Supplemental Digital Content for:

Suzetrigine, a Non-Opioid $Na_V1.8$ Inhibitor for Treatment of Moderate-to-Severe Acute Pain: Two Phase 3 Randomized Clinical Trials

Table of Contents

Section 1: List of Investigators **4**

Section 2: Methods **6**

Inclusion Criteria 6

Exclusion Criteria 7

Perioperative Pain Management 11

Other Secondary Efficacy Outcomes 14

Statistical Analysis 14

Section 3: Supplementary Results **17**

Section 4: Supplementary Figures **18**

eFigure 1 Clinical Trial Design Schematics 18

eFigure 2 Percentage of Pain Reduction in the Abdominoplasty Phase 3 Trial 19

eFigure 3 Percentage of Pain Reduction in the Bunionectomy Phase 3 Trial 22

Section 5: Supplementary Tables **25**

eTable 1. Disposition 25

eTable 2. Pain Intensity Difference at 48 Hours 25

eTable 3. Secondary Endpoint: Time to ≥1-point Reduction in NPRS From Baseline Compared to Placebo 26

eTable 4. Secondary Endpoint: Proportion of Participants Reporting Good or Excellent on the Patient Global Assessment at 48 Hours Compared to Placebo 26

eTable 5. Secondary Endpoint: Incidence of Vomiting or Nausea Compared to HB/APAP 26

eTable 6. Secondary Endpoint: SPID24 Compared to Placebo 27

eTable 7. Secondary Endpoints: Rescue Medication 27

Section 6: References..... 28

Section 1: List of Investigators

First Name	Last Name	Academic Degree(s)	Institution	Location	Abdominoplasty Trial	Bunionectomy Trial
Todd	Bertoch	M.D.	JBR Clinical Research	Salt Lake City, UT	X	X
Dominick	D'Aunno	M.D.	Houston Heights Hospital	Houston, TX	X	X
Grant	Garbo	M.D.	Endeavor Clinical Trials, LLC	San Antonio, TX	X	X
George	Konis	M.D.	Woodland International Research Group, LLC	Little Rock, AR	X	X
Timothy	Melson	M.D.	Shoals Medical Trials, Inc	Sheffield, AL	X	X
Jessica	McCoun	M.D.	Atlanta Center for Medical Research	Atlanta, GA	X	X
Daneshvari	Solanki	M.D.	First Surgical Hospital	Bellaire, TX	X	X
Louise	Taber	M.D.	Arizona Research Center	Phoenix, AZ	X	X
Joshua	Terry	M.D.	Shoals Medical Trials, Inc	Sheffield, AL	X	X
Nick	Brown	M.D.	Kansas Spine and Specialty	Wichita, KS	X	
Brandon	Broome	M.D.	South Texas Spine & Surgical Hospital	San Antonio, TX	X	
Shankar	Lakshman	M.D.	New Hope Research Development	Tarzana, CA	X	
Arash	Matian	M.D.	Alliance Research Institute	Canoga Park, CA	X	
Hernan	Salazar	M.D.	Endeavor Clinical Trials, LLC	San Antonio, TX	X	

First Name	Last Name	Academic Degree(s)	Institution	Location	Abdominoplasty Trial	Bunionectomy Trial
Babak	Alavynejad	D.P.M.	New Hope Research Development	West Covina, CA		X
Fabien	Anayati	D.P.M.	Alliance Research Institute	Canoga Park, CA		X
Alina	Beaton	M.D.	Pacific Research Network	San Diego, CA		X
Tanya	Bogle	M.D	ForCare Clinical Research	Tampa, FL		X
Joseph	Caporusso	D.P.M.	Futuro Clinical Trials, LLC	McAllen, TX		X
Brian	Chalkin	D.O.	The Orthopaedic Center	Tulsa, OK		X
J. Richard Lee	Evanson	D.O.	Legent Orthopedic Hospital	Carrollton, TX		X
Alfredo	Fernandez	M.D.	Clinical Pharmacology of Miami	Miami, FL		X
Steven	Folkerth	M.D.	Midwest Clinical Research Center, LLC	Dayton, OH		X
Seth	Forman	M.D.	ForCare Clinical Research	Tampa, FL		X
Ray	Grundmeyer	M.D.	Kansas Spine and Specialty Hospital	Wichita, KS		X
Fardin	Hakakian	D.P.M.	New Hope Research Development	Tarzana, CA		X
Chad	Howze	D.P.M.	Endeavor Clinical Trials, LLC	San Antonio, TX		X
Clark	Larsen	D.P.M.	Wasatch Clinical Research	Salt Lake City, UT		X
David	Vanderweide	M.D.	Houston Physicians Hospital	Webster, TX		X
Peter	Winkle	M.D.	Anaheim Clinical Trials	Anaheim, CA		X
John	Zimmerman	D.P.M.	Trovare Clinical Research	Bakersfield, CA		X

Section 2: Methods

Inclusion Criteria

Abdominoplasty and Bunionectomy Trials: Before Surgery

- Willing to sign and date an informed consent form
- Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures
- Males and females aged 18 through 80 years of age with a body mass index (BMI) of 18.0 to 40.0 kg/m2, inclusive

Abdominoplasty Trial Only: Before Surgery

Scheduled to undergo a standard ("full") abdominoplasty procedure that:

- included a horizontally oriented incision approximately extending to each anterior superior iliac spine;
- included umbilical dissection and relocation, and plication of the fascia of the rectus muscle above and/or below the umbilical stalk;
- did NOT include a vertically oriented supra-umbilical incision or collateral procedures (e.g., liposuction)

Bunionectomy Trial Only: Before Surgery

Scheduled to undergo a primary unilateral bunionectomy with distal first metatarsal osteotomy (i.e., Austin procedure) and internal fixation under regional anesthesia (Mayo and popliteal sciatic block)

Abdominoplasty and Bunionectomy Trials: After Surgery

Participant was lucid and able to follow commands. All analgesic guidelines were followed during and after the surgery.

Abdominoplasty Trial Only: After Surgery

Participant had an abdominoplasty procedure duration of ≤3 hours and reported pain of ≥4 on the Numerical Pain Rating Scale (NPRS) and moderate or severe pain on the Verbal Categorical Rating Scale (VRS) at rest within 4 hours after surgery completion on Day 1

Bunionectomy Trial Only: After Surgery

Participant reported pain of ≥4 on the NPRS and moderate or severe pain on the VRS at rest within 9 hours after removal of the popliteal sciatic block on Day 1

Exclusion Criteria

Abdominoplasty and Bunionectomy Trials: Before Surgery

- History of any illness or any clinical condition that, in the opinion of the investigator, might have confounded the results of the trial or posed an additional risk in administering study drug to the participant. This included, but was not limited to, the following:
    - History of relevant drug or food allergies
    - History of significant respiratory, cardiovascular, metabolic, hematologic, neurologic, or psychiatric disease
    - History or presence of clinically significant pathology
    - History of cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years)

- History of cardiac dysrhythmias requiring anti-arrhythmia treatment(s) within the last 2 years; or history or evidence of abnormal study ECGs that, in the opinion of the investigator or medical monitor, would have precluded participation in the trial; or history of QT prolongation or standard 12-lead ECG (performed in triplicate) demonstrating median QTcF >450 msec at the screening visit or on day -1 (pre-procedure)
- Presence of an automated implantable cardioverter defibrillator, cardiac resynchronization therapy device, or pacemaker
- History of significant hepatic disease, including but not limited to hepatic cirrhosis, portal hypertension, moderate or severe hepatic impairment (defined as Child-Pugh Class B or Class C).
- Alanine aminotransferase or aspartate aminotransferase values >2.5 × upper limit of normal
- History of severe renal impairment defined as estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73m^2 calculated using the subject's measured serum creatinine; the suggested calculation method for eGFR is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
- Any other abnormal laboratory results indicative of significant medical disease that, in the opinion of the investigator, would have precluded participation in the trial
    - History of any sensory abnormality that, in the opinion of the investigator, may have confounded the ability of the participant to assess postoperative pain
    - Participants who had a painful physical condition that, in the opinion of the investigator, may have confounded the assessments of postoperative pain

    - A known or clinically suspected infection with human immunodeficiency virus or hepatitis B or C viruses
- Any prior surgery within 1 month before the first study drug dose unless approved by the medical monitor
- American Society of Anesthesiologists physical status classification of ≥3
- Chronic use of opioids or non-steroidal anti-inflammatory drugs (NSAIDs) with dose escalation within 30 days before admission and/or unwilling or unable to stop analgesics at least 5 half-lives or 2 days (whichever was longer) before admission
- Participants who started new medications that were not at a stable dose for at least 14 days prior to the scheduled surgical procedure and before dosing with investigational product
- Participants unwilling to receive any protocol-related medicine (e.g., ibuprofen, acetaminophen, fentanyl, hydrocodone)
- Participants with a history of allergy or significant adverse event (AE) to any opioid and/or NSAID that, in the opinion of the investigator, would have significantly increase the chance of AEs from medicines used in the trial
- Participants with sleep apnea and/or on a home continuous positive airway pressure machine
- History of peptic ulcer disease or gastrointestinal bleeding that, in the opinion of the investigator or medical monitor, would have precluded participation in the trial
- Female participants who were pregnant, nursing, or planning to become pregnant during the trial or within 30 days after the last study drug dose.
- Male participants with a female partner who was pregnant, nursing, or planning to become pregnant during the study or within 30 days after the last study drug dose

- Participated in a previous study investigating suzetrigine or in another investigational study within 30 days of the first dose of study drug
- Evidence of misuse, aberrant use, or addiction to alcohol or an illicitly used drug of abuse in the past 3 years, or had a positive test for drugs of abuse
- A positive drug screen for a known prescribed concomitant medication that was not otherwise exclusionary (e.g., benzodiazepines) did not disqualify participants;
- Use of the substances, activities, or devices during the specified times including but not limited to: other investigational drugs or devices, analgesic medications that were not part of standard-of-care during admission, oral steroids, medications, herbal and dietary supplements known to be moderate or strong inducers or inhibitors of CYP3A, grapefruit or grapefruit juice, pomelos, star fruit, Seville oranges and their juices, alcohol, or strenuous exercise
- Participant, or close relative of the participant, was the investigator or a sub-investigator, research assistant, pharmacist, trial coordinator, or other staff directly involved with the conduct of the trial at that site

<u>Abdominoplasty Trial Only: Before Surgery</u>

- Prior history of abdominoplasty
- History of intra-abdominal and/or pelvic surgery (including hysterectomy and Cesarean section) that resulted in any complications (e.g., postoperative infections, incisional infections or dehiscence, wound infections, or re-exploration/redo surgery for the same condition) or, in the opinion of the investigator or medical monitor, would have precluded participation in the trial

Bunionectomy Trial Only: Before Surgery

Prior history of bunionectomy or other foot surgery on the index foot; or bunionectomy on the opposite foot as part of this trial

Abdominoplasty and Bunionectomy Trials: After Surgery

Standard 12-lead ECG (performed in triplicate) demonstrating median QTcF >450 msec at baseline (Day 1 predose).

Abdominoplasty Trial Only: After Surgery

- Participant had medical complications during the abdominoplasty that, in the opinion of the investigator, should have precluded randomization.
- Participant had a non-standard abdominoplasty and/or collateral procedure(s) during the abdominoplasty.

Bunionectomy Trial Only: After Surgery

Participant had a Type 3 deformity requiring a base wedge osteotomy or concomitant surgery such as hammertoe repair, or had medical complications during the bunionectomy that, in the opinion of the investigator, should have precluded randomization.

Perioperative Pain Management

Below are analgesic medications that were permitted as part of perioperative pain management pre- and intra-operative and postoperative.

Abdominoplasty: Pre- and intra-operative

- Intravenous (IV) midazolam (≤2 mg) and/or fentanyl citrate (≤50 µg) could be used preoperatively.

- IV fentanyl citrate and propofol (doses at the discretion of the anesthesia provider) could be used for anesthesia induction.
- Only IV general anesthesia with propofol and fentanyl citrate was used for anesthesia maintenance.
- After completing the rectus plication, the rectus fascia was infiltrated above and below the umbilicus with 1% lidocaine without epinephrine for a total of approximately 4 mg/kg.
- Total fentanyl citrate from induction through emergence could not exceed 250 μg.
- A record (date and time of administration) was kept of all medication use through surgery completion.

Abdominoplasty: Postoperative

- Postoperative supplemental analgesic medication was permitted in the postanesthesia care unit per the following guidelines:
    - Fentanyl citrate (12.5 to 25 μg IV as needed) could be administered if the participant was: (1) not lucid enough for randomization but deemed to be in severe pain per clinical judgement and/or (2) unable to swallow oral medications.
    - Randomization could not occur until at least 15 minutes after the last administration of supplemental analgesic medication.
- The use of abdominal binders was permitted.
- The use of ice packs was NOT permitted.
- No pain treatments (except the permitted supplemental analgesic medication) are allowed from surgery completion through the first dose of study drug.

Bunionectomy: Pre- and intra-operative

- IV midazolam and/or fentanyl was administered, followed by IV propofol, a popliteal sciatic block (≤0.5% ropivacaine), and a Mayo block (2% lidocaine without epinephrine). NSAIDs could not be administered.

Bunionectomy: Postoperative

- A continuous popliteal sciatic block infusion (0.2% ropivacaine) was started at an initial rate between 1 to 3 mL/h after surgery and remained in place until approximately 3AM, but no later than 5AM on Day 1. Removal of the popliteal sciatic block ("block removal") was defined as removal of the infusion catheter and/or completion of the ropivacaine infusion.
- Postoperative supplemental analgesic medications were permitted before the time of popliteal block removal per the following guidelines:
    - Acetaminophen (975 to 1000 mg) could be administered q6h as needed until 6 hours before removal of the popliteal block for participants with NPRS score of 4 through 6 after surgery.
    - Fentanyl citrate (12.5 to 25 µg IV) could be administered every 2 hours as needed until 1.5 hours before removal of the popliteal block for participants with NPRS score of 7 or above after surgery.
    - Ropivacaine boluses and/or infusion rate changes could be used as needed prior to removal of the popliteal block for participants with NPRS score of ≥4; boluses could not be used at the time of block removal.
- The use of ice packs was NOT permitted.

- A record (date and time of administration) was kept of all medication use prior to removal of the popliteal block. An unscheduled NPRS was completed immediately before each administration of supplemental analgesic medication except when an administration of supplemental analgesic medication occurred within 30 minutes after a preceding administration.
- No pain treatments were allowed from the time of block removal through the first dose of study drug.

Other Secondary Efficacy Outcomes

- Time to ≥1-point reduction in NPRS from baseline compared to placebo
- Proportion of participants reporting good or excellent on the Patient Global Assessment (PGA) at 48 hours compared to placebo
- Incidence of vomiting or nausea compared to HB/APAP
- Time-weighted SPID as recorded on the NPRS from 0 to 24 hours (SPID24) compared to placebo
- Time to first use of rescue medication compared to placebo
- Proportion of participants using rescue medication from 0 to 48 hours compared to placebo
- Total rescue medication usage from 0 to 48 hours compared to placebo

Statistical Analysis

Participants were analyzed according to their randomized treatment for efficacy analysis and their actual received treatment for safety analysis.

Primary endpoint and imputation scheme:

The following imputation scheme for NPRS scores was used in the primary analysis of the primary estimand: 1) scores during the rescue period (within 6 hours after rescue medication) were replaced by the pre-rescue score; 2) missing scores following treatment discontinuation were imputed using the baseline score when discontinuation was due to an AE and with the last score prior to discontinuation when discontinuation was due to other reasons; 3) missing scores for subjects who completed the treatment but with missing data from a certain time point to 48 hours were imputed with the last score; and 4) intermittently missing scores were imputed using linear interpolation. This analysis evaluated the treatment effect of suzetrigine monotherapy versus placebo had subjects not used rescue medication.

The treatment effect of suzetrigine was also evaluated in an post hoc supplementary analysis without imputation for rescue medication use, which is similar to what would be seen with multimodal therapy in the real-world setting. This analysis differs from the primary analysis in that the observed NPRS scores within 6 hours after rescue medication were used instead of being imputed. This analysis evaluated the treatment effect of suzetrigine + rescue medication (if used) versus placebo + rescue medication (if used), which was the effect of suzetrigine in a multimodal real-world setting.

Analysis of key secondary endpoints:

SPID48 for suzetrigine compared to HB/APAP was analyzed using the same imputation scheme and model as for the primary analysis of the primary endpoint. For the time to ≥2-point reduction in NPRS from baseline for suzetrigine compared to placebo, the time for each individual participant was calculated first and then the Kaplan-Meier method was used to estimate the

median time for each treatment group. A log-rank test was used to compare the survival curves between suzetrigine and placebo. The same imputation scheme as in the primary analysis was used. Post hoc analyses without imputation for rescue medication were also performed for the two key secondary endpoints.

A hierarchical testing procedure was used to control the overall type I error at a significance level of 0.05 for the primary and key secondary endpoints. Other secondary endpoints were not controlled for multiplicity; therefore, all *P* values are nominal.

Time to ≥1-point reduction in NPRS from baseline for suzetrigine compared to placebo and time to first use of rescue medication for suzetrigine compared to placebo were analyzed in the same way as described for time to ≥2-point reduction in NPRS from baseline.

The PGA of study drug is a single-item assessment of patient perceptions of the method of pain control with the study drug and was evaluated on a 4-point Likert scale (poor, fair, good, or excellent).[1] The proportion of participants reporting good or excellent on the PGA at 48 hours for suzetrigine compared to placebo was summarized descriptively, and the Cochran-Mantel-Haenszel test, stratified by the baseline NPRS category (<8, ≥8), was conducted to compare suzetrigine and placebo. Participants who discontinued study drug treatment for any reason prior to 48 hours and participants with missing PGA at 48 hours were considered non-responders (i.e., not reporting good or excellent on the PGA).

Incidence of vomiting or nausea for suzetrigine compared to HB/APAP was the proportion of participants reporting adverse events (AE)s of vomiting or nausea from the first dose of study drug through completion of study participation. When computing these proportions, participants with multiple occurrences of either event were counted once and participants who experienced

both events were also only counted once. This variable was summarized descriptively, and Pearson's chi-squared test was conducted to compare suzetrigine and HB/APAP.

SPID24 for suzetrigine compared to placebo was analyzed in the same way as described for the primary outcome.

The proportion of participants using rescue medication from 0 to 48 hours for suzetrigine compared to placebo was summarized descriptively, and the Cochran-Mantel-Haenszel test, stratified by the baseline NPRS category (<8, ≥8), was conducted to compare suzetrigine and placebo.

Total rescue medication usage from 0 to 48 hours for suzetrigine compared to placebo was summarized descriptively, and the Wilcoxon rank-sum test, stratified by the baseline NPRS category (<8, ≥8), was conducted to compare suzetrigine and placebo.

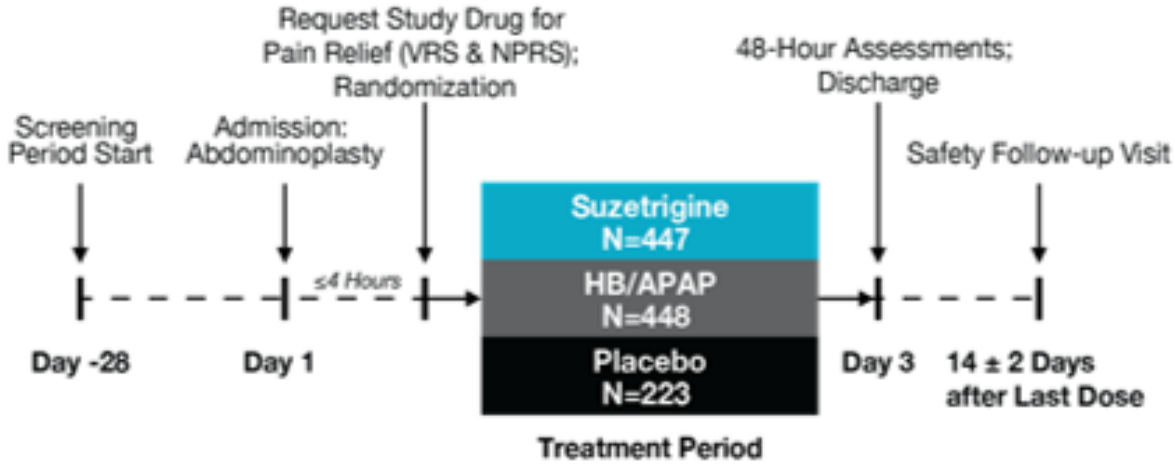
Section 3: Supplementary Results

It is important to recognize that while a ≥2-point reduction from baseline is clinically meaningful for within-group changes from baseline, the clinically meaningful change for between group difference is generally lower. In both trials, mean PID at 48 hours for suzetrigine was -3.4 (**; Supplemental Digital Content, eTable2**) corresponding to a relative NPRS reduction from baseline of 47% and 51% for abdominoplasty and bunionectomy, respectively. This was similar to the -3.2 (43% reduction) after abdominoplasty and -3.6 (53% reduction) after bunionectomy in participants treated with HB/APAP (**Supplemental Digital Content eTable2**). Pain relief was similar in a post-hoc analysis of PID at 48 hours without imputation for ibuprofen rescue (**Figure 2B and 2D**).

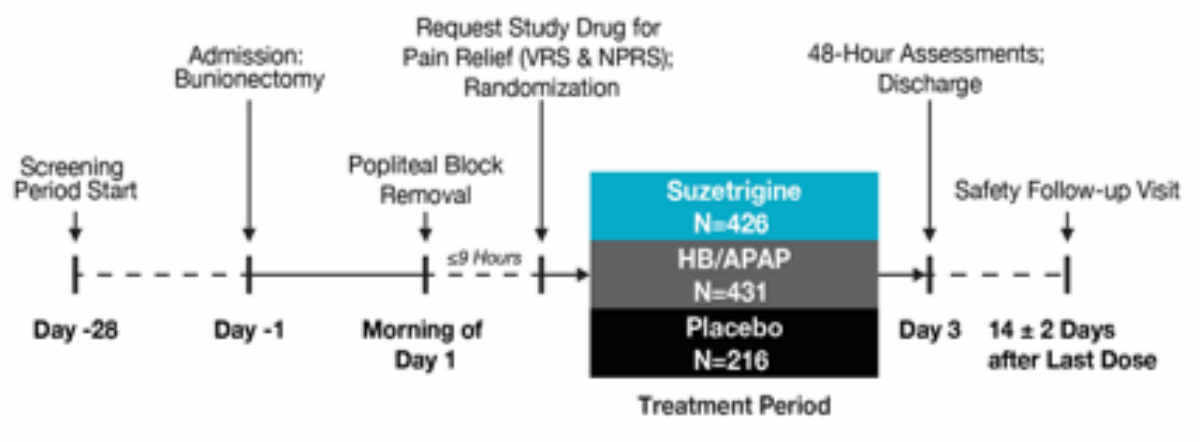
Section 4: Supplementary Figures

eFigure 1 Clinical Trial Design Schematics

A. Abdominoplasty



B. Bunionectomy



HB/APAP: hydrocodone bitartrate/acetaminophen; **NPRS:** numeric pain rating scale; **VRS:** verbal categorical rating scale

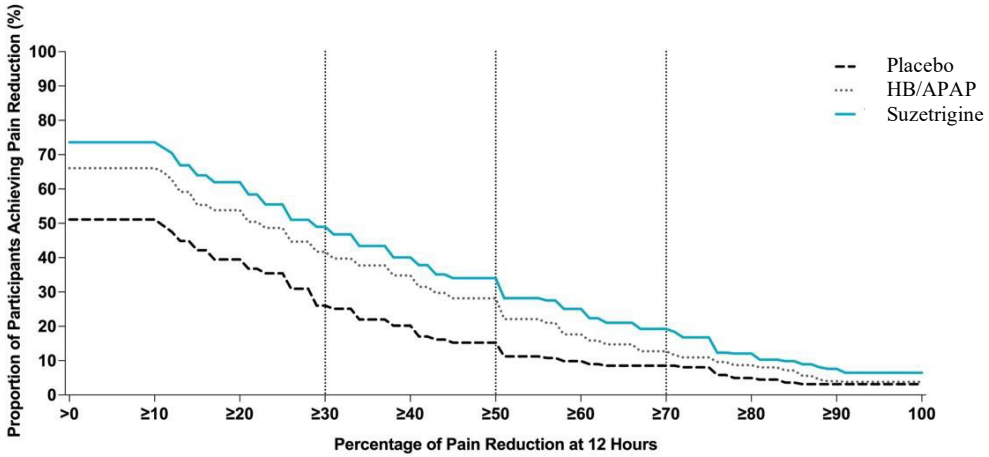
Notes: Panel A shows study design schematic for the abdominoplasty trial and Panel B shows study design schematic for bunionectomy trial. In both trials, suzetrigine tablets were administered orally as a 100-mg loading dose (0 hours) followed by a 50-mg maintenance dose at 12, 24, and 36 hours after the first dose of study drug. HB/APAP was administered orally as a 5-mg/325-mg capsule as follows: 0 hours (first dose) and at 6, 12, 18, 24, 30, 36, and 42 hours after the first dose of study drug. To maintain the blind, all participants received the same number of tablets and capsules in a double-dummy design.

eFigure 2 Percentage of Pain Reduction in the Abdominoplasty Phase 3 Trial

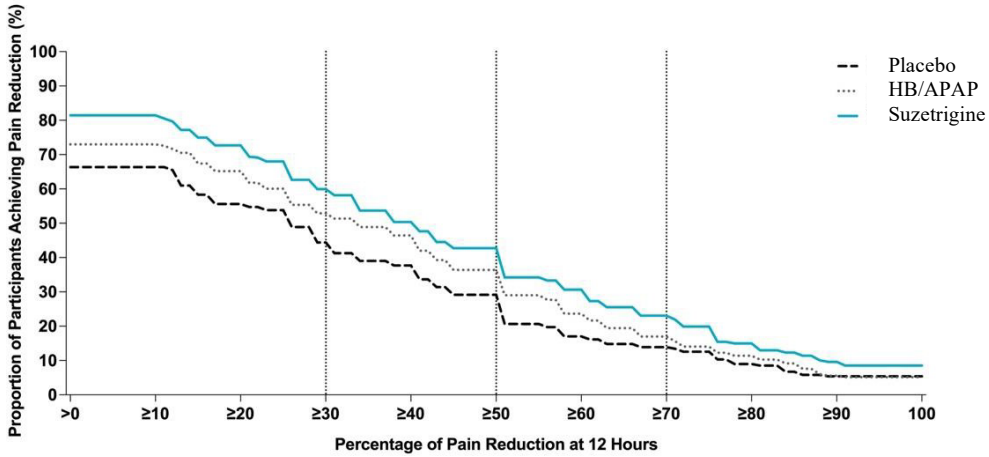
Abdominoplasty

A. Percentage of Pain Reduction at 12 Hours

With Imputation: 12 Hours

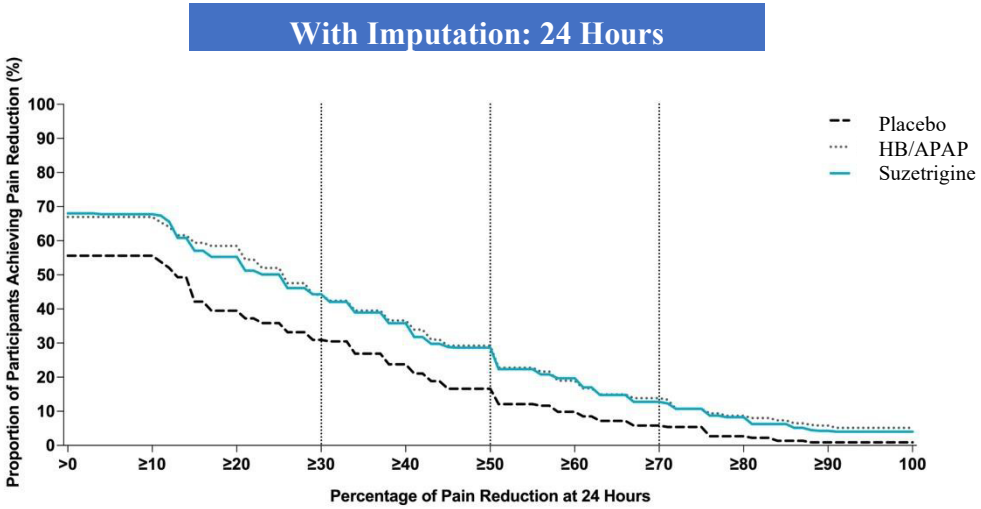


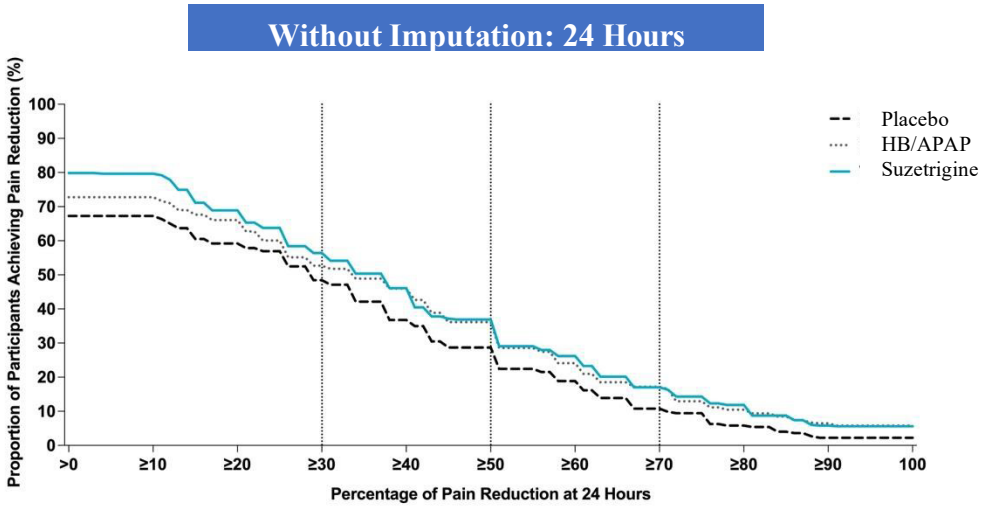
Without Imputation: 12 Hours



	Proportion of participants with	Placebo N = 223	HB/APAP N = 448	Suzetrigine N = 447
With Imputation	≥ 30% reduction in NPRS	**26.0%**	41.7%	**49.0%**
	≥ 50% reduction in NPRS	**15.2%**	28.1%	**34.0%**
	≥ 70% reduction in NPRS	**8.5%**	12.7%	**19.2%**
Without Imputation	≥ 30% reduction in NPRS	**44.4%**	52.9%	**60.0%**
	≥ 50% reduction in NPRS	**29.1%**	36.4%	**42.7%**
	≥ 70% reduction in NPRS	**13.9%**	17.0%	**23.0%**

B. Percentage of Pain Reduction at 24 Hours

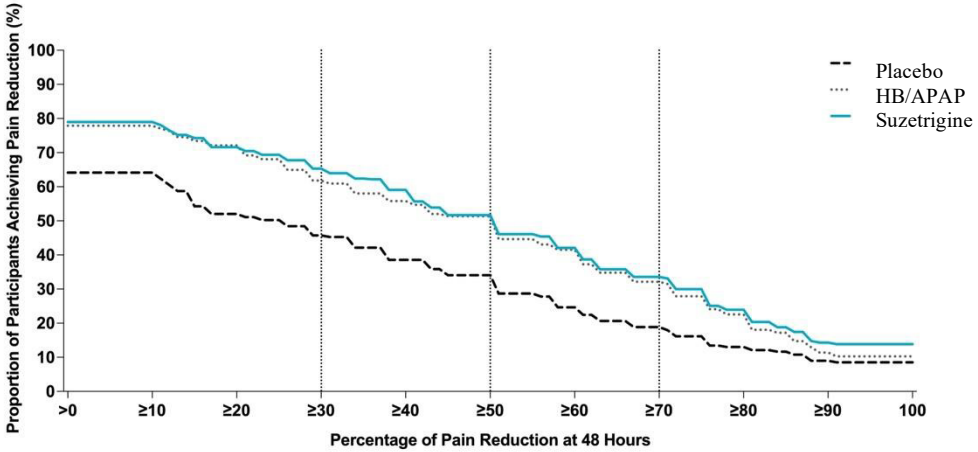




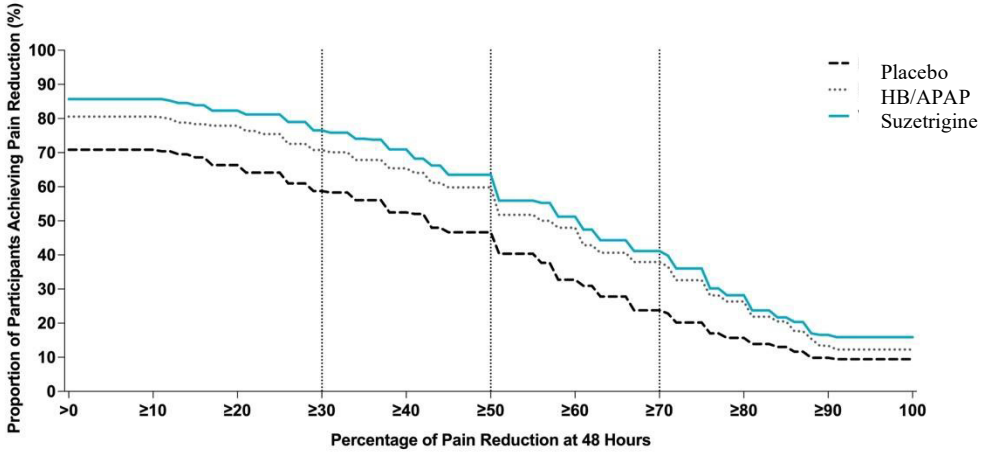
	Proportion of participants with	Placebo N = 223	HB/APAP N = 448	Suzetrigine N = 447
With Imputation	≥ 30% reduction in NPRS	**30.9%**	44.2%	**44.3%**
	≥ 50% reduction in NPRS	**16.6%**	29.2%	**28.6%**
	≥ 70% reduction in NPRS	**5.8%**	13.8%	**12.8%**
Without Imputation	≥ 30% reduction in NPRS	**48.4%**	52.7%	**56.4%**
	≥ 50% reduction in NPRS	**28.7%**	36.2%	**36.9%**
	≥ 70% reduction in NPRS	**10.8%**	17.2%	**17.0%**

C. Percentage of Pain Reduction at 48 Hours

With Imputation: 48 Hours



Without Imputation: 48 Hours



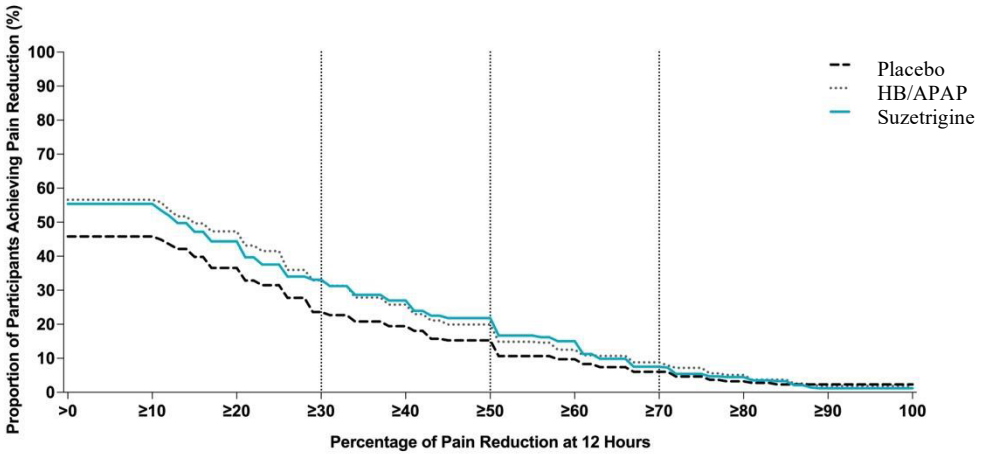
	Proportion of participants with	Placebo N = 223	HB/APAP N = 448	Suzetrigine N = 447
With Imputation	≥ 30% reduction in NPRS	**45.7%**	61.8%	**65.3%**
	≥ 50% reduction in NPRS	**34.1%**	51.3%	**51.7%**
	≥ 70% reduction in NPRS	**18.8%**	32.1%	**33.6%**
Without Imputation	≥ 30% reduction in NPRS	**58.7%**	70.8%	**76.5%**
	≥ 50% reduction in NPRS	**46.6%**	59.8%	**63.5%**
	≥ 70% reduction in NPRS	**23.8%**	37.9%	**41.2%**

eFigure 3 Percentage of Pain Reduction in the Bunionectomy Phase 3 Trial

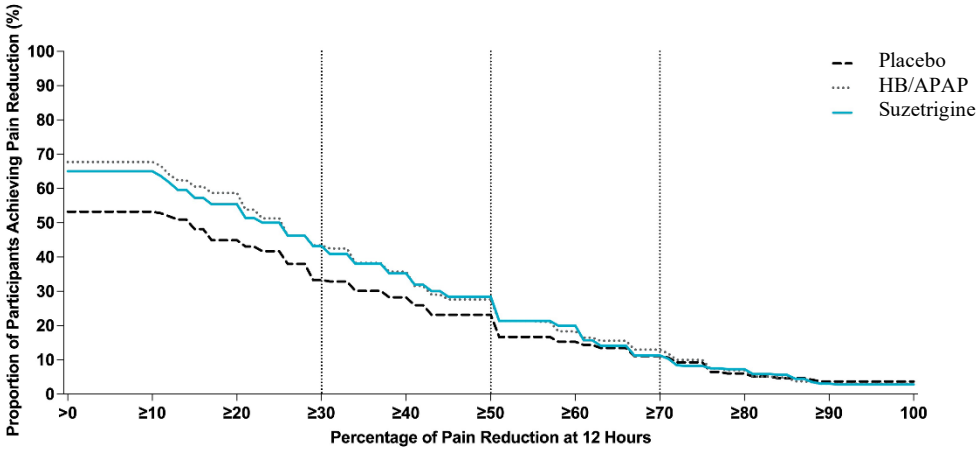
Bunionectomy

A. Percentage of Pain Reduction at 12 Hours

With Imputation: 12 Hours



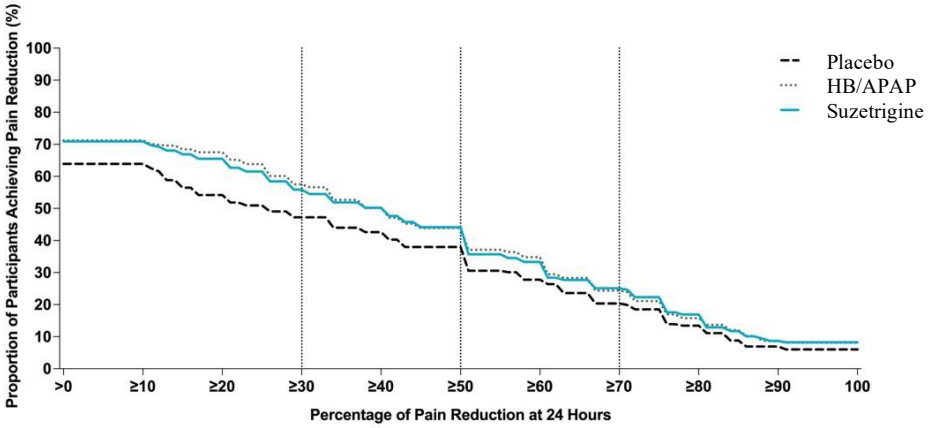
Without Imputation: 12 Hours



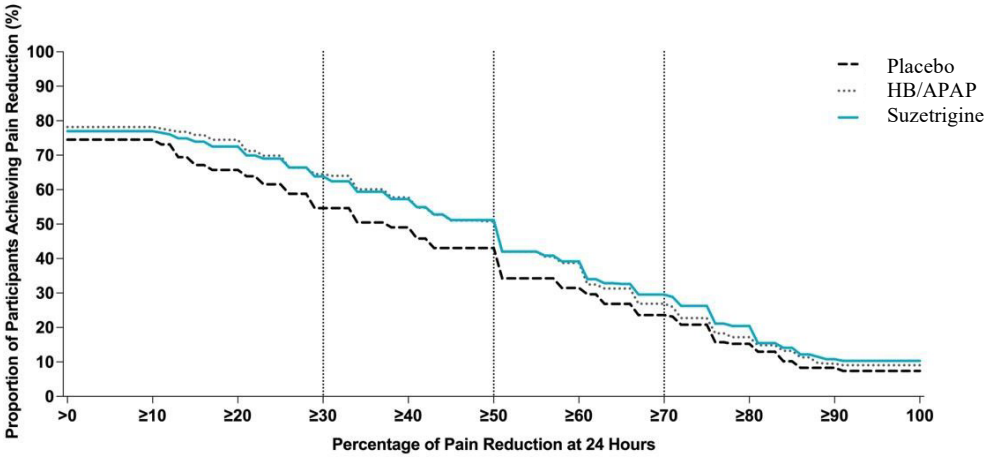
	Proportion of participants with	Placebo N = 216	HB/APAP N = 431	Suzetrigine N = 426
With Imputation	≥ 30% reduction in NPRS	**23.6%**	32.9%	**33.1%**
	≥ 50% reduction in NPRS	**15.3%**	20.0%	**21.8%**
	≥ 70% reduction in NPRS	**6.0%**	8.8%	**7.5%**
Without Imputation	≥ 30% reduction in NPRS	**33.3%**	43.4%	**43.2%**
	≥ 50% reduction in NPRS	**23.1%**	27.6%	**28.4%**
	≥ 70% reduction in NPRS	**11.1%**	13.0%	**11.3%**

B. Percentage of Pain Reduction at 24 Hours

With Imputation: 24 Hours



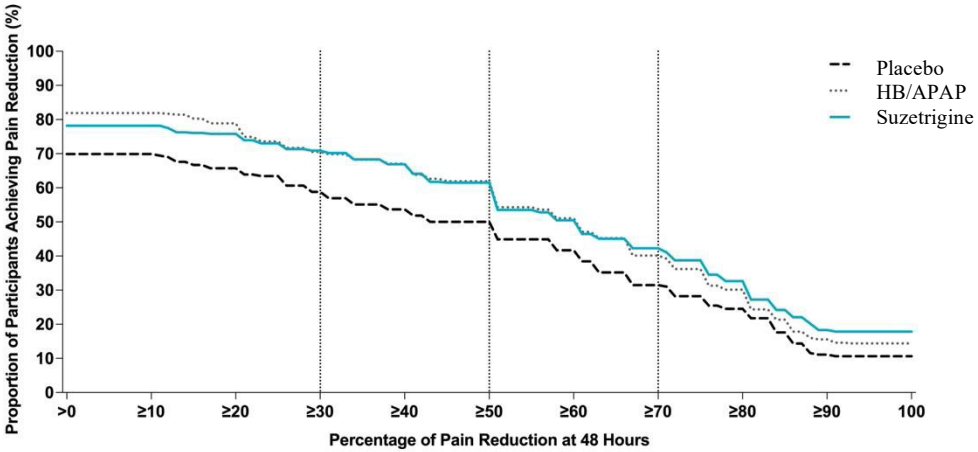
Without Imputation: 24 Hours



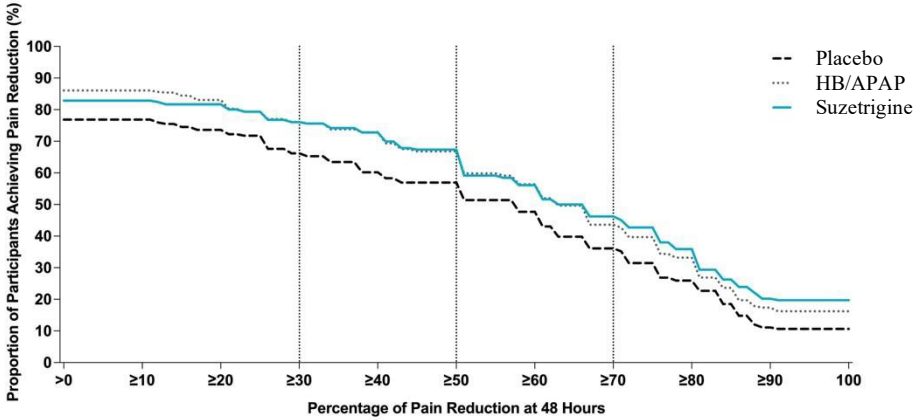
	Proportion of participants with	Placebo N = 216	HB/APAP N = 431	Suzetrigine N = 426
With Imputation	≥ 30% reduction in NPRS	**47.2%**	57.5%	**55.9%**
	≥ 50% reduction in NPRS	**38.0%**	43.9%	**44.1%**
	≥ 70% reduction in NPRS	**20.4%**	24.4%	**25.1%**
Without Imputation	≥ 30% reduction in NPRS	**54.6%**	64.5%	**63.8%**
	≥ 50% reduction in NPRS	**43.1%**	50.8%	**51.2%**
	≥ 70% reduction in NPRS	**23.6%**	26.9%	**29.6%**

C. Percentage of Pain Reduction at 48 Hours

With Imputation: 48 Hours



Without Imputation: 48 Hours



	Proportion of participants with	Placebo N = 216	HB/APAP N = 431	Suzetrigine N = 426
With Imputation	≥ 30% reduction in NPRS	**58.8%**	70.5%	**70.9%**
	≥ 50% reduction in NPRS	**50.0%**	61.9%	**61.5%**
	≥ 70% reduction in NPRS	**31.5%**	40.1%	**42.3%**
Without Imputation	≥ 30% reduction in NPRS	**66.2%**	76.1%	**76.1%**
	≥ 50% reduction in NPRS	**56.9%**	66.8%	**67.4%**
	≥ 70% reduction in NPRS	**36.1%**	43.6%	**46.2%**

Section 5: Supplementary Tables

eTable 1. Disposition

	Abdominoplasty			Bunionectomy		
	Suzetrigine N = 447	**HB/APAP N = 448**	**Placebo N = 223**	**Suzetrigine N = 426**	**HB/APAP N = 431**	**Placebo N = 216**
Completed study drug, n (%)	396 (88.6)	382 (85.3)	168 (75.3)	372 (87.3)	389 (90.3)	177 (81.9)
Discontinued study drug, n (%)	51 (11.4)	66 (14.7)	55 (24.7)	54 (12.7)	42 (9.7)	39 (18.1)
Reason for discontinuation from study drug, n, (%)						
Lack of efficacy	42 (9.4)	59 (13.2)	48 (21.5)	51 (12.0)	34 (7.9)	35 (16.2)
Adverse event	6 (1.3)	5 (1.1)	1 (0.4)	0	1 (0.2)	0
Participant refused further dosing (not due to AE)	0	0	1 (0.4)	1 (0.2)	3 (0.7)	0
Physician decision	1 (0.2)	1 (0.2)	3 (1.3)	0	0	0
Other non-adherence	0	0	0	1 (0.2)	1 (0.2)	2 (0.9)
Sponsor decision	1 (0.2)	0	1 (0.4)	1 (0.2)	0	0
Did not meet eligibility criteria	1 (0.2)	0	0	0	1 (0.2)	0
Other	0	1 (0.2)	1 (0.4)	0	2 (0.5)	2 (0.9)

AE: adverse event; **HB/APAP:** hydrocodone bitartrate/acetaminophen; **N**: number of participants in the analysis set; **n:** number of participants

Note: Table includes participants in any treatment group who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment.

eTable 2. Pain Intensity Difference at 48 Hours

	Abdominoplasty			Bunionectomy		
	Suzetrigine N = 447	**HB/APAP N = 448**	**Placebo N = 223**	**Suzetrigine N = 426**	**HB/APAP N = 431**	**Placebo N = 216**
Pre-Specified Analysis With Rescue Imputation						
Baseline NPRS, mean	7.3	7.4	7.5	6.7	6.8	6.8
Pain Intensity Difference at 48 hours, mean	-3.4	-3.2	-2.3	-3.4	-3.6	-2.6
Percent reduction in mean NPRS at 48 hours (%)	47%	43%	31%	51%	53%	38%
Post-Hoc Analysis Without Rescue Imputation (as treated)						
Baseline NPRS, mean	7.3	7.4	7.5	6.7	6.8	6.8
Pain Intensity Difference at 48 hours, mean	-4.0	-3.7	-3.0	-3.7	-3.8	-3.0
Percent reduction in mean NPRS at 48 hours (%)	55%	50%	40%	55%	56%	44%

HB/APAP: hydrocodone bitartrate/acetaminophen; **N**: number of participants in the analysis set; **n:** number of participants; **NPRS:** numeric pain rating scale

Note: Table includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment.

eTable 3. Secondary Endpoint: Time to ≥1-point Reduction in NPRS From Baseline Compared to Placebo

	Abdominoplasty		Bunionectomy	
	Suzetrigine N = 447	**Placebo N = 223**	**Suzetrigine N = 426**	**Placebo N = 216**
Median time (minutes)	34	91	60	61
95% CI	(32, 55)	(60, 180)	(58, 65)	(34, 121)
Nominal *P* value vs. placebo (Log-rank test)	<0.0001	--	0.1315	--

CI: confidence interval; **N**: number of participants in the analysis set; **n:** number of participants; **NPRS:** numeric pain rating scale

Note: Table includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to the randomized treatment.

eTable 4. Secondary Endpoint: Proportion of Participants Reporting Good or Excellent on the Patient Global Assessment at 48 Hours Compared to Placebo

	Abdominoplasty		Bunionectomy	
	Suzetrigine N = 447	**Placebo N = 223**	**Suzetrigine N = 426**	**Placebo N = 216**
Participants reporting good or excellent on PGA at 48 hours, n (%)	303 (67.8)	111 (49.8)	263 (61.7)	115 (53.2)
Nominal *P* value vs. placebo	<0.0001	--	0.0343	--

N: number of participants in the analysis set; **n:** number of participants; **PGA;** patient global assessment

Note: Table includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment.

eTable 5. Secondary Endpoint: Incidence of Vomiting or Nausea Compared to HB/APAP

	Abdominoplasty		Bunionectomy	
	Suzetrigine N = 448	**HB/APAP N = 448**	**Suzetrigine N = 426**	**HB/APAP N = 431**
Participants with vomiting or nausea, n (%)	91 (20.3)	150 (33.5)	39 (9.2)	71 (16.5)
Nominal *P* value vs. HB/APAP	<0.0001	--	0.0014	--

HB/APAP: hydrocodone bitartrate/acetaminophen; **N**: number of participants in the analysis set; **n:** number of participants

Note: Table includes participants who received at least one dose of study drug. Participants were analyzed according to the treatment they received.

eTable 6. Secondary Endpoint: SPID24 Compared to Placebo

	Abdominoplasty		Bunionectomy	
	Suzetrigine N = 447	**Placebo N = 223**	**Suzetrigine N = 426**	**Placebo N = 216**
LS mean (SE)	48.0 (2.0)	24.2 (2.8)	30.6 (2.1)	19.8 (3.0)
LS mean difference from placebo (SE)	23.8 (3.4)	--	10.7 (3.6)	--
95% CI	(17.1, 30.5)	--	(3.6, 17.9)	--
Nominal *P* value vs. placebo	<0.0001	--	0.0032	--

CI: confidence interval; **LS mean:** least squares mean; **N**: number of participants in the analysis set; **n:** number of participants; **SE:** standard error; **SPID24:** time-weighted sum of the pain intensity difference 0 to 24 hours after the first dose of trial drug

Note: Table includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment.

eTable 7. Secondary Endpoints: Rescue Medication

	Abdominoplasty		Bunionectomy	
	Suzetrigine N = 447	**Placebo N = 223**	**Suzetrigine N = 426**	**Placebo N = 216**
Secondary Endpoint: Proportion of participants using rescue medication from 0 to 48 hours compared to placebo				
Participants using rescue medication from 0 to 48 hours, n (%)	362 (81.0)	196 (87.9)	364 (85.4)	185 (85.6)
Nominal *P* value vs. placebo	0.0237	--	0.9143	--
Secondary Endpoint: Total rescue medication usage from 0 to 48 hours compared to placebo				
Total rescue medication usage from 0 to 48 hours (mg), median	800.0	1200.0	800.0	800.0
Nominal *P* value vs. placebo[a]	0.0080	--	0.0205	--
Secondary Endpoint: Time to first use of rescue medication compared to placebo				
Time to first use of rescue medication (min), median (95% CI)	186 (158, 212)	115 (100, 132)	157 (145, 192)	185 (143, 210)
Nominal *P* value vs. placebo	<0.0001	--	0.8592	--

CI: confidence interval; **N**: number of participants in the analysis set; **n:** number of participants

Notes: Table includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment. Rescue medication was ibuprofen (400 mg orally, every 6 hours as need).

[a] *P* value is based on the Wilcoxon rank-sum test, which tests for whether the suzetrigine and placebo groups had the same distribution in total rescue medication usage from 0 to 48 hours.

Section 6: References

1 Rothman M, Vallow S, Damaraju CV, Hewitt DJ. Using the patient global assessment of the method of pain control to assess new analgesic modalities in clinical trials. Curr Med Res Opin. 2009;25(6):1433-43.