

Poster
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Suzetrigine, a Non-opioid, Pain Signal Inhibitor With the Potential for Vomiting- or Nausea-free Acute Pain Relief

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INTRODUCTION

- Opioids are effective for the management of moderate-to-severe acute pain but have safety, tolerability (including gastrointestinal tolerability issues such as vomiting and nausea), and addiction concerns¹
- Voltage-gated sodium channel 1.8 (Na_v1.8) is a therapeutic target for pain based on its role in pain signaling and its selective expression in the peripheral nervous system²
- Suzetrigine (SUZ) is a highly selective Na_v1.8 inhibitor with no addiction potential based on its mechanism of action²
- In two Phase 3 trials evaluating SUZ, the primary endpoint of the time-weighted sum of the pain intensity difference as recorded on the numeric pain rating scale (NPRS) from 0 to 48 hours compared to placebo was met with SUZ treatment having a statistically significant greater reduction in pain compared to placebo³
- SUZ is approved in the US to treat moderate-to-severe acute pain in adults
- Here we report data including a post hoc analysis from the Phase 3 SUZ trials that evaluates a clinically relevant composite endpoint to assess the benefit/risk profile of SUZ relative to hydrocodone bitartrate/acetaminophen (HB/APAP)

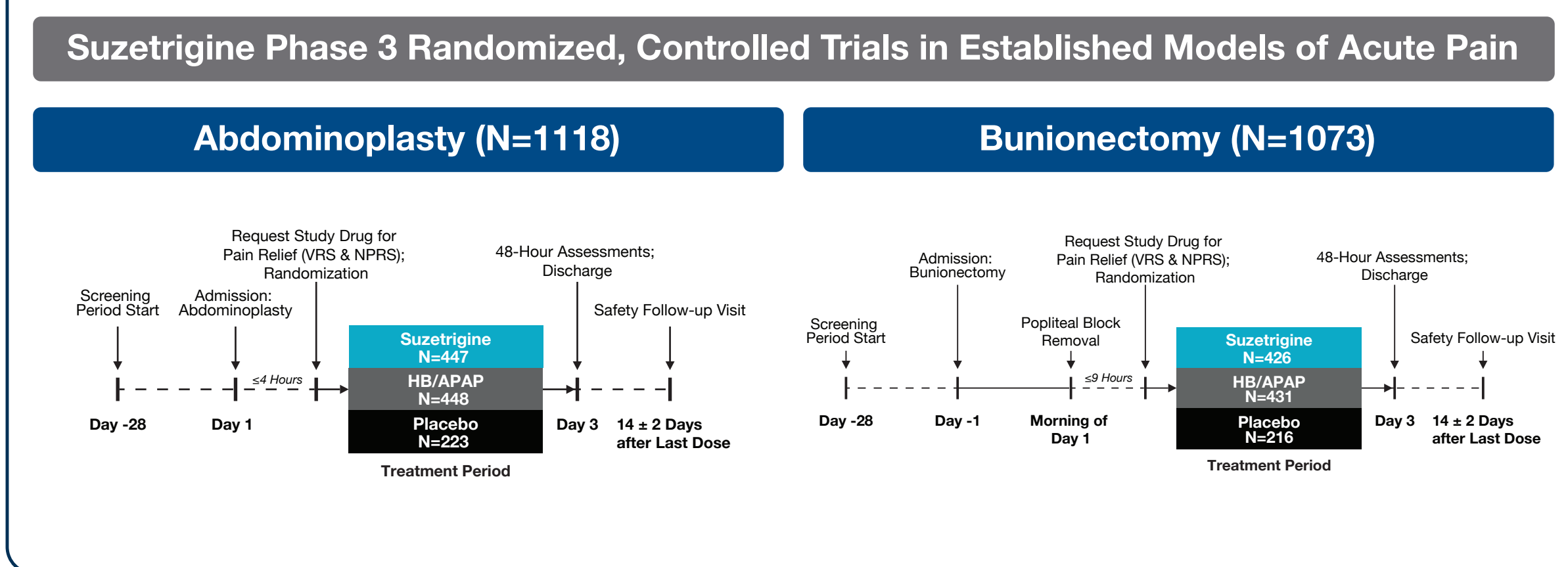
OBJECTIVE

To evaluate a clinically relevant composite endpoint to assess the benefit/risk profile of suzetrigine relative to HB/APAP

MATERIAL AND METHODS

- Two Phase 3 randomized, double-blind, placebo-controlled trials evaluated SUZ for 48 hours in participants with moderate-to-severe acute pain after abdominoplasty or bunionectomy (**Figure 1**)³
- Participants were randomized 2:2:1 to SUZ, HB/APAP, or placebo
- To evaluate a potential additional benefit of SUZ as a non-opioid analgesic, we compared the incidence of vomiting or nausea (common side effects of opioids) in participants receiving SUZ versus HB/APAP (secondary endpoint)
- The proportions of participants receiving SUZ with ≥30%, ≥50%, and ≥70% reduction from baseline in NPRS (“responders”) at 48 hours compared to placebo were analyzed as other efficacy endpoints
- In addition, a composite endpoint combining efficacy and safety (≥30%, ≥50%, and ≥70% “responders” at 48 hours who were vomiting- or nausea-free through 48 hours) was evaluated as a post hoc analysis
- All *P* values are nominal

Figure 1. Study Design



HB/APAP: hydrocodone bitartrate/acetaminophen, N: number of participants in the analysis set, NPRS: numeric pain rating scale, VRS: verbal categorical rating scale

Study Design

- Suzetrigine tablets:** 100-mg then 50-mg every 12 hours administered orally
- HB/APAP capsules:** 5-mg/325-mg every 6 hours administered orally
- Rescue medication:** ibuprofen was permitted, if needed, for pain relief. Opioids and other pain medicines were not allowed during treatment

Key Eligibility Criteria

- Age:** 18 to 80 years
- Reported pain:** moderate or severe on the VRS and ≥4 on the NPRS within 4 hours after abdominoplasty or 9 hours after removal of the popliteal sciatic nerve block (with ropivacaine) after a bunionectomy

RESULTS

In Both Trials, There Were Fewer Adverse Events of Vomiting and/or Nausea in Participants Receiving Suzetrigine Than Those Receiving HB/APAP

Table 1. Incidence of Vomiting or Nausea

Statistic	Abdominoplasty			Bunionectomy		
	Placebo N = 222	HB/APAP N = 448	SUZ N = 448	Placebo N = 216	HB/APAP N = 431	SUZ N = 426
Participants with vomiting or nausea, n(%)	56 (25.2)	150 (33.5)	91 (20.3)	25 (11.6)	71 (16.5)	39 (9.2)
<i>P</i> value versus HB/APAP ^a	—	—	<0.0001	—	—	0.0014

HB/APAP: hydrocodone bitartrate/acetaminophen, n: number of participants, N: number of participants in the analysis set, SUZ: suzetrigine
Note: Adverse events of vomiting or nausea (from the first dose of study drug through completion of trial participation) were included in the analysis. When computing incidence, participants with multiple occurrences of either event were counted once. Participants who had both events were also only counted once. Analysis was pre-specified.

^a *P* value was obtained from the Pearson’s chi-squared test. *P* values are nominal.

Participants Receiving Suzetrigine Achieved ≥30%, ≥50%, and ≥70% Response Levels at Similar Proportions to Participants Receiving HB/APAP

Table 2. Analysis of Proportion of Participants With ≥30%, ≥50%, and ≥70% Reduction in NPRS at 48 Hours

Statistic	Abdominoplasty			Bunionectomy		
	Placebo N = 223	HB/APAP N = 448	SUZ N = 447	Placebo N = 216	HB/APAP N = 431	SUZ N = 426
Proportion of participants with ≥30% reduction in NPRS at 48 hours (%)	45.7	61.8	65.3	58.8	70.5	70.9
<i>P</i> value versus placebo ^a	—	—	<0.0001	—	—	0.0018
Proportion of participants with ≥50% reduction in NPRS at 48 hours (%)	34.1	51.3	51.7	50.0	61.9	61.5
<i>P</i> value versus placebo ^a	—	—	<0.0001	—	—	0.0044
Proportion of participants with ≥70% reduction in NPRS at 48 hours (%)	18.8	32.1	33.6	31.5	40.1	42.3
<i>P</i> value versus placebo ^a	—	—	<0.0001	—	—	0.0073

HB/APAP: hydrocodone bitartrate/acetaminophen, N: number of participants in the analysis set, NPRS: numeric pain rating scale, SUZ: suzetrigine
Notes: Participants who discontinued study drug treatment before 48 hours were classified as non-responders for all 3 criteria. Analysis was pre-specified.
^a *P* values were obtained from the Cochran-Mantel-Haenszel test with adjustment for baseline NPRS (<8, ≥8). *P* values are nominal.

In Both Trials, a Higher Proportion of Participants Receiving Suzetrigine Achieved the Composite Endpoint of Vomiting- or Nausea-free ≥30%, ≥50%, and ≥70% Reduction in NPRS at 48 Hours Compared to HB/APAP

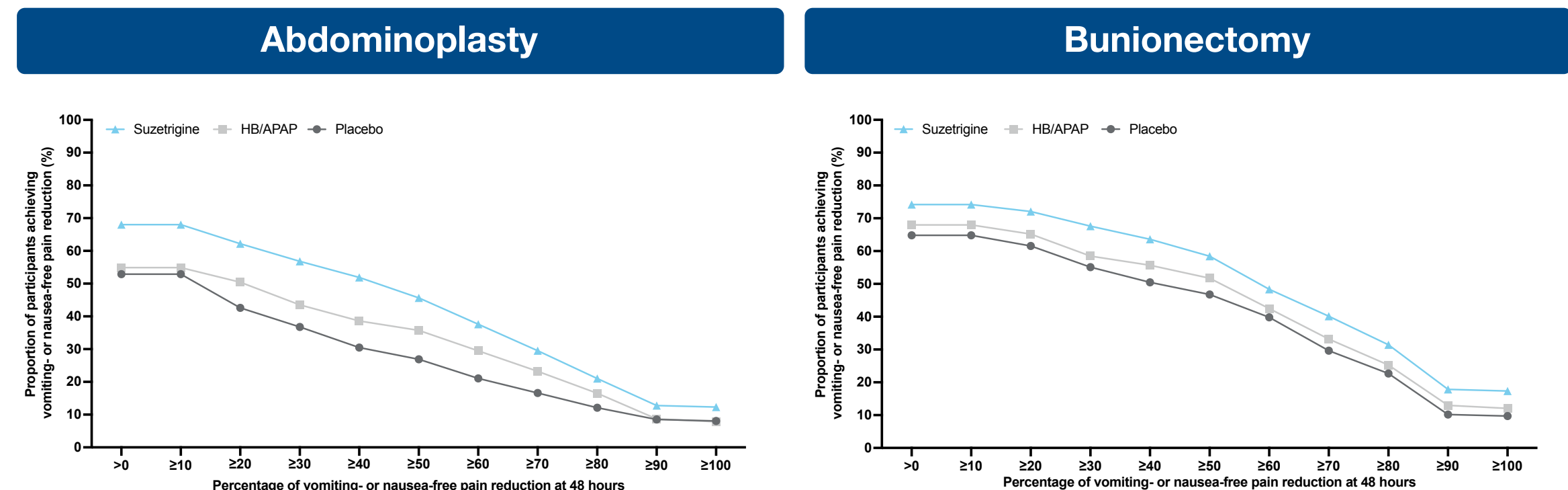
Table 3. Analysis of Proportion of Participants With Vomiting- or Nausea-free ≥30%, ≥50%, and ≥70% Reduction in NPRS at 48 Hours

Statistic	Abdominoplasty			Bunionectomy		
	Placebo N = 223	HB/APAP N = 448	SUZ N = 447	Placebo N = 216	HB/APAP N = 431	SUZ N = 426
Proportion of participants with vomiting- or nausea-free ≥30% reduction in NPRS at 48 hours (%)	36.8	43.5	56.8	55.1	58.5	67.6
<i>P</i> value versus placebo ^a	—	0.0938	<0.0001	—	0.4155	0.0016
<i>P</i> value versus HB/APAP ^a	—	—	<0.0001	—	—	0.0057
Proportion of participants with vomiting- or nausea-free ≥50% reduction in NPRS at 48 hours (%)	26.9	35.7	45.6	46.8	51.7	58.5
<i>P</i> value versus placebo ^a	—	0.0223	<0.0001	—	0.2261	0.0041
<i>P</i> value versus HB/APAP ^a	—	—	0.0025	—	—	0.0491
Proportion of participants with vomiting- or nausea-free ≥70% reduction in NPRS at 48 hours (%)	16.6	23.2	29.5	29.6	33.2	40.1
<i>P</i> value versus placebo ^a	—	0.0476	0.0003	—	0.3372	0.0081
<i>P</i> value versus HB/APAP ^a	—	—	0.0314	—	—	0.0351

HB/APAP: hydrocodone bitartrate/acetaminophen, N: number of participants in the analysis set, NPRS: numeric pain rating scale, SUZ: suzetrigine
Notes: Participants who discontinued study drug treatment before 48 hours were classified as non-responders for all 3 criteria. Analysis was post hoc.
^a *P* values were obtained from the Cochran-Mantel-Haenszel test with adjustment for baseline NPRS (<8, ≥8). *P* values are nominal.

Figure 2. Vomiting- or Nausea-free Cumulative Response at 48 Hours

Cumulative Response Pattern was Consistent: A Numerically Higher Proportion of Participants Receiving Suzetrigine Achieved a Vomiting- or Nausea-free Pain Response Compared to HB/APAP



HB/APAP: hydrocodone bitartrate/acetaminophen

DISCUSSION

- Participants receiving SUZ had higher proportions compared to placebo and similar proportions to HB/APAP of ≥30%, ≥50%, and ≥70% responders
- SUZ treatment demonstrated an improved benefit/risk profile relative to HB/APAP with respect to vomiting or nausea, with a higher proportion of participants who achieved ≥30%, ≥50%, and ≥70% response levels while not experiencing gastrointestinal side effects as measured by vomiting or nausea during the 48-hour treatment period

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Author Disclosures

TB, JM, DS, LT, JU, JO, MWS, SGW have reported personal fees from Vertex Pharmaceuticals as members of the Acute Pain Steering Committee. **JU** is a consultant and has received payment or honoraria from Pacira BioSciences. **MWS’s** institution has received funding and/or product from the following companies for other research studies of this author: Epimed International (Farmers Branch, Texas, USA), SPR Therapeutics (Cleveland, Ohio, USA), Infutronic (Natick, Massachusetts, USA), and Avanos Medical (Irvine, California, USA). **SGW** has received grants or contracts from NIH, Foundation for Opioid Response Efforts, Yale University, and Elevance Foundation and is a consultant for Cessation Therapeutics. **DD** has nothing to disclose. **IJ, ST, WK,** and **DJC** are employees of Vertex Pharmaceuticals and hold stock and/or stock options in the company

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