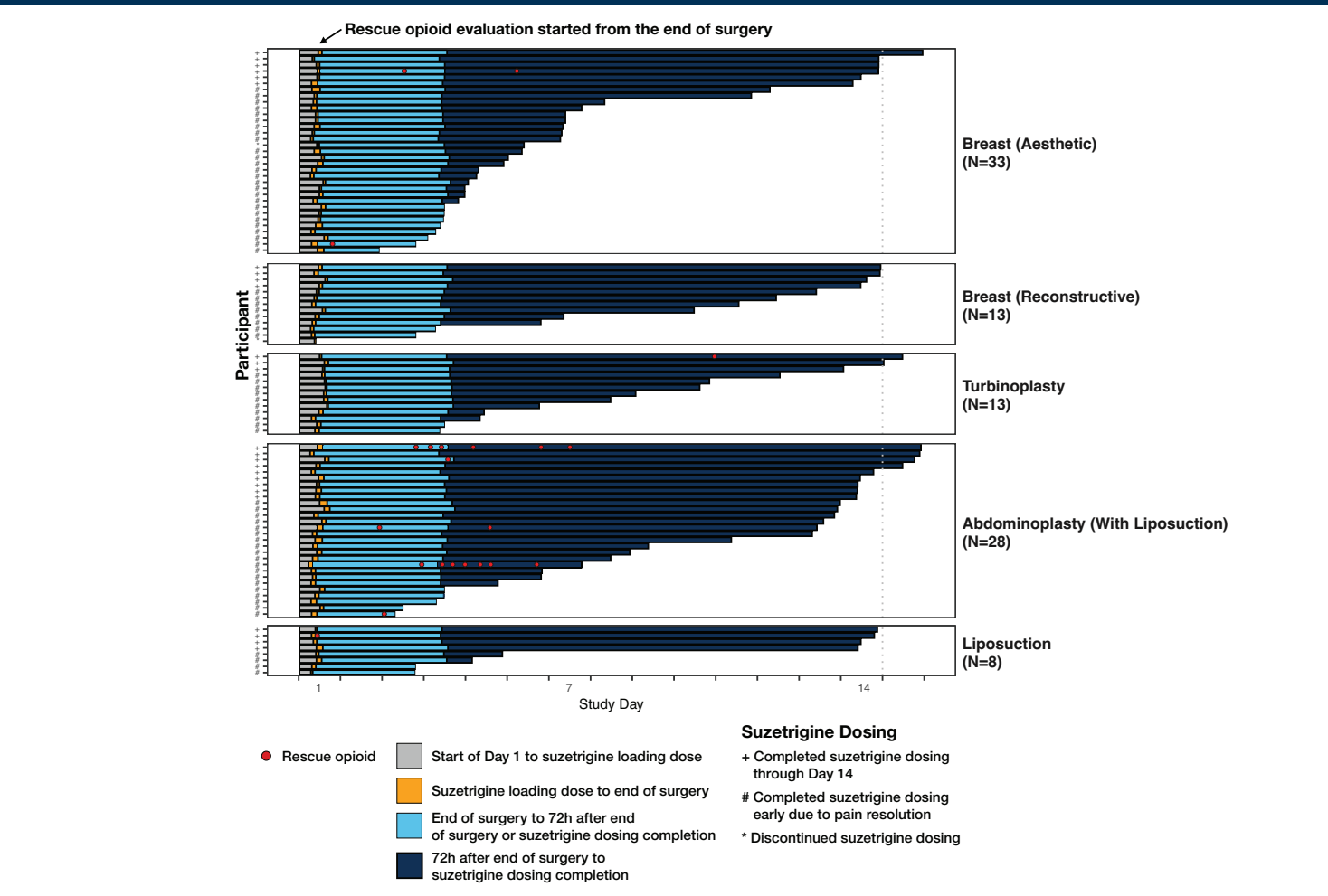
^aOnly procedures with N≥5 presented.

Figure 4. Most Participants (90.9%) Were Rescue Opioid-Free Through the End of Treatment, Which Was a Greater Proportion Than Patients Who Underwent Similar Procedures in the Literature



- ¹Rose et al. (N=170) includes reduction mammoplasty, 1st stage and 2nd stage alloplastic breast reconstruction, revision of reconstructed breast, and aesthetic surgery (e.g., abdominoplasty, brachioplasty, breast augmentation, mastopexy, augmentation mastopexy, scar revision).²Zorrilla et al. (N=266) includes breast augmentation, combined surgery, surgery with helium plasma, head & neck, abdominoplasty, liposuction with or without fat transfer, mastopexy, and other cosmetic surgeries.³Newberry et al. includes endoscopic sinus surgery.⁴Literature-based data from different studies.
- Most participants (90.9%) were rescue opioid-free through the end of treatment.
- In contrast, in the literature, <10% of patients who underwent similar procedures were rescue opioid-free.^{3,4}
- The proportion of patients who were rescue opioid-free ranged from 11.8% to 28.0% across the literature for individual surgical procedures.⁵⁻⁷

Figure 5. Participant Study Journey



Note: Only procedures with N≥5 presented.

- The mean duration of suzetrigine treatment was 9.0 days and maximum duration of treatment was 15 days.
- Most participants (90.9%) were rescue opioid-free through the end of treatment.
 - Among 9 participants with rescue opioid use, 8 participants initiated rescue opioids within 72 hours after the end of surgery.

Table 3. Among 9 (9.1%) Participants With Rescue Opioid Use, the Mean Number of Tablets Used Was 2.4 and the Mean Number of Days of Opioid Rescue Medication Usage Was 2.0

	Suzetrigine N=9
Total opioid rescue medication usage through 72 hours after the end of surgery, MME per participant^{a, b}	
Mean (SD)	8.9 (5.9)
Total opioid rescue medication usage through the end of treatment, MME per participant^a	
Mean (SD)	20.4 (25.3)
Total opioid rescue medication usage through the end of treatment, number of tablets per participant	
Mean (SD)	2.4 (2.4)
Number of days of opioid rescue medication usage through the end of treatment^a	
Mean (SD)	2.0 (1.5)

MME: morphine milligram equivalents; SD: standard deviation
Notes: Table includes participants with rescue opioid use. Rescue opioids included opioid analgesics that were taken orally between the end of surgery and the last dose of suzetrigine.
^aSum of all opioid rescue medication usage, where opioid rescue medication usage (MME) = concentration (mg) x tablets (or units) x morphine ratio.
^bIncludes 5 participants with rescue opioid usage through 72 hours after the end of surgery.
^cNumber of days with rescue opioid usage is calculated from the end of surgery through the end of treatment.

Table 4. Other Endpoints Support the Effectiveness and Opioid-Sparing Potential of Suzetrigine

	Suzetrigine N=99
Proportion of participants who remained rescue opioid-free through 72 hours after the end of surgery, n (%)^a	91 (91.9)
Proportion of participants who remained rescue opioid-free through the end of treatment, n (%)^a	90 (90.9)
Total opioid rescue medication usage through 72 hours after the end of surgery, MME per participant^{a,b}	
Mean (SD)	0.7 (2.9)
Total opioid rescue medication usage through the end of treatment, MME per participant^{a,b}	
Mean (SD)	1.9 (9.3)
Number of days of opioid rescue medication usage through the end of treatment^{a,c}	
Mean (SD)	0.2 (0.7)
Median time to first use of opioid rescue medication^{a,d,e}	NE
TSQM-9 domain scores at end of treatment^f	
Effectiveness, mean (SD)	89.7 (16.1)
Convenience, mean (SD)	92.9 (11.7)
Global satisfaction, mean (SD)	89.9 (16.1)
Participants with vomiting, nausea, or constipation, n (%)^g	20 (20.2)

MME: morphine milligram equivalents; NE: not estimable; SD: standard deviation; TSQM-9: 9-item Treatment Satisfaction Questionnaire for Medication
Notes: Rescue opioids included opioid analgesics that were taken orally between the end of surgery and the last dose of suzetrigine. The other endpoint: proportion of participants reporting good, very good, or excellent on a patient global assessment for pain control over time, is presented in Figure 2.
^aRescue opioid analyses include all participants who received at least one dose of suzetrigine.
^bSum of all opioid rescue medication usage, where opioid rescue medication usage (MME) = concentration (mg) x tablets (or units) x morphine ratio.
^cNumber of days with rescue opioid usage is calculated from the end of surgery through the end of treatment.
^dParticipants who completed treatment without opioid rescue use were censored at Day 14 (or the maximum treatment duration, whichever was later). Participants who discontinued treatment early were censored at the last dose date of suzetrigine (or end of surgery, whichever was later).
^eMedian time was estimated using the Kaplan-Meier method.
^fTSQM-9 includes three domains (i.e., effectiveness, convenience, and global satisfaction) that were summarized and normalized to a score between 0 and 100, where 0 is the worst score and 100 is the best score. 6 participants had missing TSQM-9.
^gProportion of participants reporting the adverse events of vomiting, nausea, or constipation from the first dose of study drug through the end of treatment; participants with multiple occurrences of either event were counted once.

Table 5. Pre/Intra-, and Postoperative Medication Use

	Suzetrigine N=99 n (%)
Pre/intraoperative medications	
Suzetrigine	99 (100.0)
Opioids	97 (98.0)
Local anesthetics	75 (75.8)
Gabapentin	31 (31.3)
Ibuprofen and/or acetaminophen	1 (1.0)
Muscle relaxants	1 (1.0)
Immediately postoperative IV opioid	1 (1.0)
Postoperative multimodal therapy	
Suzetrigine only ^a	12 (12.1)
Suzetrigine and ibuprofen and/or acetaminophen only	78 (78.8)
Suzetrigine and rescue opioids	
Rescue opioids, ibuprofen and/or acetaminophen	8 (8.1)
Rescue opioids, ibuprofen and/or acetaminophen, and muscle relaxants	1 (1.0)

IV: intravenous
Notes: Pre/intraoperative opioids include fentanyl and hydromorphone. Pre/intraoperative muscle relaxants: methocarbamol. Pre/intraoperative local anesthetics include lidocaine (with or without epinephrine) and bupivacaine. IV opioids: fentanyl administered before discharge.
^aParticipants who received only the suzetrigine loading dose or suzetrigine maintenance doses, without any postoperative multimodal therapy.

- The most common postoperative multimodal therapy was suzetrigine with only acetaminophen and/or ibuprofen (78.8%), while 12% used suzetrigine alone.

Table 6. Suzetrigine Was Generally Safe and Well Tolerated

	Suzetrigine N=99 n (%)
Participants with any AEs	44 (44.4)
Participants with AEs by maximum severity	
Mild	32 (32.3)
Moderate	12 (12.1)
Participants with SAEs^a	3 (3.0)
Participants with AEs leading to treatment discontinuation	0
AEs occurring in ≥3 participants	
Nausea	11 (11.1)
Blood creatine phosphokinase increased ^b	8 (8.1)
Procedural nausea ^c	6 (6.1)
Aspartate aminotransferase increased	3 (3.0)
Postoperative wound infection	3 (3.0)
Procedural vomiting ^d	3 (3.0)
Pruritus	3 (3.0)
Syncope ^d	3 (3.0)
Vomiting	3 (3.0)

AE: adverse event; SAE: serious adverse event
Note: Table includes participants who received at least one dose of suzetrigine.
^aSAEs were bradycardia, pulmonary embolism, and angioedema; none were related to suzetrigine.
^bAll AEs of blood creatine phosphokinase increased were mild and recovered without treatment. All participants were from the same site and underwent the same surgical procedure (i.e., breast augmentation). The surgeon at this site used extensive muscle dissection during the procedure. Surgical muscle dissection is associated with blood creatine phosphokinase elevations.
^cProcedural nausea and procedural vomiting are defined as the experience of nausea or vomiting after surgery, usually occurring within 24 to 48 hours.
^dAll 3 participants with events of "syncope" had a vasovagal etiology. One event was related to IV placement, one event was related to a wound dressing change, and the last event occurred when the participant first stood up after surgery.

- Suzetrigine was generally safe and well tolerated with no serious adverse events related to suzetrigine.
- Adverse events were mild or moderate in severity and consistent with the postoperative setting.

CONCLUSIONS

- Most participants (90.7%) rated the effectiveness of suzetrigine as part of multimodal therapy for treating pain as good, very good, or excellent.
- A majority of participants (90.9%) were rescue opioid-free through the end of treatment.
 - Among the 9 (9.1%) participants with rescue opioid use, the mean number of tablets used was 2.4 and the mean number of days of opioid rescue medication usage was 2.0.
- In contrast, in the literature, <10% of patients who underwent similar procedures were rescue opioid-free.³⁻⁴
- Suzetrigine was generally safe and well tolerated with no serious adverse events related to suzetrigine. Adverse events were mild or moderate in severity and consistent with the postoperative setting.

Suzetrigine demonstrated highly effective pain management and enabled opioid-free recovery for most participants (90.9%) when initiated preoperatively and as part of multimodal therapy after aesthetic/reconstructive surgeries for which opioids are commonly used postoperatively for pain management.

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Author Disclosures

JM and TB: consulting fees (Vertex); JM, WB, LZ, DC, and RS are employees of Vertex and may hold stock/stock options in the company. SL and DS have nothing to disclose.

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