Suzetrigine
"A Novel Non-opioid Analgesic"

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DISCLOSURES

Primary Investigator for H D Research

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Member of the Advisory Committee for Vertex Pharmaceuticals

- On January 30th, 2025, The US FDA approved the first non-opioid analgesic in more than 20 years.
- This approval from FDA came within 4 years compared to 12 -15 years
- HD research participated in the clinical trials for this non-opioid analgesic.
- This approval was historical, and H D Research is happy to be a part of this history.

In 1986 World Health Organization proposed **Who Analgesic Ladder** for adequate pain relief in cancer patients.

The main principles of this analgesic ladder were

1. " By the clock"
2. "By mouth"
3. " By ladder"

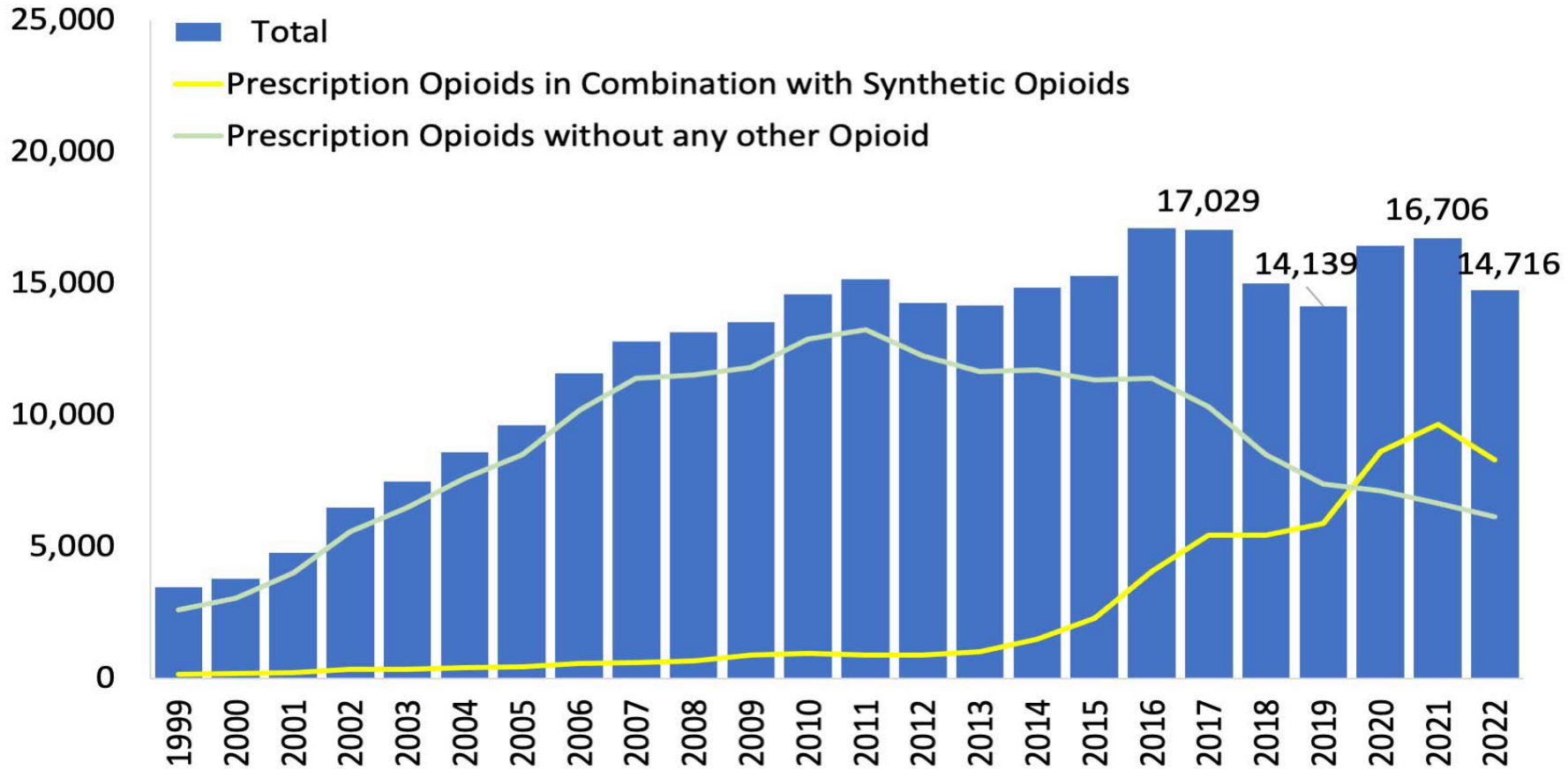
Aneka AA, Maxwell J, Cascella M.
Who analgesic ladder. Stat Pearlpublishers LLC
Last update April 2023

Stepped approach to pain management.
Reprinted with permission from World Health Organization. WHO's pain relief ladder. http://www.who.int/cancer/palliative/painladder/en/. Accessed February 25, 2013.

While the ladder's original focus was on cancer pain, its principles of using analgesics in a stepwise manner have been adopted for use in managing acute pain.

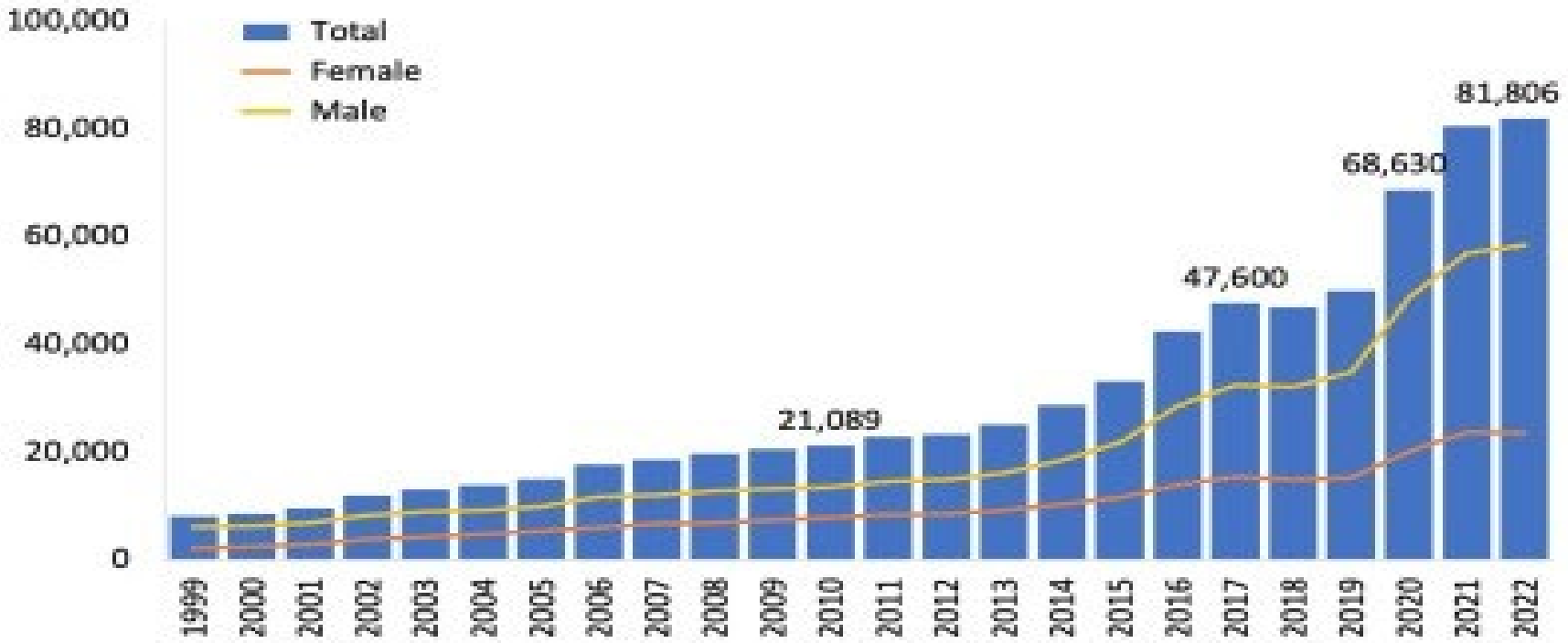
This led to increased use of opioids for acute pain resulting in the opioid crisis.

Figure 4. U.S. Overdose Deaths Involving Prescription Opioids*, 1999-2022



*Among deaths with drug overdose as the underlying cause, the prescription opioid subcategory was determined by the following ICD-10 multiple cause-of-death codes: natural and semi-synthetic opioids (T40.2) or methadone (T40.3). Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2022 on CDC WONDER Online Database, released 4/2024.

Figure 3. U.S. Overdose Deaths Involving Any Opioid* by Sex, 1999-2022



*Among deaths with drug overdose as the underlying cause, the "any opioid" subcategory was determined by the following ICD-10 multiple cause-of-death codes: natural and semi-synthetic opioids (T40.2), methadone (T40.3), other synthetic opioids (other than methadone) (T40.4), or heroin (T40.1). Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2022 on CDC WONDER Online Database, released 4/2024.

In February 2022
U. S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
issued a draft guidance to the pharmaceutical industry to develop Non-Opioid Analgesics for Acute Pain

Acute Pain
Sudden onset
Duration of less than a month
Associated with potential or actual tissue damage
Pain Related to trauma, surgery or illness

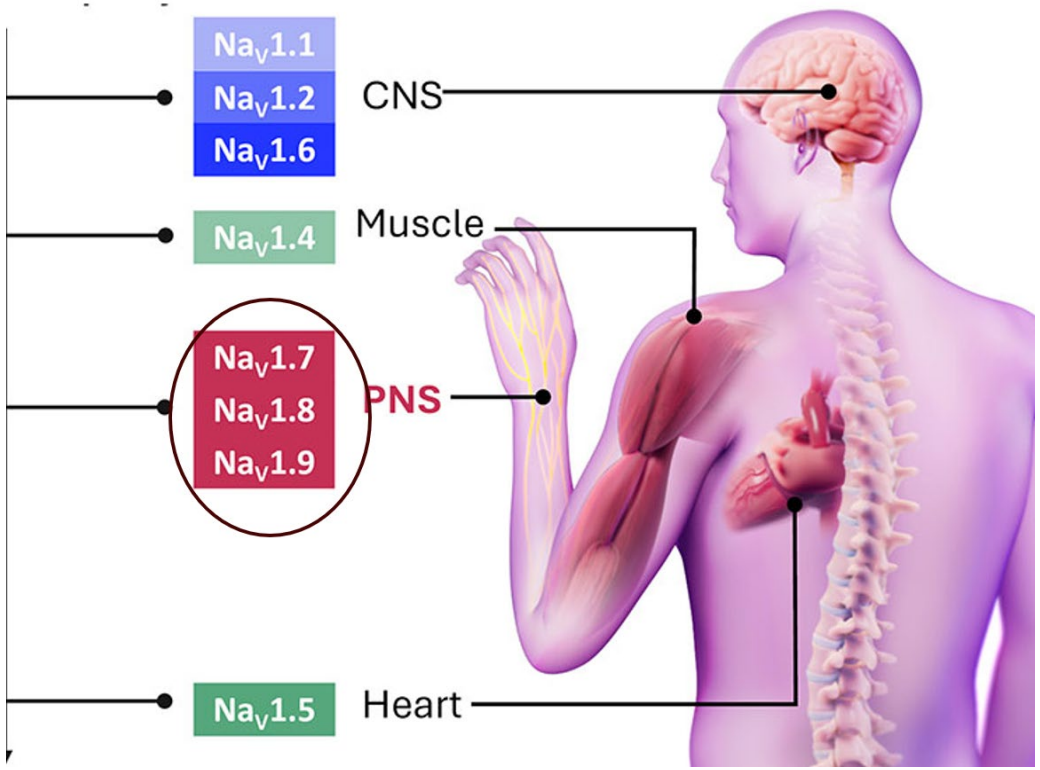
THE RACE WAS ON

Voltage Gated Sodium Channels (VGSC)

There are nine VGSC (NaV 1.1 – NaV 1.9)

They each have unique cell type, specific expression pattern and function

NaV 1.7, NaV 1.8 and NaV 1.9 are expressed in peripheral nociceptors and play a crucial role in initiation and propagation of pain impulses.



Characteristics of these sodium channels

- Activation is voltage dependent; there is rapid inactivation and there is high sodium selectivity.
- NaV 1.7, 1.8 and 1.9 are expressed in nociceptors and play a crucial role in initiation and transmission of pain signals.
- Importance of NaV 1.7 was realized when research showed that mutation in gene encoding NaV1.7 (SCN9A) leads to a condition called **congenital insensitivity to pain (CIP).**
- Could there be an ultimate analgesic that can block NaV 1.7, NaV 1.8, or NaV 1.9 ?
- A drug was then developed that could block NaV 1.8
- This drug was VX548 which was approved by FDA as **SUZETRIGINE**

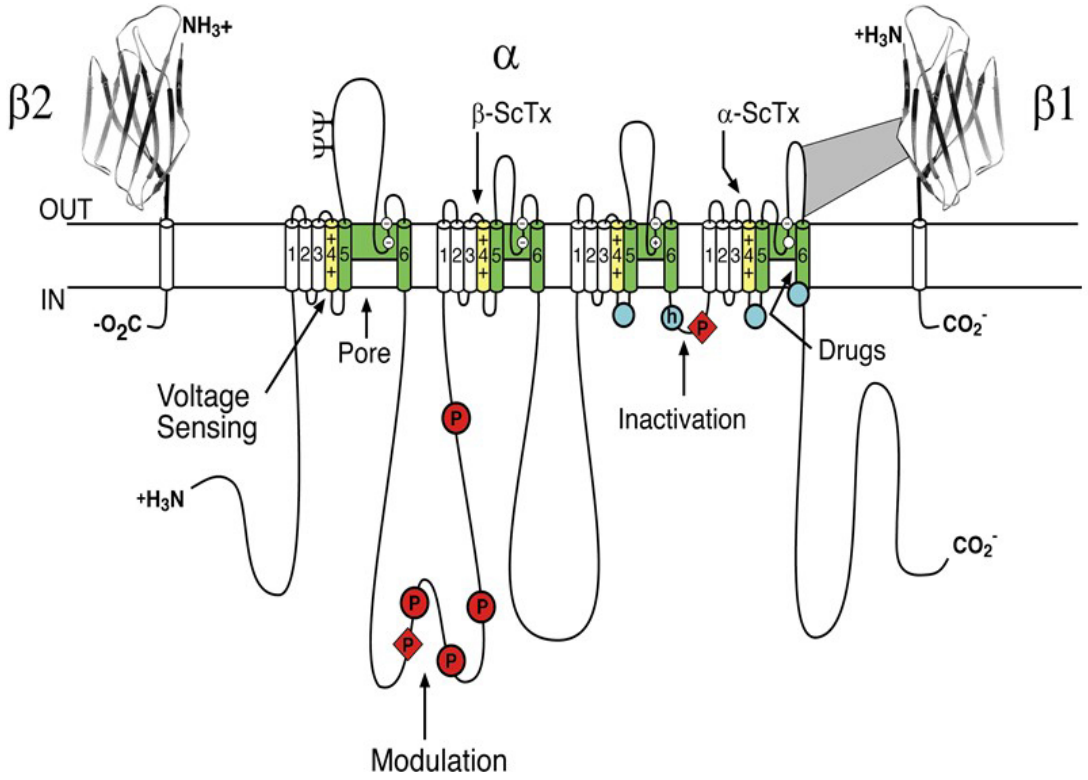
Why NaV 1.8?

- Selectively expressed in peripheral nociceptors and DRG
- It contributes to transmission of both acute and chronic pain

  It is 31,000-fold more selective for NaV 1.8
- It is **not** expressed in the central nervous system.
- It remains active when depolarized

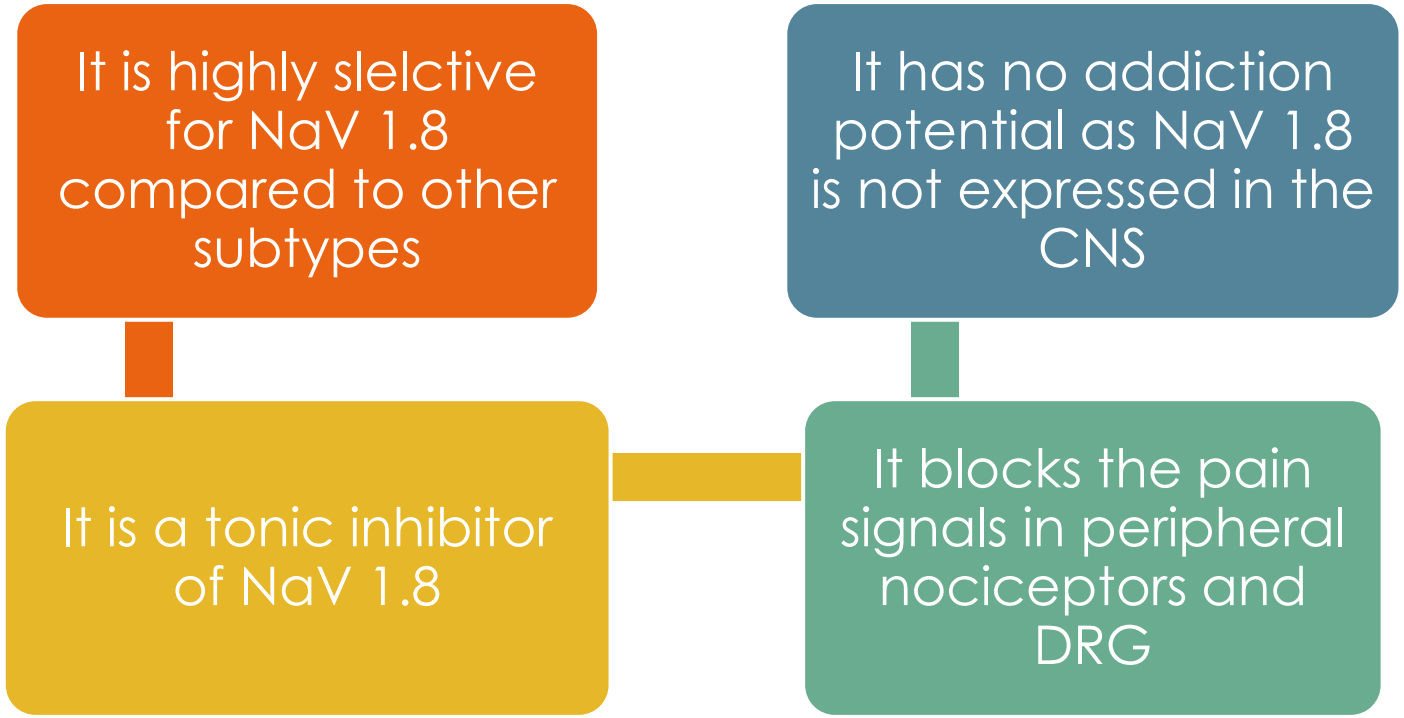
Structure and Function of Voltage Gated Sodium Channels (VGSC)

1. Voltage gated sodium channels are transmembrane proteins.
2. It has an Alpha subunit and a Beta1 subunit.
3. Alpha subunit has 4 homologous domains
4. Each domain has 6 transmembrane segments.
5. Segment S4 is sensitive to change in the membrane potential. (Voltage Sensor)
6. S5 and S6 segments form the pore.



https://guidetopharmacology.org

Suzetrigine



Clinical Trials

1. **Phase II Trial**

It answers the question does the experimental drug improve the condition
It is tested in 100-300 subjects

2. **Phase III Trial**

- This is a critical step in drug development
- Its aim is to prove that new drug is safe, effective and better than existing one
- The study involves large group of patients (hundreds or thousands)
- These are multi-center randomized double blind studies
- Successful trial results are then submitted to regulatory agencies for approval of the drug

3. **Phase III Single Arm Study**

- Subjects and the researcher knew what drug is being given

Clinical Trials with Suzetrigine

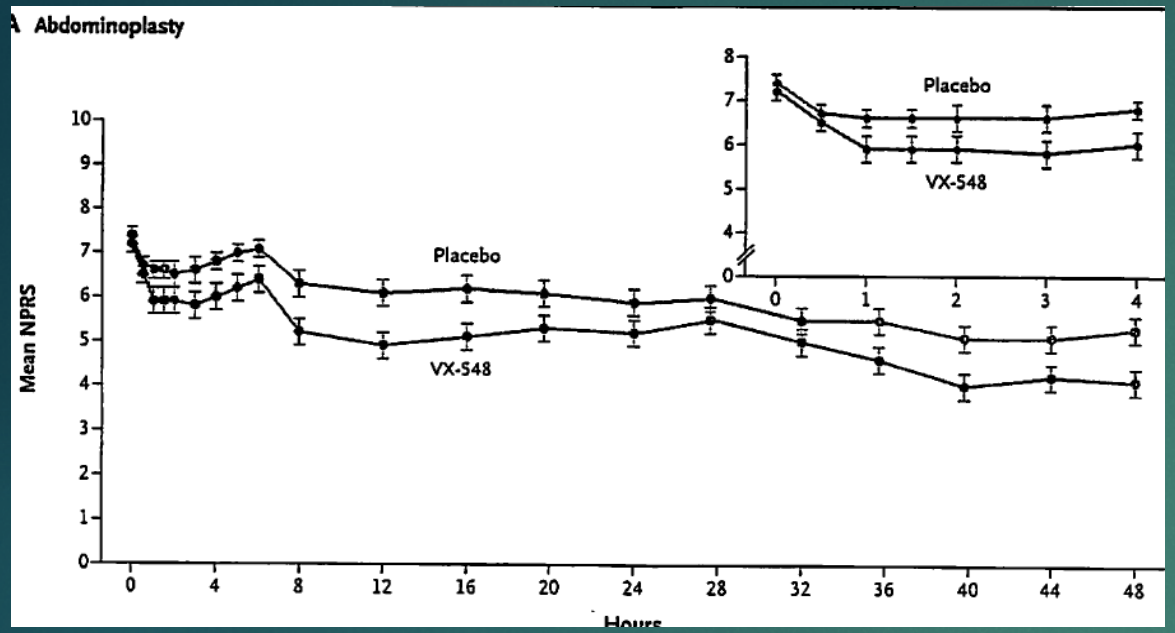
Two phase II randomized, active and placebo-controlled trials were conducted with bunionectomy as the bone pain model abdominoplasty as the soft tissue model.

Two Phase III randomized, active and placebo-controlled trials were conducted with bunionectomy as the bone pain model abdominoplasty as the soft tissue model.

One Phase III single arm study was conducted for surgical and non-surgical pain

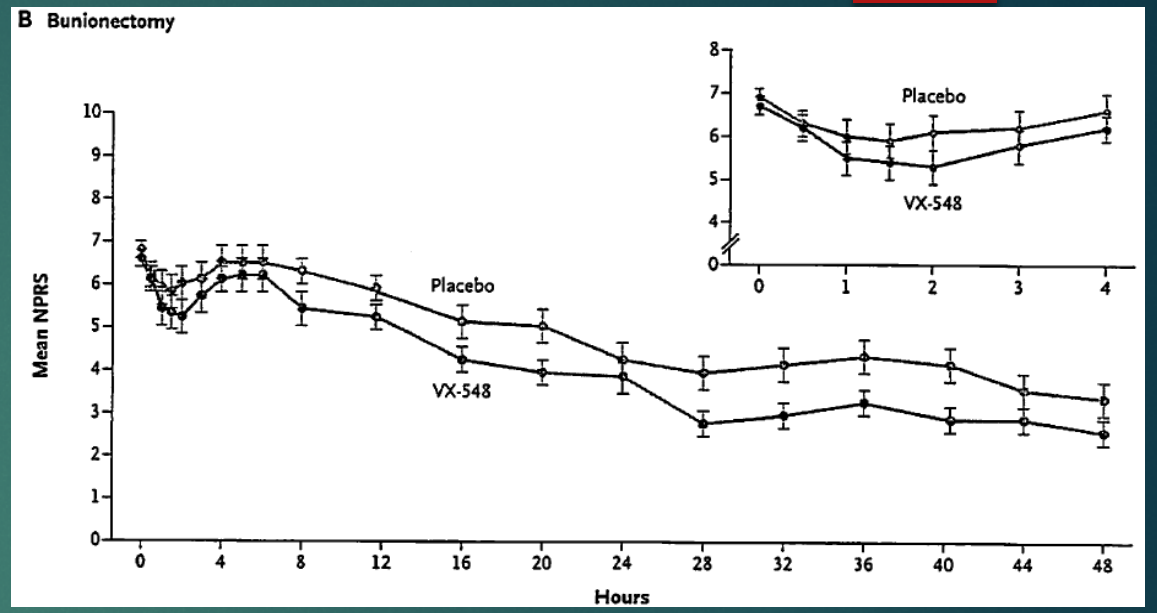
Results of Phase II Trial

N - 303



Mean NPRS : 7.2-7.4

N - 274



Mean NPRS: 6.6-6-9

In both these studies only dose that provided clinically meaningful analgesia was a loading dose of 100 mg followed by 50 mg every 12 hours.

Jones J, Correll DJ, Lechner SM et al, N Engl J Med. 2023; 389(5): 393-405

Phase III Trial
3 groups: Suzetrigine, Placebo and Hydrocodone

Abdominoplasty

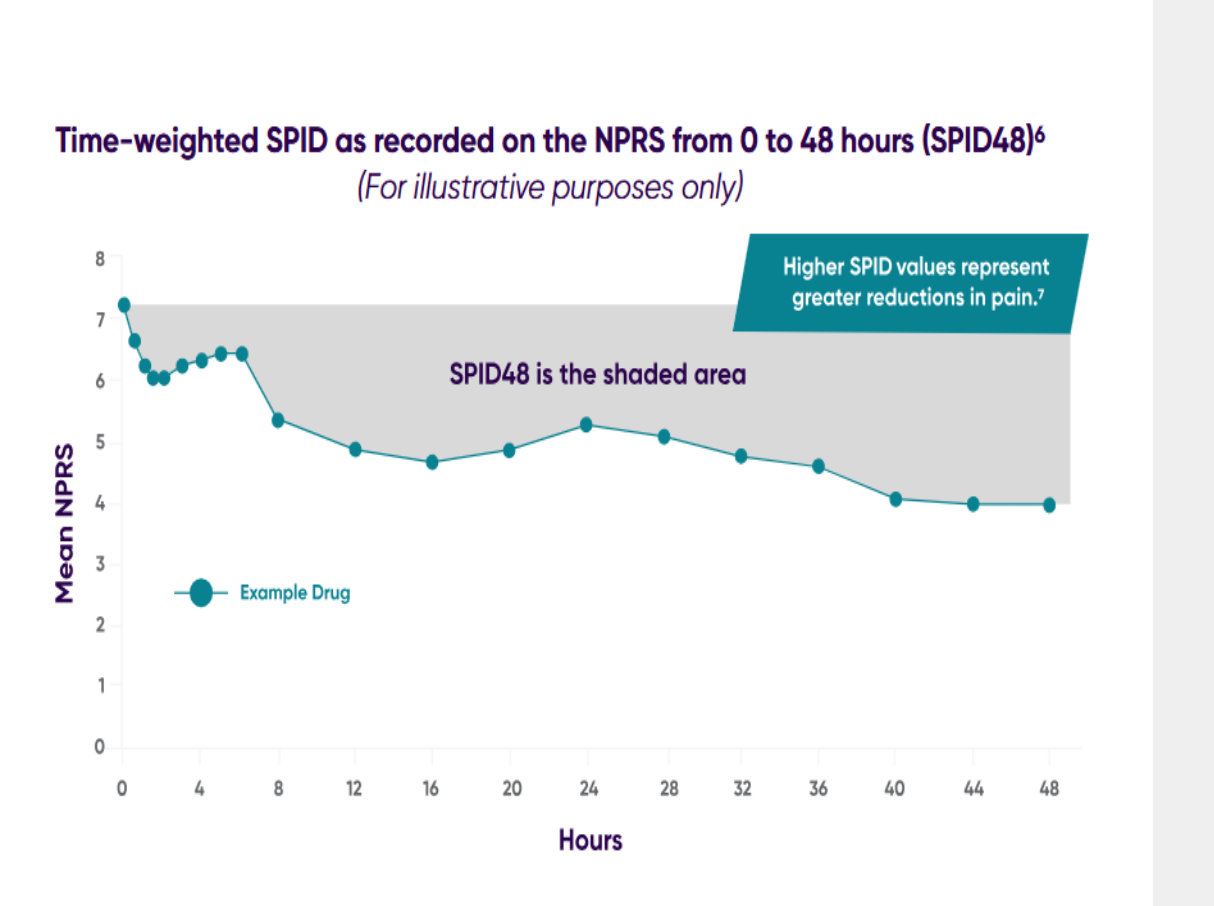
- Abdominoplasty done under GA
- Number of subjects 1,118
- Randomized to one of the groups
- Ibuprofen 400 mg every 6 hours was allowed for rescue after the first dose

Bunionectomy

- Bunionectomy done under Mayo block and continuous popliteal sciatic nerve block
- Number of subjects 1,073
- Randomized within 9 hours of removal of popliteal catheter
- Ibuprofen 400 mg every 6 hours was allowed for rescue after the first dose

In both these trials analgesic efficacy was evaluated using SPID 48

What is SPID?



- SPID: **S**um of **P**ain **I**ntensity **D**ifference
- PID: **P**ain **I**ntensity **D**ifference
- SPID is used to evaluate analgesic efficacy.
- Pain intensity is measured using NPRS
- PID is calculated as the difference in pain intensity at a specific time compared to baseline pain intensity
- Difference in pain intensity is multiplied by the duration on interval since the previous assessment and SPID is calculated.
- Higher the SPID score greater is the analgesic effect

NPRS Reduction From Baseline At 48 hours

Abdominoplasty

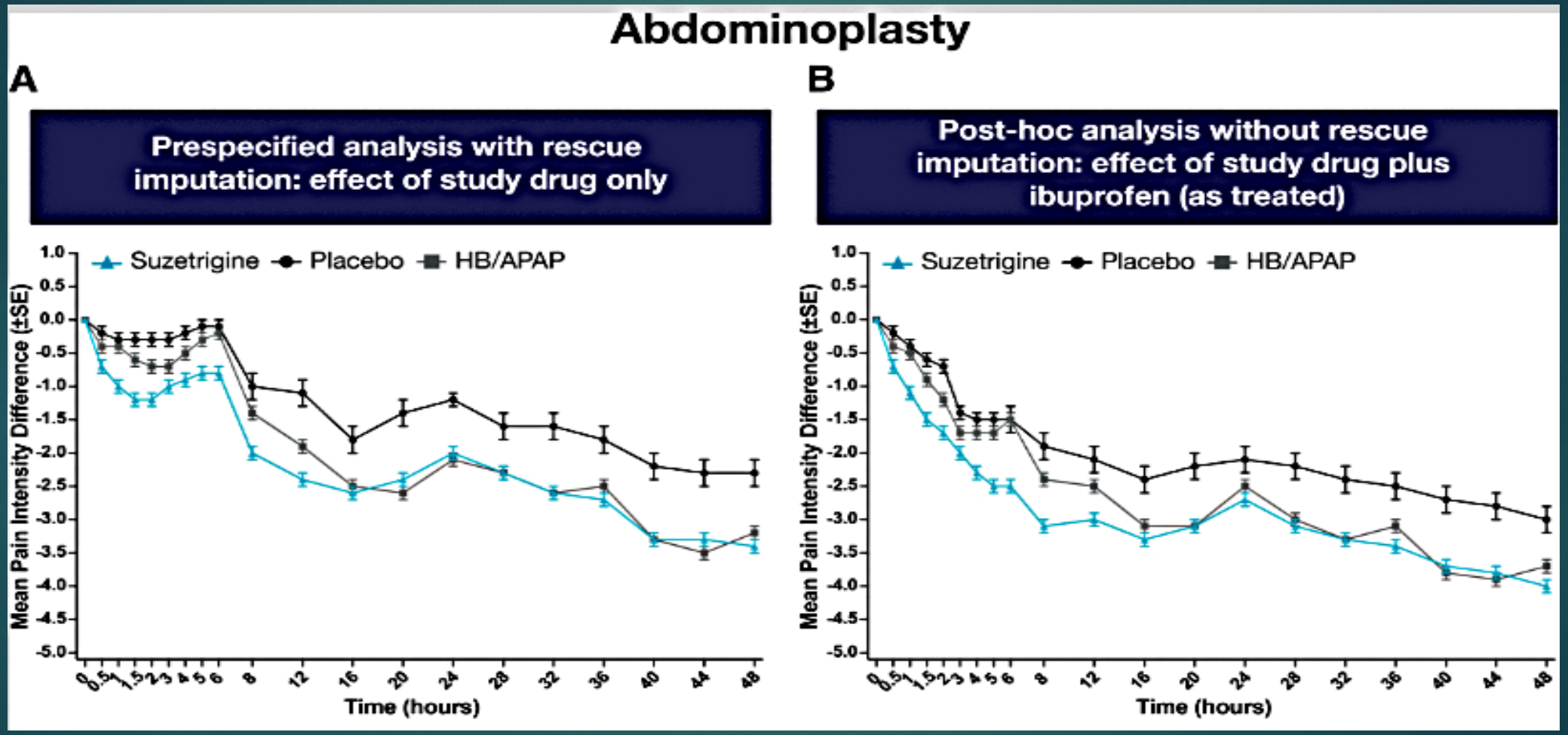
	Placebo N = 223	HB/APAP N = 448	Suzetrigine N = 447
Baseline NPRS mean	7.5	7.4	7.3
Change from baseline at 48 hours mean	-2.3	-3.2	-3.4
% reduction from baseline In mean NPRS	31%	43%	47%

Bunionectomy

	Placebo N+216	HB/APAP N = 431	VX 548 N= 426
Baseline NPRS mean	6.8	6.8	6.7
Change from baseline at 48 hours mean	-2.6	-3.6	-3.4
% reduction from baseline in mean NPRS	38%	53%	51%

Phase III Randomized, Placebo and Active controlled Trial Results

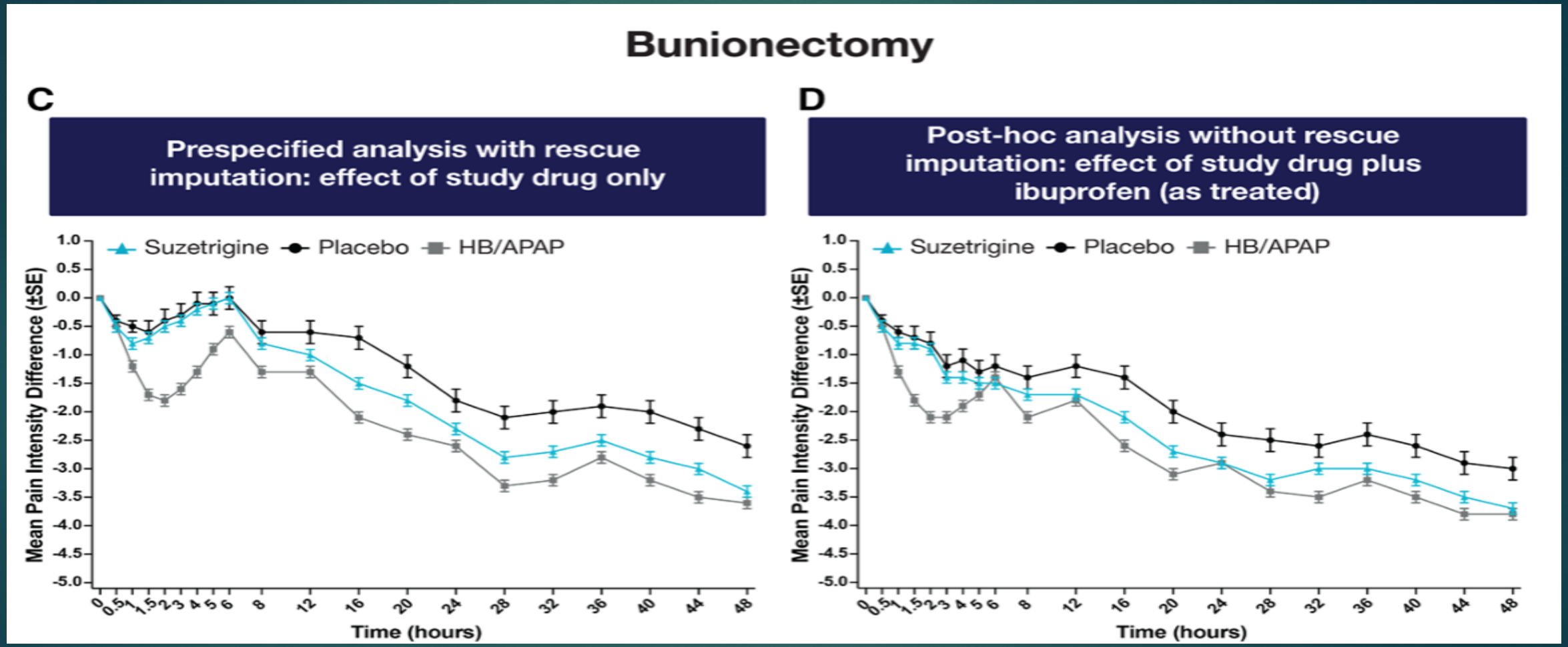
N: 1,118



Bertoch T, D'Aunno D, McCoun J, Solanki D et, al. Anesthesiology 2025; 142: 1085-99

Phase III Randomized, Placebo and Active controlled Trial Results

N: 1,073



Bertoch T, D'Aunno D, McCoun J, Solanki D et, al. Anesthesiology 2025; 142: 1085-99

Suzetrigine was superior to placebo

Primary Endpoint was Met in Both Trials

	Abdominoplasty		Bunionectomy	
Primary Endpoint: SPID48 Compared to Placebo	**Suzetrigine N=447**	**Placebo N=223**	**Suzetrigine N=426**	**Placebo N=216**
With Rescue Imputation (monotherapy)				
LS mean (SE)	118.4 (4.3)	70.1 (6.1)	99.9 (4.5)	70.6 (6.3)
LS mean difference from placebo	48.4	--	29.3	--
95% CI	(33.6, 63.1)	--	(14.0, 44.6)	--
P value versus placebo	<0.0001	--	0.0002	--
Without Rescue Imputation (representative of multimodal therapy in real-world setting)				
LS mean (SE)	153.0 (4.5)	105.4 (6.4)	128.8 (4.7)	100.1 (6.6)
LS mean difference from placebo	47.7	--	28.8	--
95% CI	(32.4, 62.9)	--	(12.9, 44.6)	--
Nominal *P* value versus placebo*	<0.0001	--	0.0004	--

Table includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment.
*Analyses for SPID48 compared to placebo without rescue imputation are ad hoc; therefore, *P* values are nominal.

LS mean: Least Square

Bertoch T, D'Aunno D, McCoun J, Solanki D et, al. Anesthesiology 2025; 142: 1085-99

Suzetrgine had rapid onset of meaningful analgesia

	Abdominoplasty		Bunionectomy	
	Suzetrigine N=447	Placebo N=223	Suzetrigine N=426	Placebo N=216
With Rescue Imputation (monotherapy)				
Median time (minutes)	119	480	240	480
95% CI	(90, 180)	(477, 705)	(117, 477)	(476, 716)
Nominal *P* value vs. placebo* (Log rank test)	<0.0001	--	0.0016	--
Without Rescue Imputation (representative of multimodal therapy in real-world setting)				
Median time (minutes)	91	180	122	180
95% CI	(89, 116)	(175, 235)	(115, 177)	(120, 245)
Nominal *P* value vs. placebo† (Log rank test)	<0.0001	--	0.0353	--

Suzetrigine was not superior to HB/APAP

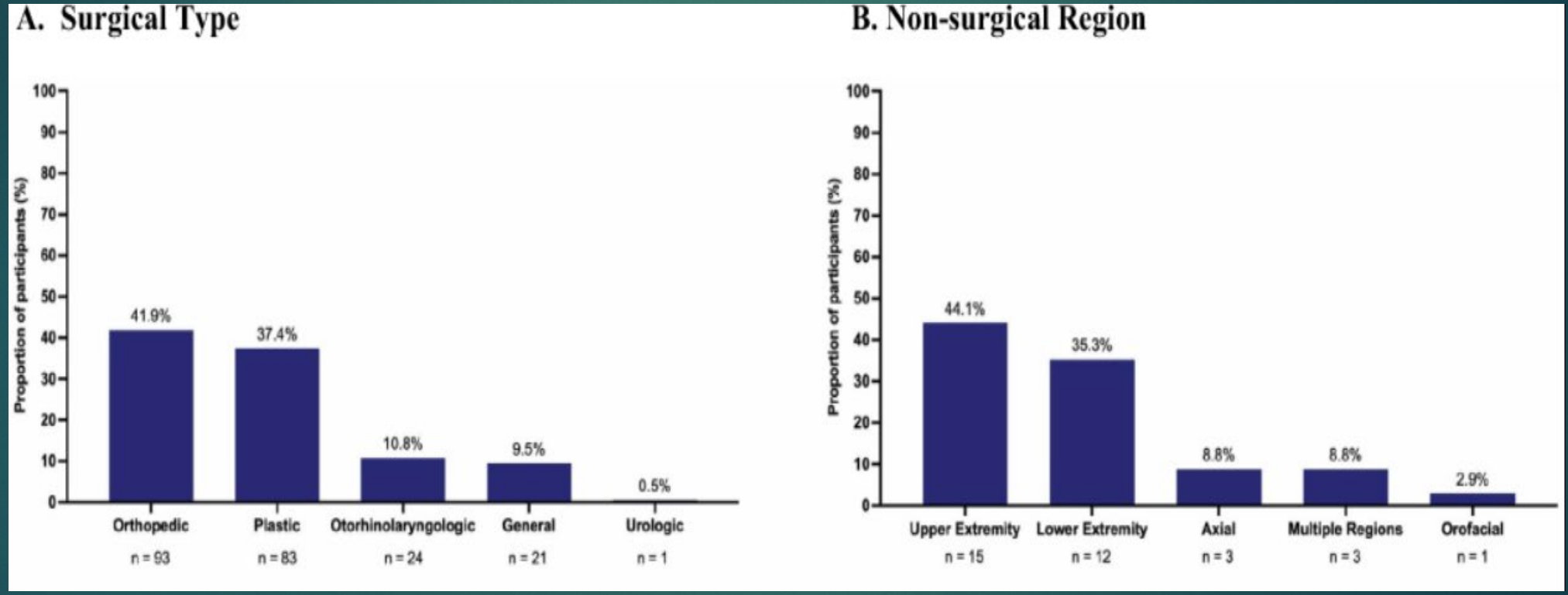
	Abdominoplasty		Bunionectomy	
	Suzetrigine N=447	HB/APAP N=448	Suzetrigine N=426	HB/APAP N=431
With Rescue Imputation (monotherapy)				
LS mean (SE)	118.4 (4.3)	111.8 (4.3)	99.9 (4.5)	120.1 (4.5)
LS mean difference from HB/APAP	6.6	--	-20.2	--
95% CI	(-5.4, 18.7)	--	(-32.7, -7.7)	--
P value vs. HB/APAP	0.2781	--	0.0016	--
Without Rescue Imputation (representative of multimodal therapy in real-world setting)				
LS mean (SE)	153.0 (4.5)	141.0 (4.5)	128.8 (4.7)	140.6 (4.7)
LS mean difference from HB/APAP	12.0	--	-11.8	--
95% CI	(-0.5, 24.4)	--	(-24.8, 1.2)	--
Nominal *P* value vs. HB/APAP*	0.0595	--	0.0752	--

Note: Table includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment.
*Analyses for SPID48 compared to HB/APAP without rescue imputation are ad hoc; therefore, *P* values are nominal.

Phase 3 Single Arm Study for Surgical and non-surgical pain

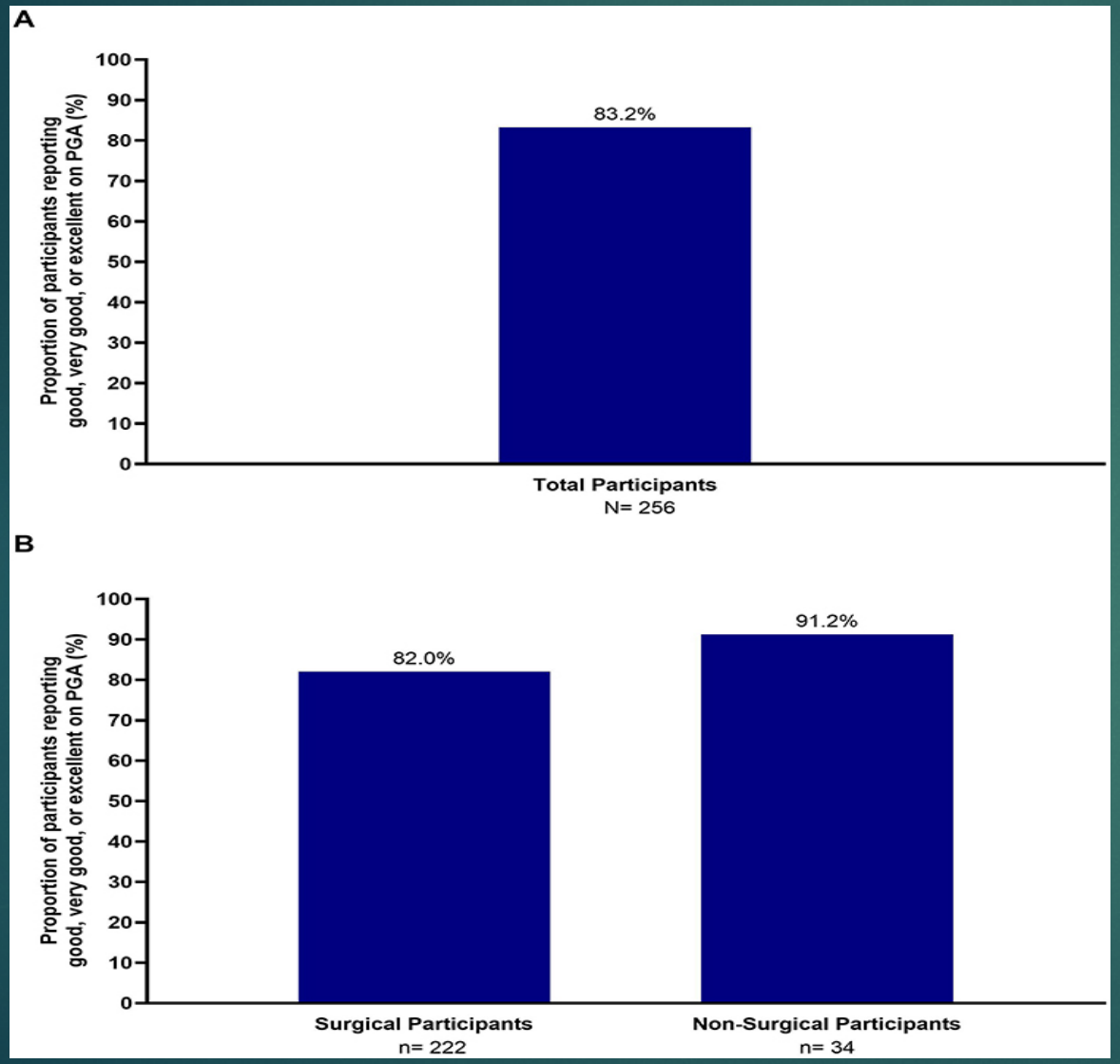
N:257

Mean NPRS : 6.7



McCoun J, Winkle P, Solanki D, Urban J et. al. Journal of Pain Research 2025: 18; 1569-1576

Phase III Single Arm Study for Surgical and non-surgical pain



Global assessment:

Pain relief was good, very good or excellent

McCoun J, Winkle P, Solanki D, Urban J et. al. Journal of Pain Research 2025: 18; 1569-1576

Adverse Effect	Placebo N = 438 n (%)	HB/APAP N = 879 N (%)	Suzetrigine N = 874 N (%)
Nausea	79 (18.0)	209 (23.8)	120 (13.7)
Constipation	33 (7.5)	61 (6.9)	62 (7.1)
Headache	31 (7.1)	77 (8.8)	40 (4.6)
Dizziness	28 (6.4)	47 (5.3)	33 (3.8)
Pruritus	7 (1.6)	30 (3.4)	18 (2.1)
Vomiting	9 (2.1)	37 (4.2)	17 (1.9)

Adverse effects of Suzetrigine

Clinical Use of Suzetrigine

- Loading dose of 100 mg by mouth on an empty stomach
- Continue with 50 mg by mouth every 12 hours with or without food
- Onset on action is 30-60 minutes
- Its half-life is 24 hours
- It is metabolized in the liver by **CYP3A4 enzyme**
- The primary metabolite is M6-SUZ that is less potent than parent drug
- It is excreted in the feces and urine
- Higher doses are not recommended because of its potential side effect on Nav 1.5 that is expressed in the cardiac tissue

Drug-Drug Interactions

Suzetrigne levels can be increased by CYP 3A4 inhibitors and decreased by CYP 3A4 Inducers

1. Decrease in the dose is recommended if used with with CYP 3A4 inhibitor

2. CYP 3A4 inducers can decrease the efficacy of Suzetrigine

3. Female patients should be advised to use additional contraceptive methods if they are using hormonal contraceptives containing progestins other than levonorgestrel and norethidrone. Suzetrigine itself is a CYP3A4 enzyme inducer

4. This can speed up the metabolism of some of these oral contraceptives and make them ineffective.

Conclusion

Positive Points

1. It is a **non-opioid** analgesic
2. It is given orally
3. It needs to be taken on an empty stomach
4. It is given every 12 hours
5. Analgesia is similar to hydrocodone
6. There is no addiction potential
7. Side effect profile is better than opioids
8. It will be a useful agent for **multimodal analgesic** therapy

Negative Points

1. It **will not** replace **opioid** for acute pain
2. Drug drug interactions can cause problems
3. It is expensive. Each pill costs $15.50.
4. It is not covered by Insurance
5. If covered, it is a non-preferred drug
6. Co-pay is higher
7. Clinical trial was conducted only for 14 days
6. Long-term side effects?
8. Counselling for additional contraception is needed in childbearing age women

This novel non-opioid analgesic with comparable analgesia to opioids and lack of addiction potential could possibly help alleviate the opioid crisis!!!!

Is our euphoria premature?

Questions

Thank you!!!!