Suzetrigine as Part of Multimodal Therapy Enables Opioid-Free Recovery After Laparoscopic or Arthroscopic Procedures

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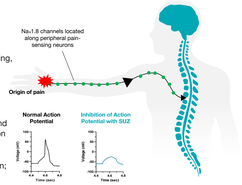
INTRODUCTION

- **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$_V$1.8

- Na$_V$1.8 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 addiction[1]

Suzetrigine

- **Oral, small molecule, non-opioid** highly selective for Na$_V$1.8
- **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 therapy[2]

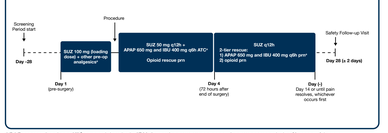
KEY OBJECTIVES

- 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

- 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 laparoscopic and arthroscopic procedures wherein historically opioids are commonly used ≥72 hours postoperatively for pain management.[3]

Figure 1. Study Design



APAP: acetaminophen; **ATC**: around the clock; **IBU**: ibuprofen; **pre-op**: preoperative; **prn**: as needed; **q6h**: every 6 hours; **q12h**: every 12 hours; **SUZ**: suzetrigine
Notes: Other preoperative analgesics were administered at approximately the same time as the loading dose of suzetrigine.
[a] A participant for whom ibuprofen was contraindicated could take acetaminophen alone instead of the acetaminophen and ibuprofen regimen.

- Preoperative multimodal therapy was prespecified as acetaminophen (1000 mg, oral or IV) for all participants and ibuprofen (600 mg, oral) for all participants except those undergoing arthroscopic rotator cuff repair (who received an interscalene nerve block, celecoxib [200 mg, oral] and dexamethasone [4 mg, IV] instead).
- Postoperative multimodal was prespecified as acetaminophen (650 mg, q6h, oral) and ibuprofen (400 mg, q6h, oral) standing for 72 hours and as a first-tier rescue medication thereafter. Opioid (oxycodone or hydromorphone) was the second-tier rescue.

Key Eligibility Criteria

- Age ≥ 18 years
- BMI ≥ 18.0 to ≤ 40.0 kg/m^2
- Scheduled to undergo a procedure that is in one of the following categories that would typically be treated with opioid therapy for at least 72 hours postoperatively:
  - Laparoscopic intraperitoneal or retroperitoneal procedure
  - Arthroscopic orthopedic procedure

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
- Incidence of vomiting, nausea, or constipation through the end of treatment

Other Endpoint (Safety)

- Safety and tolerability

[a]This 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 Had a Broad Range of Orthopedic, Abdominal, and Gynecologic Surgical Procedures

	Suzetrigine N=47
Age (years)	
Mean (SD)	51.9 (14.8)
Min, max	22, 76
≥65, n (%)	8 (17.0)
Sex, n (%)	
Male	23 (48.9)
Female	24 (51.1)
Race, n (%)	
White	40 (85.1)
Black or African American	5 (10.6)
Asian	1 (2.1)
American Indian or Alaska Native	1 (2.1)
Ethnicity, n (%)	
Hispanic or Latino	4 (8.5)
Not Hispanic or Latino	43 (91.5)
BMI (kg/m^2), mean (SD)	28.54 (4.67)
Surgical procedure, n (%)	
Orthopedic	27 (57.4)
Knee[a]	18 (38.3)
Rotator cuff repair	8 (17.0)
Other[b]	1 (2.1)
Abdominal	14 (29.8)
Hernia repair with mesh	14 (29.8)
Gynecologic	6 (12.8)
Hysterectomy	2 (4.3)
Other[c]	4 (8.5)

BMI: body mass index; **SD**: standard deviation
Note: Table includes participants who received at least one dose of suzetrigine.
[a] Orthopedic knee procedures included knee arthroscopy with or without meniscectomy, with or without chondroplasty, with or without synovectomy.
[b] The other orthopedic procedure was a shoulder arthroscopy with biceps tenodesis and capsular shift/labral repair.
[c] Other gynecologic procedures by participant included laparoscopic salpingectomy; laparoscopy, lysis of peritoneal adhesions, and right salpingectomy; diagnostic laparoscopy with peritoneal biopsy; and laparoscopy, surgical, salpingectomy (partial/total salpingectomy), and removal of intrauterine device.

- Most participants (91.5%) completed treatment with suzetrigine.
- Four participants discontinued suzetrigine; none were due to lack of efficacy or adverse events related to suzetrigine.

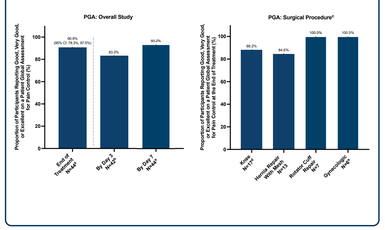
Table 2. Most Participants Completed Treatment With Suzetrigine

	Suzetrigine n (%)
Dosed with suzetrigine	47
Completed treatment	43 (91.5)
Reason for completion of treatment	
Pain resolution	23 (48.9)
Completed dosing until Day 14	20 (42.6)
Discontinued treatment	4 (8.5)
Reason for discontinuation of treatment	
Adverse event[a]	1 (2.1)
Lost to follow-up	1 (2.1)
Did not meet eligibility criteria	1 (2.1)
Other[b]	1 (2.1)

Note: Table includes participants who received at least one dose of suzetrigine.
[a] Participant (knee procedure) discontinued treatment due to right lumbar back pain, which was considered not related to suzetrigine.
[b] Participant inadvertently submitted that their pain resolved on Day 1 in the e-diary. Study drug was discontinued per protocol; the discontinuation occurred on Day 6.

- Most participants (90.9%) 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).
  - 83.3% and 93.2% 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.

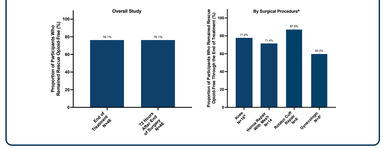
Figure 2. Most Participants (90.9%) Rated the Effectiveness of Suzetrigine as Part of Multimodal Therapy as Good, Very Good, or Excellent on a Patient Global Assessment, Which Was Consistent Across Surgical Procedures



CI: confidence interval; **PGA:** patient global assessment
[a] At the End of Treatment and Day 7, 3 participants were not included in the analysis because they did not have any PGA in the effectiveness evaluation period.
[b] At Day 3, 5 participants were not included because they did not have any PGA on or before Day 3.
[c] Only procedures with N ≥5 are presented.

- Most participants (76.1%) were rescue opioid-free through 72 hours after the end of surgery and through the end of treatment.
- Proportion of participants who remained rescue opioid-free at the end of treatment was generally consistent across surgical procedures.

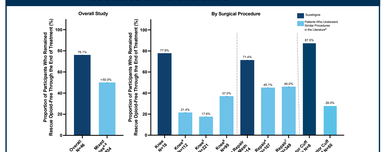
Figure 3. Most Participants (76.1%) Were Rescue Opioid-Free Through the End of Treatment; Results Were Generally Consistent Across Surgical Procedures



[a] Only procedures with N ≥5 are presented.
[b] Orthopedic knee procedures included knee arthroscopy with or without meniscectomy, with or without chondroplasty, with or without synovectomy.
[c] Gynecologic procedures included hysterectomy; laparoscopic salpingectomy; laparoscopy, lysis of peritoneal adhesions, and right salpingectomy; diagnostic laparoscopy with peritoneal biopsy; and laparoscopy, surgical, salpingectomy (partial/total salpingectomy), and removal of intrauterine device.

- Most participants (76.1%) were rescue opioid-free through the end of treatment.
- In contrast, in the literature, <50% of patients who had similar surgical procedures were rescue opioid-free.[4-8]

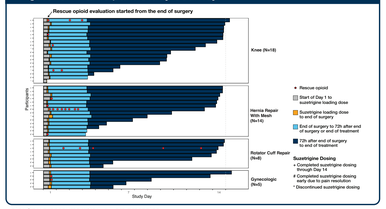
Figure 4. Most Participants (76.1%) Were Rescue Opioid-Free Through the End of Treatment, Which Was a Greater Proportion Than Patients Who Underwent Similar Procedures in the Literature



[a] Literature-based data from different studies.

- The mean duration of suzetrigine treatment was 10.4 days and maximum duration of treatment was 15 days.
- Out of 47 participants, 11 (23.9%) used rescue opioids.
  - All participants who had rescue opioid use initiated rescue opioids within 72 hours post-surgery.
  - One participant had additional rescue opioid use after 72 hours post-surgery.

Figure 5. Participant Study Journey



Note: Only procedures with N ≥5 are presented.

Table 3. Among the 11 (23.9%) Participants With Rescue Opioid Use, the Mean Number of Tablets Used Was 2.2, and the Mean Number of Days of Opioid Rescue Medication Usage Was 1.7

	Suzetrigine N= 11
Total opioid rescue medication usage through 72 hours after the end of surgery, MME per participant[a]	
Mean (SD)	14.7 (15.8)
Total opioid rescue medication usage through the end of treatment, MME per participant[a]	
Mean (SD)	16.7 (17.2)
Total opioid rescue medication usage through the end of treatment, number of tablets per participant	
Mean (SD)	2.2 (2.3)
Number of days of opioid rescue medication usage through the end of treatment	
Mean (SD)	1.7 (1.3)

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.
[a] Sum of all opioid rescue medication usage, where opioid rescue medication usage (MME) = concentration (mg) x tablets (or units) x morphine ratio.

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

	Suzetrigine N= 47
Participants who remained rescue opioid-free through 72 hours after the end of surgery, n (%)[a]	35 (76.1)
Participants who remained rescue opioid-free through the end of treatment, n (%)[a]	35 (76.1)
Total opioid rescue medication usage through 72 hours after the end of surgery, MME per patient[a, b]	
Mean (SD)	3.5 (9.8)
Total opioid rescue medication usage through the end of treatment, MME per patient[a, b]	
Mean (SD)	4.0 (10.9)
Number of days of opioid rescue medication usage through the end of treatment[a]	
Mean (SD)	0.4 (1.0)
Median time to first use of opioid rescue medication[a, c, d]	NE
Participants with vomiting, nausea, or constipation, n (%)[a]	7 (14.9)

MME: morphine milligram equivalents; **MMT**: multimodal therapy; **NE**: not estimable; **SD**: standard deviation
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**.
[a] Includes 46 participants with MMT information.
[b] Sum of all opioid rescue medication usage, where opioid rescue medication usage (MME) = concentration (mg) x tablets (or units) x morphine ratio.
[c] Participants 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).
[d] Median time was estimated using the Kaplan-Meier method.
[e] Proportion 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.

- Among 38 participants who continued suzetrigine after the initial 72-hour postoperative period, 50.0% used suzetrigine alone.

Table 5. Pre/Intraoperative and Postoperative Medication Use

	Suzetrigine N=47 n (%)
Pre/intraoperative medications	
Suzetrigine	47 (100.0)
Opioids	42 (89.4)
Acetaminophen	46 (97.9)
NSAIDs	45 (95.7)
Local anesthetics[a]	42 (89.4)
Steroids	17 (36.2)
Immediately postoperative IV opioid	10 (21.3)
Postoperative multimodal therapy within initial 72-hour postoperative period	41
Participants who continued dosing suzetrigine postoperatively	
Suzetrigine only	2 (4.9)
Suzetrigine and ibuprofen and/or acetaminophen only	29 (70.7)
Suzetrigine and rescue opioids	
Rescue opioids, ibuprofen and/or acetaminophen	10 (24.4)
Postoperative multimodal therapy after initial 72-hour postoperative period through the end of treatment	
Participants who continued dosing suzetrigine after the initial 72-hour postoperative period	38
Suzetrigine only	19 (50.0)
Suzetrigine and ibuprofen and/or acetaminophen only	18 (47.4)
Suzetrigine and rescue opioids	
Rescue opioids, ibuprofen and/or acetaminophen	1 (2.6)

IV: intravenous; **NSAIDs**: non-steroidal anti-inflammatory drugs
Notes: Pre/intraoperative opioids: fentanyl, fentanyl citrate, hydromorphone, hydrochloride; NSAIDs: ibuprofen, celecoxib, ketorolac; local anesthetics: lidocaine (with or without epinephrine), lidocaine hydrochloride, bupivacaine, ropivacaine (with or without epinephrine); steroids: dexamethasone, dexamethasone sodium phosphate; IV opioids: fentanyl, fentanyl citrate, pethidine.
[a]Local anesthetics includes nerve blocks and/or infiltration.

- Suzetrigine was generally safe and well tolerated.
- Adverse events were mild or moderate in severity and consistent with the postoperative setting.[9]
- None of the participants had an adverse event of vomiting.
- One participant had a serious adverse event (aspiration) that was considered to be not related to suzetrigine.

Table 6. Suzetrigine Was Generally Safe and Well Tolerated

	Suzetrigine N=47 n (%)
Participants with any AEs	19 (40.4)
Participants with AEs by maximum severity	
Mild	10 (21.3)
Moderate	9 (19.1)
Participants with SAEs[a]	1 (2.1)
Participants with AEs leading to treatment discontinuation[b]	1 (2.1)
AEs occurring in ≥2 participants	
Constipation	4 (8.5)
Nausea	3 (6.4)
Blood bicarbonate decreased	2 (4.3)
Post procedural swelling	2 (4.3)
Pruritus	2 (4.3)
Rash[c]	2 (4.3)
Urinary tract infection	2 (4.3)
Vulvovaginal mycotic infection	2 (4.3)

AE: adverse event; **SAE**: serious adverse event
Note: Table includes participants who received at least one dose of suzetrigine.
[a]One participant (knee procedure) had a serious adverse event (aspiration) that was considered to be not related to suzetrigine.
[b]One participant (knee procedure) discontinued treatment due to right lumbar back pain that was considered to be not related to suzetrigine.
[c]The two AEs of rash were localized (i.e., abdomen and under the breast) and were not considered to be related to suzetrigine.

CONCLUSIONS

- Most participants (90.9%) rated the effectiveness of suzetrigine as part of multimodal therapy for treating pain as good, very good, or excellent.
- A majority of participants (76.1%) were rescue opioid-free through the end of treatment.
  - Among the 11 (23.9%) participants with rescue opioid use, the mean number of tablets used was 2.2 and the mean number of days of opioid rescue medication usage was 1.7.
- In contrast, in the literature, <50% of patients who had similar surgical procedures were rescue opioid-free.[4-8]
- 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.[9]

Suzetrigine demonstrated highly effective pain management and enabled opioid-free recovery for most (76.1%) participants when initiated preoperatively as part of MMT after a variety of laparoscopic abdominal and gynecologic, as well as arthroscopic procedures for which opioids are commonly used postoperatively for pain management.

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Author Disclosures

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