Suzetrigine for Acute Pain: Effectiveness and Value

Draft Evidence Report

December 9, 2024

Prepared for

©Institute for Clinical and Economic Review, 2024

ICER Staff and Consultants	The University of Colorado Modeling Group
David M. Rind, MD, MSc Chief Medical Officer Institute Clinical and Economic Review **Dmitriy Nikitin, MSPH** Senior Research Lead Institute for Clinical and Economic Review **Woojung Lee, PharmD, PhD** Associate Director of Health Economics and Decision Modeling Institute for Clinical and Economic Review **Daniel Ollendorf, PhD, MPH** Chief Scientific Officer and Director of Health Technology Assessment Methods and Engagement Institute for Clinical and Economic Review	**Brett McQueen, PhD** Associate Professor, Department of Clinical Pharmacy University of Colorado Anschutz Medical Campus **Michael J. DiStefano, PhD** Assistant Professor, Department of Clinical Pharmacy University of Colorado Anschutz Medical Campus **Antal Zemplenyi, PhD** Visiting Research Associate, University of Colorado Anschutz Medical Campus *The role of the University of Colorado is limited to the development of the cost-effectiveness model, and the resulting ICER report does not necessarily represent the view of the University of Colorado.*

DATE OF PUBLICATION: December 9, 2024

How to cite this document: Rind DM, McQueen B, Nikitin D, Lee W, DiStefano MJ, Raymond F, Zemplenyi A, Ollendorf D. Suzetrigine for Acute Pain; Draft Evidence Report. Institute for Clinical and Economic Review, December 9, 2024. https://icer.org/assessment/acute-pain-2025/

David Rind served as the lead author for the report. Dmitriy Nikitin led the systematic review and authorship of the comparative clinical effectiveness section of this report with assistance from Finn Raymond and Sol Sanchez. Brett McQueen, Antal Zemplenyi and Michael Distefano developed the cost-effectiveness model and authored the corresponding sections of the report. Woojung Lee conducted analyses for the budget impact model. Daniel Ollendorf provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Temiwunmi Shobanke, Kelsey Gosselin, Anna Geiger, Marie Philips and Yasmine Kayali for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs. For more information about ICER, please visit www.icer.org.

The funding for this report comes from non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers (PBMs), or life science companies. ICER receives approximately 23% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

About the Midwest CEPAC

The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. The Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The Midwest CEPAC Panel is an independent committee of medical evidence experts from across Midwest, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about the Midwest CEPAC is available at https://icer.org/who-we-are/people/independent-appraisal-committees/midwest-comparative-effectiveness-public-advisory-council-m-cepac/

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:

Expert Reviewers

Benjamin Friedman, MD
Professor of Emergency Medicine
Montefiore-Einstein University
Dr. Benjamin Friedman has no relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous 36 months from health care manufacturers or insurers.

Sergey Motov, MD
Professor of Emergency Medicine
SUNY Downstate Health Sciences University
Dr. Sergey Motov has received honoraria in excess of $5,000 dollars from Vitalis, Inc.

Kit Simpson, DrPH
Professor of Health Care Leadership and Management
Medical University of South Carolina
Dr. Kit Simpson has no relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous 36 months from health care manufacturers or insurers.

Nicole Hemmenway
Chief Executive Officer
US Pain Foundation
Nicole Hemmenway is an employee of the US Pain Foundation. The US Pain Foundation receives greater than 25% of funding from health care companies, industry groups, family foundations, and individual donors.

Cindy Steinberg
Director of Advocacy and Policy
US Pain Foundation
Cindy Steinberg is an employee of the US Pain Foundation. The US Pain Foundation receives greater than 25% of funding from health care companies, industry groups, family foundations, and individual donors.

None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of the draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from who we requested input from, or who have submitted public comments so far, please visit: https://icer.org/wp-content/uploads/2024/12/ICER_Acute-Pain_Stakeholder-List_For-Publication_120924.pdf

Table of Contents

Executive Summary ES1
1. Background 1
2. Patient and Carer Perspectives 3
Health Equity Considerations 4
3. Comparative Clinical Effectiveness 6
3.1. Methods Overview 6
Scope of Review 6
Evidence Base 6
3.2. Results 8
Clinical Benefits 8
Harms 13
Qualitative Overview of Harms of Short-term Use of NSAIDs and Opioids 14
Uncertainty and Controversies 15
Additional Stakeholder Input 16
3.3. Summary and Comment 17
Subgroup Analyses and Heterogeneity 19
4. Long-Term Cost Effectiveness 20
4.1. Methods Overview 20
4.2. Key Model Assumptions and Inputs 21
Clinical Inputs 23
Health State Utilities 23
Cost Inputs 24
4.3. Results 24
Base-Case Results 24
Sensitivity Analyses 25
Scenario Analyses 27
Threshold Analyses 28
Model Validation 28
Uncertainty and Controversies 29

4.4 Summary and Comment 30
5. Benefits Beyond Health and Special Ethical Priorities 31
6. Health Benefit Price Benchmark 33
7. Potential Budget Impact 34
7.1. Overview of Key Assumptions 34
7.2. Results 35
References 37
A. Background: Supplemental Information A1
A1. Definitions A1
A2. Potential Cost-Saving Measures in Acute Pain A2
A3. Patient Input on Clinical Trial Design A3
B. Patient Perspectives : Supplemental Information B1
B1. Methods B1
C. Clinical Guidelines C1
American Pain Society, American Society of Regional Anesthesia, and American Society of Anesthesiologists C1
Centers for Disease Control and Prevention C1
Society of Hospital Medicine C2
D. Comparative Clinical Effectiveness: Supplemental Information D1
D1. Detailed Methods D1
PICOTS D1
Data Sources and Searches D6
Study Selection D10
Data Extraction D10
Evaluation of Clinical Trial Diversity D17
Results United States Population D18
Results: Bunionectomy D19
Results: Abdominoplasty D19
Assessment of Level of Certainty in Evidence D20
Assessment of Bias D20
D2. Network Meta-Analysis Methodology and Results D20

NMA Methods D21
Sensitivity Analyses D31
NMA Limitations D32
D3. Evidence Tables D33
D4. Ongoing Studies D45
D5. Previous Systematic Reviews and Technology Assessments D47
Cochrane Review: Single Dose Analgesics for Acute Postoperative Pain in Adults D47
E. Long-Term Cost-Effectiveness: Supplemental Information E1
E1. Detailed Methods E1
Description of evLY Calculations E2
Target Population E2
Treatment Strategies E3
Model Structure E3
E2. Model Inputs and Assumptions E3
Model Inputs E3
E3. Results E6
E4. Sensitivity Analyses E6
E5. Heterogeneity and Subgroups E9
Prior Economic Models E9
F. Potential Budget Impact: Supplemental Information F1
Methods F1

List of Acronyms and Abbreviations Used in this Report

AEs	Adverse events
AIAN	American Indian or Alaskan Native
APAP	Acetaminophen
APP	Acute postoperative pain
BID	Twice a day
BMI	Body Mass Index
CDR	Clinical Trial Diversity Rating
CE	Cost-effectiveness
CI	Confidence interval
CV	Cardiovascular
DPSGC	Diclofenac Potassium liquid filled Soft Gelatin Capsule
EA	Epidural analgesia
EQ-5D	EuroQol-5 Dimension mapping tool
ER	Extended release
evLYs	Equal-value life year
FDA	Food and Drug Administration
HB	Hydrocodone bitartrate
HB/APAP	Hydrocodone bitartrate/acetaminophen
HCl	Hydrochloride
HIDI	Health Improvement Distribution Index
IQR	Interquartile range
IR	Immediate release
LSM	Least squares mean
LYs	Life years
MAT	Medication-assisted therapy
MCID	Minimum clinically important difference
mg	Milligram
N	Number of participants
NA	Not applicable
NC	Not calculated
NE	Not estimated
NHPI	Native Hawaiian or Pacific Islander
NMA	Networking meta-analysis
NNT	Number needed to treat
NPRS	Numeric Pain Rating Scale
NR	Not reported
NRS	Numerical Rating Scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
OUD	Opioid use disorder
PDRR	Participant to Disease-prevalence Representation Ratio
PGA	Patient Global Assessment
PO	Per oral
Q12H	Every 12 hours
Q24H	Every 24 hours
Q4-6h	Every four to six hours
Q6H	Every six hours
QALY	Quality-adjusted life year
SC	Subcutaneous

SD	Standard deviation
SE	Standard error
SPID	Sum of the pain-intensity difference
SPID48	Sum of the pain-intensity difference from 0 up to 48 hours
TID	Three times a day
US	United States
VAS	Visual Analog Scale
VRS	Verbal Categorical Rating Scale

Executive Summary

One consensus working definition of acute pain is "the physiologic response to and experience of noxious stimuli that can become pathologic, is normally sudden in onset, time limited, and motivates behaviors to avoid potential or actual tissue injury."[1] Acute pain is ubiquitous though it frequently does not require specific treatment. A retrospective cross-sectional study using two nationally representative datasets from 2019 estimated that 80.2 million patients in the US annually experience pain requiring prescription medication treatment for less than three months.[2]

In the postoperative setting, many patients are treated with opioid analgesics to manage their pain.[3] Opioids can have important side effects including sedation, respiratory depression, confusion, falls, and constipation, but a primary concern with opioid prescriptions for acute pain is the risk of developing persistent opioid use and/or opioid use disorder (OUD).[4] This risk is uncertain and can vary widely, in part based on the definition used and underlying patient and medication risk factors.[5-7] It is estimated that approximately 108,000 people in the US died from opioid overdoses in 2022 and that nearly 15,000 of those deaths involved prescription opioids.[8] An analysis from 2017 found that annual health care costs from OUD were nearly $35 billion, criminal justice costs (including lost productivity of those incarcerated) were $23 billion, and other lost productivity was more than $92 billion.[9]

Given concerns about opioids, safer analgesic medications could be beneficial. Generally, however, nearly all other systemic analgesics used for acute pain are either nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, and use of more than one pain medication to allow for greater analgesia with fewer side effects is typically recommended.[3] Suzetrigine (VX-548; Vertex Pharmaceuticals) is an oral small-molecule inhibitor of the voltage-gated sodium channel $Na_v1.8$ that has been studied for the treatment of acute post-surgical pain and represents a new class of analgesic medication.[10] The drug is administered every 12 hours. Suzetrigine is currently undergoing Food and Drug Administration (FDA) priority review with a target action date of January 30th, 2025.[11]

In this report, we assess suzetrigine as a treatment for acute pain. Suzetrigine is also being studied for chronic pain but, while that may be a later indication for the drug, it is currently being evaluated by the FDA for acute pain and, as such, this report focuses only on that indication. The evidence for suzetrigine comes primarily from two similar Phase III randomized trials comparing it to placebo and to the opioid hydrocodone 5 mg in combination with acetaminophen 325 mg (HB5/APAP325); one trial included patients after bunionectomy and the other after abdominoplasty. Across the two trials, 873 patients received suzetrigine, 879 patients received HB5/APAP325, and 439 patients received placebo. Patients treated with suzetrigine had greater and faster reductions in pain than those treated with placebo. Suzetrigine appeared to have similar efficacy to HB5/APAP325 for

abdominoplasty, but slower onset of pain relief for bunionectomy. Adverse effects of suzetrigine were similar to placebo and nausea appeared less common than with HB5/APAP325.

We also conducted a network meta-analysis to compare suzetrigine to higher-dose oral opioids and to NSAIDs, both with or without acetaminophen. Confidence intervals were widely overlapping, making it hard to come to definite conclusions about relative efficacy. Rates of development of OUD after short-term administration of opioids for acute pain are uncertain, as are rates of NSAID adverse effects (e.g., acute kidney injury, gastrointestinal bleeding, acute coronary syndrome) when used in the post-operative setting.

We have some uncertainties in assessing the efficacy of suzetrigine because of lack of data on use of rescue medication in the Phase III trials as well as lack of clarity on how pain scores were imputed after rescue medication. This information is likely to become available when the trials are published. Additionally, for comparison with opioids, the dose of HB/APAP used in the clinical trials was lower and administration every six hours less frequent than many patients would be treated with postoperatively. We have concerns about as-yet-unknown harms of suzetrigine as we would for any drug with a new mechanism of action; we are particularly concerned about whether there could be an increased risk for cardiac arrhythmias given inhibition of $Na_v1.8$ and possible acute renal injury given a study in people with diabetes.[12]

The above uncertainties inform our ratings that the evidence for suzetrigine for the treatment of acute pain in comparison with no systemic treatment, in comparison with opioid analgesics, and in comparison with NSAIDs are all promising but inconclusive (**P/I**). Our reasoning for these ratings differs for each comparison and is discussed in detail in Section 3.3 along with consideration of which patients might be more appropriate for early treatment with suzetrigine should it be approved. As safety data become available with real world use, assessment of net benefit is likely to change.

We conducted an economic analysis that modeled the long-term cost-effectiveness of one week of treatment with suzetrigine compared with HB5/APAP325 using a placeholder price for suzetrigine of $420 for a one-week course. The model was primarily driven by risks of OUD from this short course of an opioid analgesic. Due to the lifetime costs and harms of OUD, and assuming a wide range of estimates of OUD risk, treating with suzetrigine would be slightly cost-saving relative to opioid therapy while producing greater health benefits ("dominant"). The cost effectiveness of suzetrigine largely depends on the actual risk of OUD from a one-week course of an opioid analgesic or suzetrigine.

1. Background

While definitions and estimates of prevalence vary, one consensus working definition of acute pain is "the physiologic response to and experience of noxious stimuli that can become pathologic, is normally sudden in onset, time limited, and motivates behaviors to avoid potential or actual tissue injury."[1] The meaning of "time limited" also varies, and in the prior working definition the following was noted: acute pain typically lasts up to seven days; prolongations up to 30 days are common; prolongations beyond 90 days reflect chronic pain; between 30 and 90 days, pain may be "subacute" but this is not well defined.[1]

Acute pain is ubiquitous though it frequently does not require specific treatment or drug therapy. In medical care settings, pain is particularly common. In a series of surgical patients, only 10% had no pain, while 12% had severe-to-extreme pain at discharge and 54% had moderate-to-severe pain at discharge.[13] Pain is also common in emergency department settings and on inpatient medical services.[14,15] A retrospective cross-sectional study using two nationally representative datasets from 2019 estimated that 80.2 million patients in the US annually experience pain requiring prescription medication treatment for less than three months.[2]

In the postoperative setting, many patients are treated with opioid analgesics.[3] Opioids can have important side effects including sedation, respiratory depression, confusion, falls, and constipation, but a primary concern with opioid prescriptions for acute pain is the risk of developing persistent opioid use and/or opioid use disorder (OUD).[4] This risk is uncertain and can vary widely, in part based on the definition used and underlying patient and medication risk factors.[5-7] A series in surgical patients found that 3.1% of patients who had not previously used opioids continued to use opioids for more than 90 days after major elective surgery.[16] However, this does not distinguish between continued use due to continued pain and continued use because of OUD.

It is estimated that approximately 108,000 people in the US died from opioid overdoses in 2022 and that nearly 15,000 of those deaths involved prescription opioids.[8] However, the number of deaths involving prescription opioids has been generally decreasing since 2017.[17] An analysis from 2017 found that annual health care costs from OUD were nearly $35 billion, criminal justice costs (including lost productivity of those incarcerated) were $23 billion, and other lost productivity was more than $92 billion.[9]

Given concerns about opioids, safer analgesic medications could be beneficial. Generally, however, nearly all other systemic analgesics used for acute pain are either nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, and use of more than one pain medication to allow for greater analgesia with fewer side effects is typically recommended.[3] Suzetrigine (VX-548; Vertex Pharmaceuticals) is an oral small-molecule inhibitor of the voltage-gated sodium channel $Na_v1.8$ that has been studied for the treatment of acute post-surgical pain and represents a new class of

analgesic medication.[10] The drug is administered every 12 hours. Suzetrigine is currently undergoing FDA priority review with a target action date of January 30th, 2025.[11]

Table 1.1 Intervention of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Suzetrigine	Selective inhibitor of $Na_v1.8$	Oral	100 mg oral loading dose, subsequent 50 mg maintenance dose every 12 hours

mg: milligrams

2. Patient and Carer Perspectives

While many patients and patient groups are more focused on issues around chronic pain, we heard from multiple stakeholders about the need for safer medications to treat moderate-to-severe acute pain. We also heard that concerns around opioids are leading to undertreatment of acute pain in some patients who could benefit from short courses of opioids, but also heard that because opioids are inexpensive and widely available, they continue to be overused in other settings. Overall, though, we heard that the frequency with which opioids are being prescribed and the number of doses being prescribed have both dramatically decreased over the past decade.

We heard widely differing views on the risk of OUD after limited treatment with opioids. Some stakeholders emphasized individual anecdotes related by patients or their families where addiction seemed to occur after a single dose of an opioid medication. Others stressed that studies suggest very low rates of opioid addiction in patients given less than a week of treatment. We also heard about fear of addiction among patients and their caregivers. We spoke with one patient with recent acute pain who, despite receiving good pain relief with opioids after various surgeries, and despite having no side effects from opioids or difficulties with discontinuation, would have preferred a medication with no addiction risk even if it were somewhat less effective for pain control.

We heard that different types of pain elicit different responses and that this has implications for functioning during pain. The example was provided of different types of headaches where patients with migraine try to limit activity while patients with cluster headache tend to pace.

We heard from patients and clinicians that there are a limited number of options for treating acute pain, and so expanding the “toolbox” would be beneficial. We heard that some of the concerns with the use of opioids that are unrelated to OUD, such as sedation, can be beneficial in patients with severe time-limited causes of pain, and that adverse effects of opioids, including confusion and constipation, can be particularly problematic for some groups of patients such as older patients. We also heard about the problems with NSAIDs, which can also be worse in older patients, including risks for gastrointestinal bleeding, renal injury, and myocardial infarction.

We heard that education for patients around appropriate use of opioid pain medication may reduce the risk of developing OUD. For instance, counseling that opioids should only be used when other medications are not sufficiently effective.

We heard the education for providers around the efficacy of multimodal pain management would improve clinical decision making and outcomes.

We heard that inadequate treatment for acute pain can lead to patients seeking emergency care that is time-consuming for the patient, resource-intensive for the health care system, and costly for all involved.

We heard that the availability of additional pain medication options may be particularly important for patients with a prior history of OUD. In such patients, even short courses of opioids can lead to recurrence of OUD. However, we also heard from a patient with chronic pain who reports long-term benefits with opioid treatment without development of OUD. This patient felt that only opioid treatment allowed them to function.

Multiple stakeholders described that having an oral medication that is more potent than NSAIDs would provide an option for treatment that currently is really only filled by opioids. There was hope that suzetrigine might bridge this efficacy gap.

The individual patients we spoke with described mixed experiences with post-surgery pain management in the setting of having chronic pain. One patient faced issues with inadequate pain control and hesitancy from nurses to provide sufficient opioid medication, while another patient had good results using oxycodone and other medications with effective pain relief and limited side effects. Both of these patients expressed openness to exploring non-opioid pain management alternatives that could provide similar benefits without the risks of addiction.

Health Equity Considerations

We heard a number of health equity concerns from patient groups and providers:

- As discussed above, we heard that because opioids are inexpensive and widely available, in some underserved settings they may be preferentially prescribed, placing underserved patients at higher risk of developing OUD than is warranted. In contrast, we also heard that pain is less adequately managed in racial and ethnic minority groups and that patients from such groups are less likely to be prescribed opioid medications even when these medications would be appropriate.
- We heard of concerns that undertreatment of pain may relate to clinician implicit or explicit bias including concerns around pain tolerance and OUD risk in specific patient groups, and that education to improve cultural competency in providers is needed. We heard that stigma around risk of OUD in specific patient groups may affect both provider willingness to prescribe opioids and patient willingness to be treated with opioids.
- We heard that underserved communities are less likely to have access to multimodal pain management that may include physical therapy, regional anesthesia, and/or nerve blocks. This may occur for economic reasons and because of limited local availability of such therapies.

- We heard that undertreatment of pain can have important short-term and long-term psychological consequences including anxiety, depression, and ongoing mental health challenges.
- We heard that pain medication side effects may be particularly problematic for older individuals and for those with disabilities.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review are described in Supplement D1. A research protocol is published on Open Science Framework and is registered with PROSPERO (CRD42024577939).

Scope of Review

We aimed to assess the clinical effectiveness and safety of suzetrigine as an add-on to non-systemic treatments for patients with moderate to severe acute pain, and compare the therapy to receiving no systemic therapy for pain (as represented by placebo arms in clinical trials), non-opioid analgesics (including NSAIDs, acetaminophen, or a combination of both), or opioid analgesics alone or in combination with acetaminophen.

The scope of review examined patient important outcomes that included pain control, physical functioning, patient-assessed quality of life, and short and long-term adverse events. The full scope of our review is provided in Supplement D1.

Evidence Base

Our evidence base for this review included five clinical trials within the suzetrigine clinical development portfolio: two pivotal trials, NAVIGATE-1 and NAVIGATE-2; one single-arm Phase III trial; and two Phase II trials.[10,18] Four of the trials provided direct evidence of the comparative clinical effectiveness and safety of suzetrigine against placebo and hydrocodone bitartrate 5 mg/acetaminophen 325 mg (HB5/APAP325). Study results from NAVIGATE-1 and 2 are not currently presented in a peer-reviewed article and were accessed as a conference presentation that was given during the annual American Society of Anesthesiologists conference in October 2024. Other than for examining harms, we excluded data from the lower suzetrigine doses tested in Phase II trials since these doses were not carried forward to Phase III trials.

NAVIGATE-1 and 2 were Phase III trials that evaluated the efficacy and safety of suzetrigine oral tablets (100 mg then 50 mg every 12 hours) in adults who underwent bunionectomy and abdominoplasty procedures, respectively. Patients were eligible for these studies if they had post-operative acute pain that was moderate or severe (a score of four or greater out of ten on the Numeric Pain Rating Scale [NPRS]; see Supplement A1 for additional definitions). Suzetrigine was administered as a post-operative analgesic and compared against a combination capsule of HB5/APAP325 as well as placebo, both administered every six hours. In the bunionectomy trial, patients received randomized treatment within nine hours after resolution of a popliteal sciatic

nerve block with ropivacaine. Ropivacaine is a local anesthetic that inhibits sodium channels less selectively than suzetrigine, a targeted $Na_v1.8$ channel inhibitor.[19] Trial participants were assessed on the drug's impact on pain intensity as measured by the NPRS and time-weighted sum of the pain intensity difference from 0 to 48 hours following surgery (SPID48). SPID48 calculates the difference in pain scores at prespecified time points versus baseline score and is cumulative for all measurements taken within the follow-up period of 48 years. A greater SPID48 value represents greater reduction in pain intensity. Suzetrigine was also studied in a single-arm trial in a broader population that included patients undergoing different types of surgery (e.g., orthopedic, plastic) as well as non-surgical pain.

We conducted a network meta-analysis (NMA) to compare suzetrigine to higher-dose oral opioids and to NSAIDs, both with or without acetaminophen. This analysis included an additional eight randomized controlled trials and seven interventions. (Supplement D2.3 for Baseline Characteristics) (Supplement D2 for additional NMA analysis details).

Table. 3.1. Overview of Key Studies for Suzetrigine[18]

Trial		NAVIGATE-1	NAVIGATE-2
		Bunionectomy	**Abdominoplasty**
N		**1073**	**1118**
Arms		-SUZ orally (100 mg followed by 50 mg every 12 hours) -HB/APAP orally (5 mg/325 mg every six hours) -Placebo orally	
Age, mean		48	42
Sex, %	**Female**	85	98
	Male	15	2
Race, %	**White**	71	70
	Black or African American	24	27
	Other*	5	4
NPRS, mean		6.8	7.4
NPRS category, %	**<8**	64	51
	≥8	36	49
VRS, %	**Moderate**	67	59
	Severe	33	41

HB/APAP: hydrocodone bitartrate/acetaminophen, mg: milligram, N: number of participants, NPRS: Numeric Pain Rating Scale, SD: standard deviation, VRS: Verbal Categorical Rating Scale

*Other includes Asian, American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, Other, Multiracial, or Missing.

Evaluation of Clinical Trial Diversity

We rated the demographic diversity (race/ethnicity, sex, age) of the participants in the pivotal suzetrigine trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool (Table 3.2).[20] See Supplement D1 for full details of CDR methods and results.

Table. 3.2. Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)

Trial	Race and Ethnicity	Sex	Age (Older Adults)
NAVIGATE-1	Poor	Poor	Not Rated
NAVIGATE-2	Poor	Poor	Not Rated

Race and Ethnicity: The pivotal trials achieved adequate representation of White and Black/African American participants relative to US census data and surgery-specific prevalence estimates. However, the trials received a Poor rating (6/12 points) due to insufficient reporting of Asian and Hispanic/Latino participant demographics.

Sex: Most participants in both trials were women (85-98%). While this matches the typical gender ratio for these elective surgeries (abdominoplasty and bunionectomy), the drug is intended to treat acute pain - a condition that affects men and women equally. Due to this underrepresentation of men, both trials received a Poor rating in this category when compared to US census data.

Age: Neither trial reported the proportion of trial participants that were ≥65 years old and were not rated on this category.

3.2. Results

Clinical Benefits

Reduction In Pain

Post-surgery, patients were assessed on the intensity of their pain using the Numeric Pain Rating Scale. This score was presented in several formats across the randomized controlled trials: a time-weighted sum of the pain intensity difference from 0 to 48 hours (SPID48) as the primary efficacy endpoint, other measurements took the form of a mean change in NPRS from baseline, a time-to analysis in drop of two points on the NPRS, and the proportion of patients that achieved a 30, 50, and 70% reduction in pain. In the single-arm study, trial participants were assessed on the drug's perceived efficacy on managing pain via the Patient Global Assessment over 14 days of treatment and on adverse events over 28 days.

Suzetrigine versus No Systemic Therapy (Placebo)

Patients treated with suzetrigine had a higher SPID48 (greater reduction in pain over 48 hours) than those in the placebo arm in both the bunionectomy and abdominoplasty trials (Table 3.3). When patients took rescue medication (ibuprofen) for additional pain relief, their SPID48 scores were imputed for six hours afterward using the last observation carried forward approach. This means that if a trial participant took ibuprofen, their most recent pain score was used as a placeholder for the next six hours of data collection, assuming no change in pain levels. Analysis showed that including the pain-relieving effects of ibuprofen (without imputation) resulted in higher SPID48 values in both the suzetrigine and placebo groups. Suzetrigine demonstrated statistically significant improvement in SPID48 compared to placebo.

In both trials, suzetrigine had a more rapid onset of pain relief via decrease in the NPRS of two points or greater, a threshold considered to be clinically meaningful. In the abdominoplasty trial, it took patients treated with suzetrigine a median of approximately two hours to achieve a ≥2 decrease in NPRS, versus a median of eight hours for placebo. Patients in the post-bunionectomy population achieved a ≥2 decrease in NPRS within a median of four hours in the suzetrigine arm versus eight hours in the placebo arm.

The proportions of patients who achieved a 30, 50, and 70% reduction in pain were not publicly reported in the current presentation of NAVIGATE-1 and 2 trial evidence. A 30% reduction in pain is generally considered clinically meaningful, although there is no universally agreed upon threshold.[21-23] In previous Phase II trials, a higher percentage of patients in the suzetrigine group reached this threshold compared to the placebo group: 61% versus 48% for abdominoplasty, and 83% versus 68% for bunionectomy.

In a separate single-arm trial that evaluated suzetrigine's effectiveness across both surgical and non-surgical pain conditions over 14 days of follow-up, 83% of the 256 participants rated the treatment as good, very good, or excellent using the Patient Global Assessment.

Table 3.3. Direct Evidence: Suzetrigine Versus Placebo[18]

Trial		NAVIGATE-1		NAVIGATE-2	
		Bunionectomy		Abdominoplasty	
Arms		SUZ	Placebo	SUZ	Placebo
N		426	216	447	223
With Rescue Imputation (monotherapy)					
SPID48	LSM (SE)	99.9 (4.5)	70.6 (6.3)	118.4 (4.3)	70.1 (6.1)
	LSM difference vs. placebo (95% CI)	29.3 (14, 44.6)		48.4 (33.6, 63.1)	
	P value	0.0002		<0.0001	
Time to ≥2-point reduction in NPRS, minutes	Median (95% CI; P value)	240 (117, 477)	480 (476, 716)	119 (90, 180)	480 (477, 705)
	P value*	0.0016		<0.0001	
Without Rescue Imputation (representative of multimodal therapy in real-world setting)					
SPID48	LSM (SE)	128.8 (4.7)	100.1 (6.6)	153 (4.5)	105 (6.4)
	LSM difference vs. placebo (95% CI)	28.8 (12.9, 44.6)		47.7 (32.4, 62.9)	
	P value†	0.0004		<0.0001	
Time to ≥2-point reduction in NPRS, minutes	Median (95% CI; P value)	122 (115, 177)	180 (120, 245)	91 (89, 116)	180 (175, 235)
	P value†	0.0353		<0.0001	

CI: confidence interval, LSM: least squares mean, N: number of participants in the analysis set, NPRS: numeric pain rating scale, SE: standard error, SPID48: time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours

*P value for the endpoint of time to ≥2-point reduction in NPRS from baseline is nominal due to the break in hierarchical testing.

†Analyses without rescue imputation are ad hoc; therefore, P values are nominal.

Suzetrigine versus Hydrocodone Bitartrate/Acetaminophen

The efficacy of suzetrigine was compared to hydrocodone bitartrate 5 mg/acetaminophen 325 mg (HB5/APAP325) as a secondary outcome in the NAVIGATE-1 and 2 trials. HB5/APAP325 was superior to suzetrigine in the bunionectomy trial in the imputed analysis of monotherapy but this difference was not statistically significant when analyzed data included rescue therapy with ibuprofen (Table 3.3). No statistically significant differences were seen in the abdominoplasty trial. Of note, although non-inferiority margins were not specified, it does not appear that these trials were powered *a priori* as non-inferiority trials. A time-to pain reduction analysis comparing suzetrigine and HB5/APAP325 was not reported.

Table 3.4. Direct Evidence: Suzetrigine Versus HB/APAP[18]

Trial		NAVIGATE-1		NAVIGATE-2	
		Bunionectomy		Abdominoplasty	
Arms		SUZ	HB/APAP	SUZ	HB/APAP
N		426	431	447	448
With Rescue Imputation (monotherapy)					
SPID48	LSM (SE)	99.9 (4.5)	120.1 (4.5)	118.4 (4.3)	111.8 (4.3)
	LSM difference vs. HB/APAP (95% CI)	-20.2 (-32.7, -7.7)		6.6 (-5.4, 18.7)	
	P value	0.0016		0.2781	
Without Rescue Imputation (representative of multimodal therapy in real-world setting)					
SPID48	LSM (SE)	128.8 (4.7)	140.6 (4.7)	153.0 (4.5)	141.0 (4.5)
	LSM difference vs. HB/APAP (95% CI)	-11.8 (-24.8, 1.2)		12 (-0.5, 24.4)	
	P value*	0.0752		0.0595	

CI: confidence interval, HB/APAP: hydrocodone bitartrate/acetaminophen, LSM: least squares mean, N: number of participants in the analysis set, NPRS: numeric pain rating scale, SE: standard error, SPID48: time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours

*Analyses without rescue imputation are ad hoc; therefore, P values are nominal.

Suzetrigine versus Higher Dose Opioids

In typical clinical practice of treating moderate to severe acute pain, patients may receive opioid doses that are more potent than what was studied in the suzetrigine clinical trials. We evaluated the comparative efficacy of suzetrigine to doses of opioids greater than HB5/APAP325 via a network meta-analysis. The higher dose opioids in the network were pooled using SPID48 values from their respective trials and included study arms such as oxycodone 15 mg/acetaminophen 650 mg every 12 hours and HB/APAP 7.5/325 mg every four to six hours (Supplement Table D2.2 for all included interventions).

Table 3.5 provides an overview of the calculated effect sizes (Cohen's D) between the analgesic classes. A higher effect size value indicates a greater difference between two groups on the SPID48 and greater magnitude of pain relief. Suzetrigine showed similar effectiveness to opioids in treating moderate to severe acute pain, with no statistically significant differences between treatments, however confidence intervals were wide. A general rule of thumb for interpreting Cohen's D values is that 0.20, 0.50, and 0.80 represent small, medium, and large effect sizes, respectively.[24] When compared to placebo, suzetrigine demonstrated a modest benefit, with an effect size of 0.43.

Table 3.5. NMA Results (Relative Treatment Effect Size on SPID48 Outcome)

High-Dose Opioid				
0.08 (-0.13, 0.27)	**Suzetrigine**			
0.09 (-0.08, 0.29)	0.02 (-0.12, 0.18)	**Low-Dose Opioid**		
0.16 (-0.05, 0.38)	0.08 (-0.12, 0.3)	0.07 (-0.15, 0.26)	**NSAID**	
0.5 (0.35, 0.65)	**0.43 (0.28, 0.57)**	**0.41 (0.26, 0.53)**	**0.34 (0.19, 0.49)**	**Placebo**

NSAID: Nonsteroidal anti-inflammatory drugs

Standardized mean differences greater than 0 favor the column-defining treatment. Significant results are in bold.

Suzetrigine versus NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAID) are a class of drugs that are commonly used in combination with acetaminophen as a multimodal non-opioid alternative to treating moderate to severe acute pain. Given the absence of NSAIDs as comparators in the suzetrigine clinical development program, we conducted an indirect comparison between suzetrigine and NSAIDs as a drug class on reduction in pain intensity as measured by SPID48. The list of NSAIDs included several formulations and dosages of diclofenac, indomethacin, and celecoxib (Supplement Table D2.2 for full list of interventions).

Based on indirect evidence from the network meta-analysis, suzetrigine showed comparable to NSAIDs in reducing pain intensity, however confidence intervals were wide (Table 3.5).

Other Outcomes

We sought information on suzetrigine's impact on other patient-important outcomes, including quality of life, physical functioning and interference in activities of daily living, development of chronic pain, use of rescue medication, and opioid avoidance.

In its clinical development program for acute pain, the manufacturer of suzetrigine did not include a measurement tool that assessed a patient's physical (e.g., ability to maintain movement and activities of daily living) and mental (e.g., anxiety) quality of life, which are important dimensions of pain when making treatment decisions.[25]

The percentage of trial participants who required rescue medication (ibuprofen) was a measured outcome that was used to impute SPID48 scores, but the percentages themselves were not currently reported in either Phase II or III trials. While opioids are commonly used as rescue medication in trials evaluating non-opioid interventions (e.g., NSAIDs), they were not permitted as rescue medication in these studies. Therefore, the opioid-sparing effects of suzetrigine compared to NSAIDs could not be assessed.

Given the short duration of its trials (two days for efficacy, 14 days for safety), we are not able to assess whether suzetrigine has any impact on the likelihood of patients with acute pain progressing into chronic pain.

Harms

Due to identical study designs and duration of safety data collection (14±2 days after last dose), we pooled the safety data of the four Phase II and III trials of suzetrigine (Table 3.6). Overall, suzetrigine appears to be a tolerable analgesic with a favorable safety profile. The rate of discontinuation due to adverse events was less than one percent across all study arms. Most adverse events were mild or moderate in severity. The two known life-threatening adverse events that occurred in the suzetrigine study arm, pulmonary embolism and anemia, were not considered to be treatment-related.

As expected, the incidence of nausea and vomiting was numerically higher with HB/APAP than with suzetrigine, although measures of statistical significance were not reported. Other reported adverse events were similar between suzetrigine and HB/APAP.

In addition to the four randomized controlled trials, suzetrigine was studied in a single-arm trial (N=256) and reported adverse events over a period of 28±2 days. Approximately two percent of participants discontinued suzetrigine treatment due to an adverse event. These events included accidental overdose, arrhythmia, nausea, rash, and somnolence; all except the case of arrythmia were resolved by end of study.

Due to the short-term duration of all suzetrigine trials, we cannot determine the longer-term impact of extended use on the drug's safety profile.

Table 3.6. Pooled Harms[10,18]

Arm		SUZ	HB/APAP	Placebo
N		**1010**	**1015**	**574**
Any AE, %		41	52	48
Severity of AE, %	**Mild**	27	32	32
	Moderate	13	18	15
	Severe	1	1	1
	Life-threatening*	<1	<1	0
Commonly reported AEs, %	**Nausea**	14	24	20
	Headache	6	8	7
	Constipation	7	7	7
	Dizziness	4	6	7
	Vomiting	2	5	3
Discontinuation due to AEs, %		<1	<1	<1

AE: adverse event, HB/APAP: hydrocodone bitartrate/acetaminophen

*Life-threatening AEs were pulmonary embolism (suzetrigine), anemia (suzetrigine), pulmonary embolism (HB/APAP), and intra-abdominal hematoma (HB/APAP); all were considered unlikely related or not related to study drug.

Note: Pooled data was calculated from two Phase III studies and two Phase II studies, using only the higher SUZ dose from the Phase II studies.

Qualitative Overview of Harms of Short-term Use of Opioids and NSAIDs

Harms of Short-Term Opioid Use

Opioids are not recommended as first-line therapy for many common acute pain conditions such as low back pain, neck pain, and headaches (See Supplement Section C for additional Clinical Guideline recommendations).[26] Compared to NSAIDs or acetaminophen, opioids are associated with increased risks of short-term adverse events including nausea, dizziness, and somnolence.[26] Nausea and vomiting have been identified by patients as the two most impactful adverse events associated with opioid use, with a lesser impact from constipation.[27] Opioid prescriptions for older adults require special consideration due to less predictable treatment effects compared to younger patients and a higher risk of medication reactions due to greater polypharmacy.[28]

Additionally, observational studies have found that opioid use for acute low back pain or postoperative pain is associated with an increased likelihood of developing long-term opioid use, with the risk being greater with higher initial dosages and longer durations of exposure.[26]

Harms of Short-term NSAID Use

Treatment with NSAIDs carries risks of serious harms including gastrointestinal bleeding, acute kidney injury, and cardiovascular events.[29] Risk for adverse gastrointestinal toxicity increases with age, NSAID dose, duration of treatment, prior history of ulcer, and certain concurrent medication use.[30,31] Risk for acute kidney injury increases with age and with severity of chronic kidney disease.[32,33] Risk for cardiovascular events increases with traditional cardiovascular risk factors, NSAID dose, and frequency of NSAID use.[34]

Although NSAID administration is associated with acute kidney injury during a medical admission,[35] data on the exact risk of these harms when NSAIDs are used for postoperative pain are limited.[36] For example, in a trial of intravenous ibuprofen for postoperative pain, serious adverse events were uncommon and similar in the intervention and placebo groups.[37] Similar lack of differences in treatment-related adverse events was seen in a trial comparing diclofenac, ketorolac, and placebo.[38] However, these trials were relatively small and thus unlikely to detect low frequency harms.

Uncertainty and Controversies

- We currently only have top-line results from the Phase III trials of suzetrigine. In the absence of the full peer-reviewed publication, we are uncertain what was considered *a priori* to be meaningful pain reduction. This would be particularly helpful to know, since the comparison with placebo should show improvement beyond a minimum clinically important difference (MCID), and the comparison with HB/APAP could be assessed for noninferiority using that same MCID.

- A peer-reviewed publication would also allow better assessment of the primary outcome of the Phase III trials that imputed pain scores in patients who received rescue medication. Such imputation is potentially fraught, and needs careful review.[39]

- The timing of pain reduction was delayed with suzetrigine in patients who underwent bunionectomy. Although it was hypothesized that this may reflect ongoing pain reduction with the non-selective sodium channel inhibitor ropivacaine (a related mechanism to that of suzetrigine) that had been administered for nerve block,[40] it is possible that suzetrigine pain relief may be slow for some types of pain. This may require additional study.

- Important adverse events are detected frequently after approval and marketing of novel therapeutic agents,[41] and we necessarily have concerns about potentially as-yet-undetected risks with suzetrigine. If approved, suzetrigine would be the first medication targeting $Na_v1.8$, and thus has a novel mechanism of action. We note the following as concerns that can arise with a new mechanism of action:

    - $Na_v1.8$ is encoded by the gene *SCN10A*.[42] Brugada Syndrome is an inherited condition that can result in life-threatening cardiac arrhythmias.[43] Mutations in the *SCN10A* gene have been estimated to be involved in more than 15% of cases of Brugada Syndrome.[44,45]. The postulated mechanism by which the mutations may cause Brugada Syndrome, which involves interactions with a different sodium channel, $Na_v1.5$,[45] is at least somewhat reassuring that an inhibitor of $Na_v1.8$ might not affect the risk of Brugada Syndrome.

    - A Phase II trial studying various doses of suzetrigine for 12 weeks in patients with diabetic neuropathy apparently found decreased creatinine clearance in six of 55 patients in the group treated with 69 mg daily.[12] We have limited information about this, including the degree of renal dysfunction. Additionally, this use of suzetrigine for 12 weeks for chronic pain is distinct from use for 48 hours or for seven days for acute pain and it is possible that this adverse event was due to random chance given that multiple doses and potential adverse events were studied. However, patients with diabetes are at increased risk of kidney injury,[46] and if suzetrigine caused

kidney injury, it occurred at a lower total daily dosage than is being studied for acute pain.

- As is typically the case in studies of medications for post-operative pain, the trials allowed treatment with a rescue medication, in this case ibuprofen. Data on rescue medication use are not yet available, which makes it difficult to determine how much of the effect may be due to rescue treatment. As an example, a patient treated with a relatively ineffective medication for pain who quickly seeks rescue treatment with a very effective medication might appear to have better pain relief than a patient treated with a moderately effective pain medication who delays requesting or never requests the highly effective rescue medication.

- The dose of HB/APAP used in the clinical trials was lower and administration every six hours less frequent than many patients would be treated with postoperatively. Although we attempted to compare suzetrigine to higher doses of opioids using quantitative indirect methods, the results have wide confidence intervals, making it difficult to ascertain the relative efficacy of suzetrigine to opioid analgesics.

- There is uncertainty about the risk of OUD in patients who are treated with a short course of opioid analgesics in a post-operative setting. There is also uncertainty about the risk of specific harms from NSAIDs in this setting.

- There were relatively few men in the trials of suzetrigine. Although we do not anticipate gender differences with either the benefits or harms of suzetrigine, this will be important to evaluate in real world use if suzetrigine is approved.

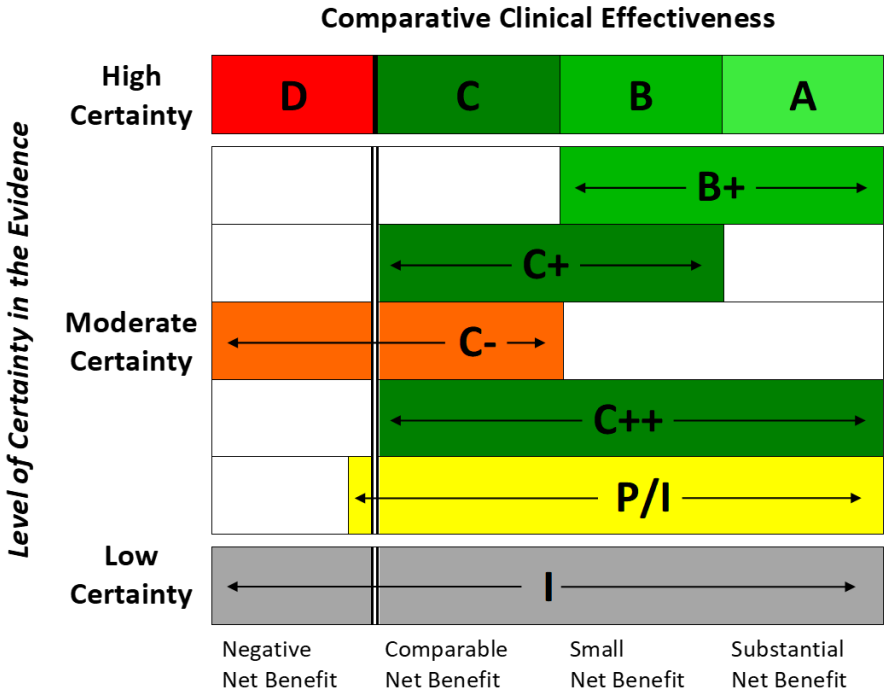
Additional Stakeholder Input

Many clinicians, including pain specialists and emergency physicians, tended to think of treatment of acute pain while the patient was being actively seen in a clinical facility. In those settings, all emphasized multimodality management of pain. Such management was seen as limiting the need for opioid medication and potentially lowering the risk of patients developing chronic pain. We heard of pain services integrated into emergency department management, where patients could be treated with regional nerve blocks using agents with extended duration of action in an attempt to mitigate symptoms on the days when pain would be expected to be most intense.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

We have uncertainties about the efficacy and safety of suzetrigine that affect our evidence ratings against the three comparator options: no systemic therapy; opioid-containing analgesics; and NSAIDs. How these uncertainties apply to each comparison are different, however, and also potentially affect patient groups who might be appropriate, if suzetrigine is approved, to receive suzetrigine before more extensive information becomes available from real world use. We discuss each comparison in turn:

- **No systemic therapy**: Suzetrigine clearly has some efficacy for post-operative pain relief although, as discussed above, our understanding of that efficacy is somewhat limited by as-yet-unavailable information from the Phase III trials on use of rescue medication and imputation of results. Also as discussed above, we have concerns around safety with therapies that have a new mechanism of action. We heard from clinical experts that multi-modal approaches to pain that use non-systemic treatments are often adequate for pain relief, but also that they are excited for the possibility of a new class of medication for pain. While awaiting additional data on safety, we feel that in comparison with no systemic therapy, the evidence for suzetrigine in the treatment of patients with acute pain is promising but inconclusive (**P/I**). Patients for whom earlier use of suzetrigine might be appropriate include those who are not candidates for other systemic therapies and for whom expert multimodal pain control is unavailable or not sufficiently effective.

- **Opioid analgesics**: The relative efficacy of suzetrigine to opioid analgesics dosed as they typically are outside of a clinical trial, with increasing doses of opioids for patients who have ongoing pain, is uncertain. Opioids can have the additional benefit in the early post-operative setting of providing sedation. Minor side effects of opioids are common, and the risk of OUD after short-term use is uncertain. While awaiting additional data on the safety and efficacy of suzetrigine, we feel that in comparison with opioids, the evidence in the treatment of patients with acute pain is promising but inconclusive (**P/I**). Patients for whom earlier use of suzetrigine might be appropriate include those who are not candidates for NSAIDs (such as those with allergies to NSAIDs) and who are at high risk for opioid harms. These potentially include elderly post-operative patients and particularly patients with a history of or at an otherwise increased risk of OUD who are currently not using opioids.

- **NSAIDs**: The relative efficacy of suzetrigine and NSAIDs is uncertain and would likely require a randomized trial to assess. NSAIDs have important safety considerations, and these must be considered in comparison with uncertain risks with suzetrigine. Some risks with NSAIDs are greater in the elderly and in those with known cardiovascular (CV) disease, but this overlaps with some of our uncertainties around risks for arrhythmias with suzetrigine. Our concerns are heightened by prior experience with a medication that was felt to be safer than standard NSAIDs, the COX-2 inhibitor rofecoxib. Rofecoxib was approved by the FDA in 1999, was widely prescribed, and was withdrawn from the market in 2004 because of concerns around CV harms.[47] While awaiting additional data on the safety of suzetrigine, we feel that in comparison with NSAIDs, the evidence in the treatment of patients with acute pain is promising but inconclusive (**P/I**). Patients for whom earlier use of suzetrigine might be appropriate include those at high risk for non-renal, non-CV harms of NSAIDs such as patients with prior gastrointestinal bleeding.

Subgroup Analyses and Heterogeneity

Patients in the abdominoplasty (NAVIGATE-2) trial had a higher average pain intensity at baseline than those in the bunionectomy (NAVIGATE-1) trial, 7.4 versus 6.8 on the NPRS.[18] A subgroup analysis was conducted in the NAVIGATE-1 trial to evaluate whether there was any difference in onset of pain relief between suzetrigine and placebo in patients with a greater baseline pain intensity (NPRS ≥6 ; mean baseline NPRS of 7.7). The median time to a ≥2 drop in NPRS in the suzetrigine arm was 115 minutes, shorter than the 240 minutes seen in the overall population and nearly identical to the 119 minutes found in the overall abdominoplasty population. This median time was significantly shorter than placebo (480 minutes) and the treatment advantage was maintained in patients who used ibuprofen as rescue medication.

Typical subgroup analyses of treatment effect by gender, race, and age were not reported. Given the low percentage of male trial participants in either pivotal trial (1.8% abdominoplasty and 15% bunionectomy), there may be greater uncertainty regarding the efficacy and safety of suzetrigine in a male population, however we have no particular reason to expect differences in efficacy based on patient sex.

Table 3.7. Evidence Ratings

Treatment	Comparator	Evidence Rating
Acute Pain		
Suzetrigine	No systemic therapy	P/I
Suzetrigine	Opioid analgesics	P/I
Suzetrigine	Nonsteroidal anti-inflammatory drugs	P/I

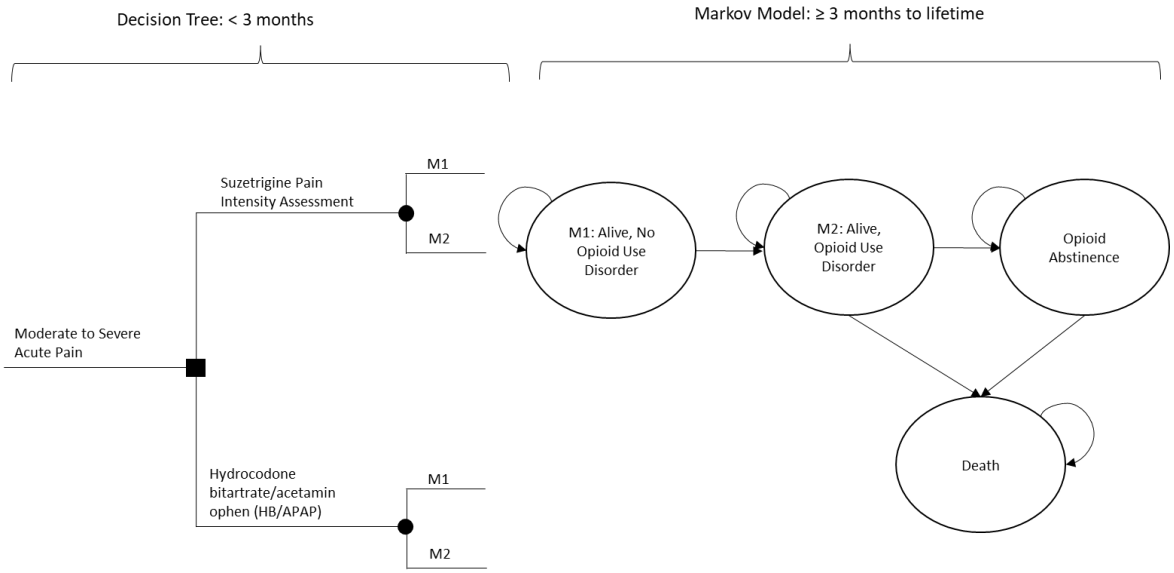
4. Long-Term Cost Effectiveness

4.1. Methods Overview

The aim of this analysis was to estimate the cost effectiveness of suzetrigine compared to HB/APAP for moderate-to-severe acute pain using a two-phase decision analytic model. We developed a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models.

The model was split into an up-front short-term decision tree (<3 months) to reflect use of acute pain medications followed by a Markov model with an annual cycle to account for lifetime outcomes from adverse effects of HB/APAP (Figure 4.1). The decision tree was used to estimate health related quality of life differences from pain intensity between suzetrigine and HB/APAP during one short-course prescription (i.e., one week). The Markov model was used to compare lifetime outcomes between treatment arms. Specifically, we estimated the lifetime adverse effects from OUD (i.e., moving from decision tree to Markov health state 2 [M2] in Figure 4.1) on direct and indirect health care costs, indirect non-health costs (e.g., criminal justice system costs), quality of life, and survival against lifetime outcomes without OUD (i.e., moving from decision tree to Markov health state 1 [M1] in Figure 4.1) using unrelated health care costs, quality of life, and average survival for the general US population. The OUD health state was characterized by excess costs, reduced survival, and decreased quality of life. The "abstinence" health state included ongoing medication-assisted therapy (MAT) costs, improved quality of life compared to the OUD state though still below that of the general population not diagnosed with OUD, and an improved mortality rate compared to OUD, though still an excess mortality versus the general population not diagnosed with OUD. Abstinence was defined consistent with practice guidelines, which include the use of FDA-approved medications for the treatment of substance use disorder and restraint from pathological pursuit of reward and/or relief that involves the use of substances and other behaviors.[17] We discounted costs and outcomes at 3% per year. The model was built in Microsoft Excel. Additional details can be found in the Supplement.

Figure 4.1. Model Structure



4.2. Key Model Assumptions and Inputs

Our model included several key assumptions (Table 4.1) and inputs (Table 4.2). Additional details can be found in the Supplement.

Table 4.1. Key Model Assumptions

Assumption	Rationale
The model focused on acute pain requiring up to one week of prescription pain medication, such as surgery or other acute events causing pain, and did not include treatment for sub-acute or chronic pain.	The expected Food and Drug Administration label for suzetrigine is consistent with acute pain treated over short intervals of time.
The proportion of patients allocated to OUD from the suzetrigine arm equaled 0%.	There is no evidence that patients in the initial acute pain phase will switch to opioids as a subsequent treatment and therefore we modeled the risk of OUD in the opioid arm only. This assumption can be relaxed with future evidence on treatment switching.
There is no further transition to OUD after three years.	The best available evidence reports the three-year incidence of OUD following an acute pain episode.
Adverse effects from opioid use were modeled over a lifetime.	Lifetime modeling of OUD allowed for capturing the delayed risk that can occur well after initial treatment and can affect patients' long-term outcomes.

Assumption	Rationale
A weighted average of quality of life for OUD was estimated for those seeking OUD treatment and those not seeking OUD treatment.	Untreated OUD significantly impacts quality of life; therefore, it was crucial to account for the health losses experienced by those not receiving treatment to reflect real-world outcomes.
Consistent with long-term evidence on OUD (sustained five-year abstinence), a proportion of patients transitioned to opioid abstinence without the chance of moving back to the OUD health state.	Long-term studies indicate that a significant proportion of patients with OUD can achieve sustained abstinence over five years or more, substantially reducing the risk of relapse to active OUD.[48,49]
For individuals in the abstinence state, ongoing medication-assisted treatment was assumed.	Evidence suggests opioid use disorder relapse rates are over 90% six months after discontinuing medication-assisted treatment.[50] Therefore, we assumed MAT will continue in the abstinent state.

MAT: medication-assisted therapy; OUD: Opioid use disorder

Table 4.2. Key Model Inputs

Input	Value [95% CI]	Source
3-year Incidence of OUD	0.43%	Schoenfeld et al., 2024[51]
5-year Proportion of Patients Achieving Abstinence from OUD	0.052	Dowell et al., 2024[52], Zhu et al. 2018[48], Authors' calculation
All-Cause Mortality from Extramedical Opioid Use (Standardized Mortality Ratio)	5.02 [4.21, 5.98]	Larney et al. 2020[53]
All-Cause Mortality Among those who are Abstinent versus those with Untreated OUD (Rate Ratio)	0.40 [0.34-0.46]	Santo et al. 2021[54]
OUD State (Disutility)	0.231	Wittenberg et al, 2016[55], Wu et al. 2016[56], Dowell et al. 2024[52], Authors' calculation
Abstinence (Disutility)	0.081	Wittenberg et al., 2016[55], Zhu et al., 2018[48], Authors' calculation
Suzetrigine, 7-day prescription	$420 (placeholder price)	IPD Analytics
HB/APAP, 7-day prescription	$10.64	US Redbook
Annual Mean Excess Health Care Costs for People with OUD	$17,370	Davenport et al., 2019[57]
Annual Cost of MAT	$7,676 [6,928-8,463]	Fairley et al., 2021[58]; Authors' calculation

HB/APAP: Hydrocodone bitartrate/acetaminophen; MAT: medication-assisted therapy; NPRS: Numeric pain rating scale; OUD: opioid use disorder

Clinical Inputs

Evidence on treatment response was derived from top-line Phase III clinical trial results announced by Vertex.[59]

Transition Probabilities

We assumed that 0% of patients treated with suzetrigine transition to OUD. Based on available data that estimated the probability of developing OUD following an acute pain episode, we assumed that 0.43% of patients treated with HB/APAP will develop OUD by three years.[51] We assume no further transition to OUD after three years. The five-year proportion of patients who transitioned to abstinence (all of whom were assumed to be receiving MAT) was 0.052. We allowed for transition to the abstinence state over the first eight years of the model (i.e., patients who transition to OUD in the third year have up to five years to transition to abstinence). We assumed no relapse from the abstinent state to OUD based on previous evidence of sustained abstinence following five years of abstinence.[49]

Mortality

For mortality in the OUD state, we identified the standardized all-cause mortality ratio for extramedical opioid use among North American cohorts.[53] For the OUD abstinence state, we assumed that the mortality rate is equivalent to all-cause mortality for those in stabilized MAT and identified the rate ratio of all-cause mortality among those in versus out of MAT among North American cohorts.[54] Gender and age-specific mortality were sourced from CDC life tables.[60]

Health State Utilities

Utilities for numeric pain rating scale (NPRS) levels at baseline and on treatment were derived from a EuroQol-5 Dimension (EQ-5D) mapping tool.[61] On treatment utility did not differ between treatment arms and exceeded the average utility of the US adult population. Therefore, utility scores from one week to three months were based on average US population EQ-5D scores (0.851). Utilities for the OUD and abstinence states were based on a nationally representative survey that used the standard gamble approach to measure health-related quality of life of different opioid misuse and treatment states, including active injection drug misuse, active prescription drug misuse, initiation and stabilization on both methadone and buprenorphine treatment, and remission.[55] We calculated weighted average utilities for the OUD and abstinence states and then converted these utilities to disutilities.

Cost Inputs

Drug Costs

To determine drug costs, we assumed that acute pain patients treated with either suzetrigine or HB/APAP would be supplied with a seven-day prescription (including any time as an inpatient and following discharge), regardless of whether all doses are ultimately needed.[26,62] For suzetrigine, we obtained a price range estimate from IPD Analytics of $40 to $80 per day. We used the midpoint of this range as a placeholder price for this analysis. For HB/APAP, we identified the median spending per dosage unit in RedBook and assumed four doses per day for one week.[63]

Non-Drug Costs

Excess health care costs for people with OUD were identified in a matched case-control study using administrative claims data across private and public payers and adjusted to represent the US population.[57] This estimate includes the excess costs of inpatient, outpatient, and behavioral health care services such as MAT. For individuals in the abstinence state, we assumed ongoing MAT. The costs of treatment with methadone and buprenorphine, inclusive of integrated psychosocial and medical support, were identified in a recent cost-effectiveness analysis of treatments for OUD.[58] We assumed equal utilization of methadone and buprenorphine when calculating a weighted average cost of MAT. Gender- and age-specific unrelated health care costs and the cost of death were added to all health states.[64]

4.3. Results

Base-Case Results

The average per person total discounted costs, life years (LYs), quality-adjusted life years (QALYs), and equal value of life years (evLYs) gained are detailed in Table 4.3. There were no differences in QALYs gained in the short-term decision tree component of the model. Over the lifetime model and at the placeholder price, suzetrigine had a total discounted cost of $197,700 with discounted QALYs, LYs, and evLYs of 18.65, 21.92, and 18.65., respectively. Undiscounted OUD cases averted per 100,000 people was 429 in the suzetrigine arm. HB/APAP had a total discounted cost of $197,900 with discounted QALYs, LYs, and evLYs of 18.61, 21.89, and 18.61, respectively.

Table 4.3. Results for the Base Case for Suzetrigine Compared to HB/APAP

Treatment	Intervention Acquisition Costs	Intervention-Related Costs†	Total Costs	OUD Cases (per 100,000)	QALYs	evLYs	Life Years
Suzetrigine	$420*	N/A	$197,700*	0	18.65	18.65	21.92
HB/APAP	$10.64	N/A	$197,900	429	18.61	18.61	21.89

evLYs: equal value of life years gained, HB/APAP: Hydrocodone bitartrate/acetaminophen, OUD: opioid use disorder, QALY: quality-adjusted life year

*Based on placeholder price

†Intervention-related costs include markup costs, administration costs, and costs of monitoring required for the intervention, as specified in clinical trials, guidelines, or package label

Table 4.4 presents the discounted lifetime incremental results, including cost per QALY gained, cost per evLY gained, cost per life year gained, and cost per OUD case averted. Total discounted costs for suzetrigine were approximately $190 less than HB/APAP; gains in QALYs, LYs, and evLYs were 0.039, 0.032, and 0.039, respectively, in relation to HB/APAP. There were 429 per 100,000 fewer OUD cases when comparing suzetrigine to HB/APAP. This resulted in incremental cost-effectiveness ratios that were dominant or less costly and more effective across all health outcomes.

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*	Cost per OUD Case Averted*
Suzetrigine	HB/APAP	Less costly, more effective	Less costly, more effective	Less costly, more effective	Less costly, more effective

evLYs: equal value of life years gained, QALY: quality-adjusted life year, OUD: opioid use disorder

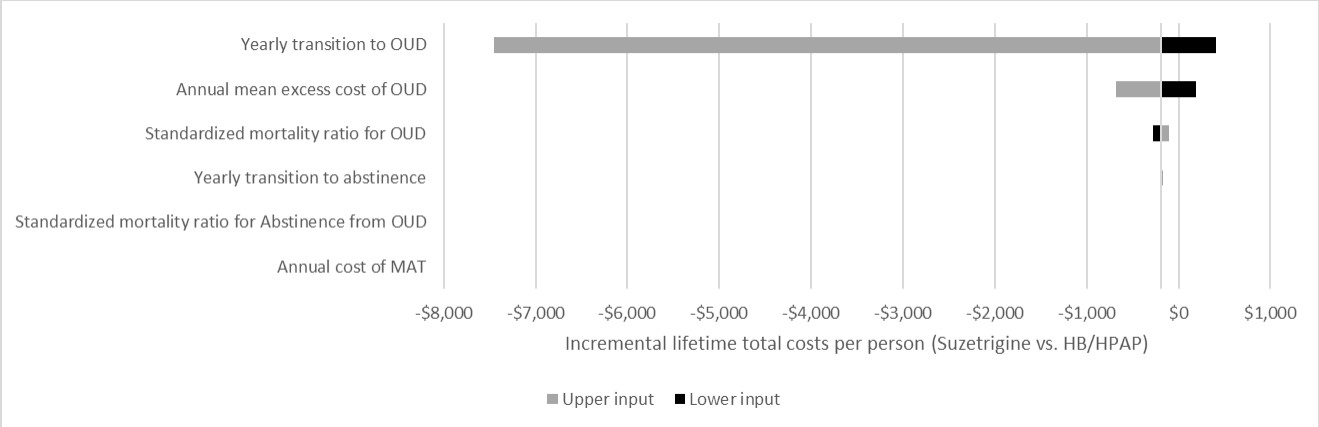
*Based on placeholder price

Sensitivity Analyses

To demonstrate the effects of uncertainty on both costs and health outcomes, we varied input parameters using available estimates of parameter uncertainty (e.g., standard errors or plausible parameter ranges). Because suzetrigine results in dominant (less costly, more effective) scenarios, we present a tornado diagram with incremental per person lifetime costs separate from incremental per person lifetime QALY and evLY estimates. Figures 4.2 and 4.3 present tornado diagrams resulting from the one-way sensitivity analyses for suzetrigine versus HB/APAP. Key drivers of cost-effectiveness estimates include the risk of OUD from a short course of HB/APAP, annual mean excess costs of OUD, and excess mortality related to OUD.

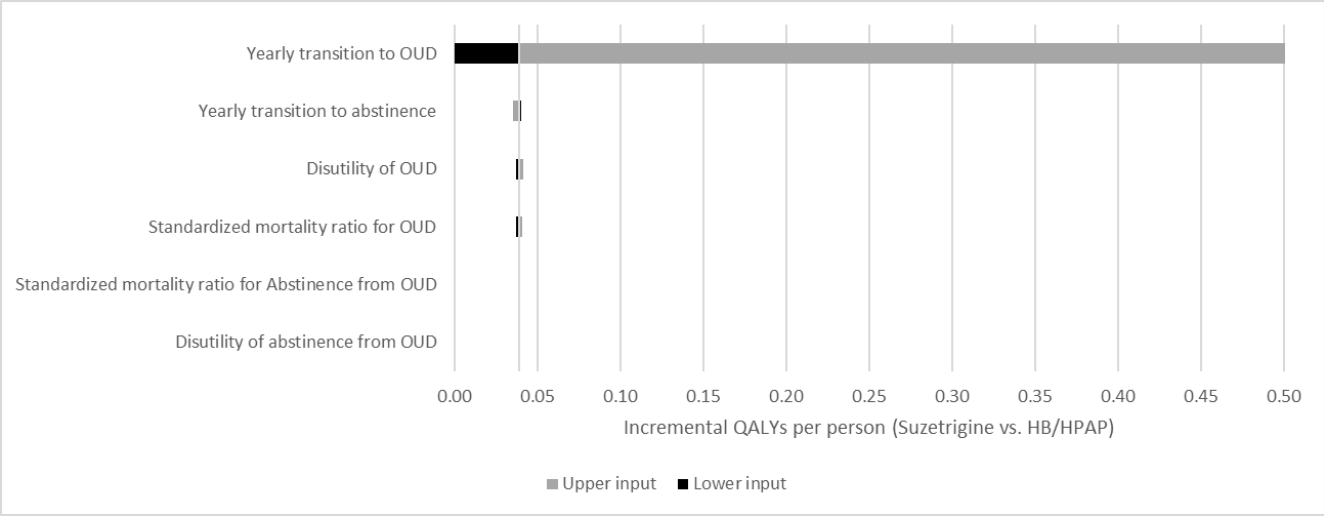
Probabilistic sensitivity analyses were also performed by jointly varying multiple model parameters over at least 1,000 simulations. Tables 4.5 and 4.6 present the probability of reaching certain cost-effectiveness thresholds for suzetrigine at the placeholder price versus HB/APAP. A total of 90% and 92% of iterations for suzetrigine versus HB/APAP were beneath a threshold of $100,000 per QALY or evLY and $150,000 per QALY or evLY, respectively.

Figure 4.2. Tornado Diagram for Incremental Lifetime Costs



HB/APAP: Hydrocodone bitartrate/acetaminophen; MAT: medication-assisted therapy; OUD: opioid use disorder

Figure 4.3. Tornado Diagram for Incremental Quality-Adjusted Life Years Gained



HB/APAP: Hydrocodone bitartrate/acetaminophen; MAT: medication-assisted therapy; OUD: opioid use disorder; QALYs: quality-adjusted life years

Table 4.5. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Suzetrigine versus HB/APAP

	Cost Effective at $50,000 per QALY Gained*	Cost Effective at $100,000 per QALY Gained*	Cost Effective at $150,000 per QALY Gained*	Cost Effective at $200,000 per QALY Gained*
Suzetrigine	85%	90%	92%	93%

QALY: quality-adjusted life year

*Based on placeholder price

Table 4.6. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results: Suzetrigine versus HB/APAP

	Cost Effective at $50,000 per evLY Gained*	Cost Effective at $100,000 per evLY Gained*	Cost Effective at $150,000 per evLY Gained*	Cost Effective at $200,000 per evLY Gained*
Suzetrigine	85%	90%	92%	93%

evLYs: equal value of life years gained

*Based on placeholder price

Scenario Analyses

Analysis 1: Modified societal perspective that includes components such as productivity losses, criminal justice and incarceration, and caregiver disutilities applied to the OUD health state.

Analysis 2: The proportion of patients with OUD in the opioid comparator arm that result in scenarios for suzetrigine that meet commonly cited cost-effectiveness thresholds using the placeholder price.

Analysis 3: Exclusion of unrelated health care and death costs.

Table 4.7. Scenario Analysis Results

Treatment	Base-Case Results*	Scenario Analysis 1*	Scenario Analysis 2*	Scenario Analysis 3*
Suzetrigine	Less costly, more effective	Less costly, more effective	0.04% with OUD by three years in the opioid arm to meet $100,000 per QALY and evLY thresholds	Less costly, more effective

*Based on placeholder price

Threshold Analyses

Tables 4.8 and 4.9 present the one-week price needed for suzetrigine to reach commonly cited cost-effectiveness thresholds.

Table 4.8. QALY-Based Threshold Analysis Results

	WAC per Unit	Weekly Price per Unit	Weekly Price to Achieve $50,000 per QALY Gained	Weekly Price to Achieve $100,000 per QALY Gained	Weekly Price to Achieve $150,000 per QALY Gained	Weekly Price to Achieve $200,000 per QALY Gained
Suzetrigine	N/A	$420*	$2,500	$4,500	$6,500	$8,500

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Price is a placeholder based on IPD Analytics projections and is for a one-week prescription

Table 4.9. evLY-Based Threshold Analysis Results

	WAC per Unit	Net Price per Unit	Weekly Price to Achieve $50,000 per QALY Gained	Weekly Price to Achieve $100,000 per QALY Gained	Weekly Price to Achieve $150,000 per QALY Gained	Weekly Price to Achieve $200,000 per QALY Gained
Suzetrigine	N/A	$420*	$2,500	$4,500	$6,500	$8,500

evLYs: equal value of life years gained, WAC: wholesale acquisition cost

*Price is a placeholder based on IPD Analytics projections and is for a one-week prescription

Model Validation

We used several approaches to validate the model. First, we had three different decision modeling experts review the model structure, assumptions, and inputs. We revised data inputs based on feedback from multiple stakeholders, including the manufacturer, patient groups, and clinical experts. As part of ICER's efforts in acknowledging modeling transparency, we offered to share the model with the relevant manufacturer for external validation. Finally, we validated outputs based on observed evidence in the literature. One specific area of validation was in reference to the cumulative incidence of OUD in the model against the cumulative incidence from the best available evidence.

Uncertainty and Controversies

The cost effectiveness of suzetrigine for acute pain compared to HB/APAP depends greatly on the incidence of OUD from a short course of HB/HPAP. We used the best available evidence from a recent study estimating the incidence of OUD following acute pain (defined as <3 months of continuous or recurrent use of pain medications within a year of opioid initiation) using commercial and Medicare claims among patients continuously insured.[51] A limitation of this study is that opioid use after the initial opioid prescription but before developing OUD was not recorded. Moreover, a general limitation of claims data is that we cannot know the reasons for filling or not filling a prescription. As such, it is possible that some patients classified as developing OUD following an acute pain episode might in fact have developed OUD due to chronic pain.

To address this limitation, we ran a scenario analysis to estimate the proportion of patients diagnosed with OUD that would result in suzetrigine meeting the commonly cited cost-effectiveness threshold of $100,000 per QALY and evLY. At the placeholder price of $420 per week, suzetrigine meets a threshold of $100,000 per evLY with a three-year cumulative risk of OUD approximately equal to 0.04% (or approximately 40 OUD cases per 100,000 people receiving opioids). This is a smaller risk than the base-case estimate of 0.43%, or 429 OUD cases per 100,000 people. It is also possible that the incidence of OUD following acute pain could be higher than the base-case estimate of 0.43%. To address this uncertainty, we have used an upper bound of 5.7% for the incidence of OUD in the one-way sensitivity analysis using existing evidence among patients in commercial, Medicare, and Medicaid plans.[65] As expected, the health risks of OUD increase substantially at a higher cumulative incidence of OUD, resulting in larger cost savings and greater health benefits for suzetrigine versus HB/APAP. Given that the transition to OUD from acute pain is highly influential on model outputs, future evidence should seek to isolate both the effect of acute pain (versus chronic pain) and the effect of initial treatment with opioids (versus non-opioids) on the risk of developing OUD.

We acknowledge that different inputs may yield alternative results. For example, the societal perspective estimates may underestimate the economic burden of OUD, especially given the heterogeneity of the impact of the opioid epidemic. Our base-case analysis included estimates of the excess costs of both OUD and continued lifetime treatment for OUD using MAT with a modified societal perspective that includes criminal justice system costs, lost productivity costs, and quality of life decrements for caregivers of persons with OUD. Other examples may include a different distribution of MAT utilization in different areas of the country or different efficacy estimates among subgroups. In general, literature-based estimates are subject to different data sources as well as heterogeneity among persons with OUD. To address any variation in input sources, we expanded our parameter uncertainty analyses to ensure we include both higher and lower estimates of inputs. In our sensitivity and scenario analyses, the conclusions were consistent with the base-case analysis.

4.4 Summary and Comment

This analysis found that the use of suzetrigine for treating moderate-to-severe acute pain is slightly cost-saving compared to HB/APAP, using the placeholder price of $420 for a short course prescription to treat acute pain. The cost savings are primarily due to averting cases of OUD, which has significant negative impacts on mortality and quality of life and is associated with excess health care costs. As such, the economic impact of suzetrigine in this model is sensitive to the incidence of OUD that would be observed after a short-course of opioids for acute pain. The societal perspective extends cost saving estimates to include lost productivity and criminal justice costs from averting cases of OUD.

5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Table 5.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There is substantial unmet need despite currently available treatments.	To inform unmet need as a benefit beyond health, the results for the absolute and proportional shortfalls have been reported below. The shortfalls were the same, regardless of whether QALY or evLY was used. QALY and evLY shortfalls: • Absolute shortfall: 0.24 • Proportional shortfall: 0.8% The absolute and proportional shortfalls represent the total and proportional health units of remaining quality adjusted life expectancy, respectively, that would be lost due to un- or under-treated illness. Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the health care system.	Acute pain is ubiquitous; however we heard from some stakeholders that populations underserved by the health care system are more likely to receive opioids for pain management because they are inexpensive, and heard from other stakeholders that such populations are broadly undertreated for pain as discussed in Section 2.

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.	Acute pain is unlikely to create a substantial burden for caregivers relative to life goals, as it is time limited. If suzetrigine leads to important reductions in the development of OUD, this could importantly affect some caregivers. Similarly, if better treatment of pain with suzetrigine leads to less long-term psychological sequelae, such as anxiety or depression, this could also improve caregiver outcomes. The effects of treating acute pain with suzetrigine on the development of chronic pain are currently unknown.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.	Suzetrigine has a new mechanism of action and so may improve access to effective treatment for patients who cannot receive other oral pain medications.

ICER did not calculate the Health Improvement Distribution Index (HIDI) because there is no reason to expect the prevalence of acute pain to vary substantially by race/ethnicity.

6. Health Benefit Price Benchmark

ICER does not provide a health benefit price benchmark as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmark that will be presented in the next version of this Report.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the total potential budgetary impact of suzetrigine compared to HB/APAP for patients with acute pain not adequately controlled with non-systemic therapies. Potential budget impact is defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. We used a placeholder price of $420 for one week of prescription and the three threshold prices (at $50,000, $100,000, and $150,000 per evLYG) for suzetrigine in our estimate of budget impact.

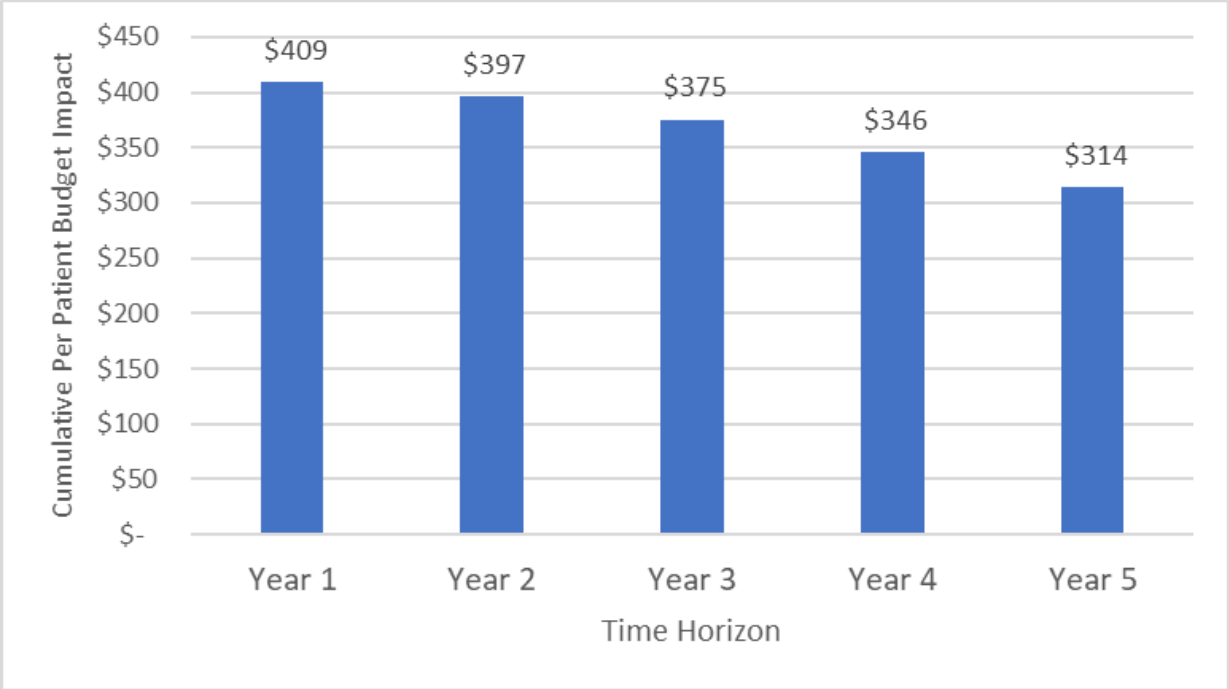
This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for suzetrigine. To estimate the size of the potential candidate population, we used inputs for the US prevalence of acute pain requiring management with prescription medication. A retrospective cross-sectional study using two nationally representative datasets from 2019 estimated that 80.2 million patients in the US annually experience acute pain, defined as requiring prescription pain medication for less than three months.[2] Among all patients with acute pain, 10.9 million patients with both acute and chronic pain were excluded to ensure alignment with the specific population studied in the cost-effectiveness analysis. The prevalence of acute pain (69.3 million) was multiplied by the proportion of acute pain patients who received one or more prescriptions or administrations of opioids (51%) to estimate the number of patients likely to receive opioids for treating acute pain each year.[2] Other types of treatment, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opioid analgesics, were not considered in estimating the number of eligible patients, as suzetrigine is anticipated to primarily displace opioids, which are the main comparator in the cost-effectiveness analysis. Applying these findings results in estimates of 35.3 million eligible patients in the US per year. For the purposes of this analysis, we will assume that 20% of these patients would initiate treatment in each of the five years, or 7.1 million patients per year.

7.2. Results

Figure 7.1 illustrates the cumulative annual per patient treated potential budget impact for suzetrigine compared to HB/ABAB. The cumulative per patient annual budget impact represents the incremental costs of suzetrigine compared to HB/ABAB per patient across all patients treated within a time horizon (including those who initiated suzetrigine in previous years), assuming suzetrigine is used with 20% uptake each year over five years. While the costs of treatment for suzetrigine occur within the first year, the cumulative incremental annual costs increase because an additional 20% of patients initiate suzetrigine each year up to year five.

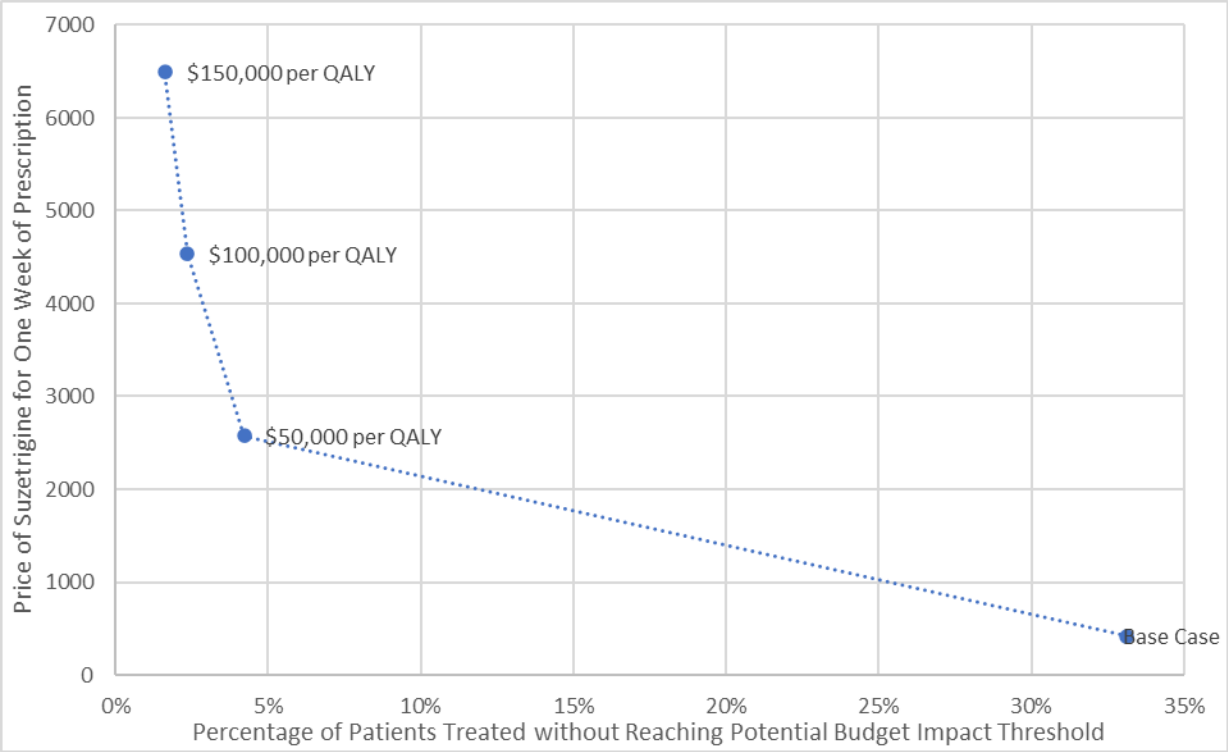
At suzetrigine's placeholder price $420 for one week of prescription, the average annual budget impact per patient was $409 in year one, with cumulative net annual costs decreasing to $314 in year five. This is because suzetrigine is taken only in the first year, with cost savings occurring in subsequent years after treatment.

Figure 7.1. Cumulative Per Patient Annual Budget Impact for Suzetrigine Compared to HB/ABAB using a Placeholder Price for Suzetrigine



Assuming a 20% uptake of suzetrigine each year, 33.1% of patients could be treated over five years at the placeholder price before reaching the ICER potential budget impact threshold of $735 million per year. Fewer percentages of eligible patients could be treated at the $50,000, $100,000 and $150,000 per evLY threshold prices (4.2%, 2.3% and 1.6%, respectively) as illustrated in Figure 7.2.

Figure 7.2. Percent Uptake Each Year Before Reaching Potential Budget Impact Threshold



References

1. Kent ML, Tighe PJ, Belfer I, et al. The ACTTION-APS-AAPM Pain Taxonomy (AAAPT) Multidimensional Approach to Classifying Acute Pain Conditions. *Pain Med*. May 1 2017;18(5):947-958. doi:10.1093/pm/pnx019
2. Andrea Lopez JJ, Ann M. Menzie, Sujith Peta, Andrea Ippolito, Jaime Rubin. An Evaluation of the Prevalence of Acute and Chronic Pain Medication Use in the United States: a Real Real-world Database Analysis. 2023:
3. Tighe P, Buckenmaier CC, 3rd, Boezaart AP, et al. Acute Pain Medicine in the United States: A Status Report. *Pain Med*. Sep 2015;16(9):1806-26. doi:10.1111/pme.12760
4. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. Mar 2008;11(2 Suppl):S105-20.
5. Jivraj NK, Raghavji F, Bethell J, et al. Persistent Postoperative Opioid Use: A Systematic Literature Search of Definitions and Population-based Cohort Study. *Anesthesiology*. Jun 2020;132(6):1528-1539. doi:10.1097/aln.0000000000003265
6. Hamilton GM, Ladha K, Wheeler K, Nguyen F, McCartney CJL, McIsaac DI. Incidence of persistent postoperative opioid use in patients undergoing ambulatory surgery: a retrospective cohort study. *Anaesthesia*. Feb 2023;78(2):170-179. doi:10.1111/anae.15900
7. Deyo RA, Hallvik SE, Hildebran C, et al. Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naïve Patients: A Statewide Retrospective Cohort Study. *J Gen Intern Med*. Jan 2017;32(1):21-27. doi:10.1007/s11606-016-3810-3
8. National Institute on Drug Abuse. Drug Overdose Deaths: Facts and Figures. Accessed October 8, 2024. https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates
9. Florence C, Luo F, Rice K. The economic burden of opioid use disorder and fatal opioid overdose in the United States, 2017. *Drug Alcohol Depend*. Jan 1 2021;218:108350. doi:10.1016/j.drugalcdep.2020.108350
10. Jones J, Correll DJ, Lechner SM, et al. Selective Inhibition of Na(V)1.8 with VX-548 for Acute Pain. *The New England journal of medicine*. Aug 3 2023;389(5):393-405. doi:10.1056/NEJMoa2209870
11. Vertex Announces FDA Acceptance of New Drug Application for Suzetrigine for the Treatment of Moderate-to-Severe Acute Pain. 2024. https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-fda-acceptance-new-drug-application-suzetrigine
12. Hang Kong AY, Tan HS, Habib AS. VX-548 in the treatment of acute pain. *Pain Manag*. Sep 2024;14(9):477-486. doi:10.1080/17581869.2024.2421749
13. Buvanendran A, Fiala J, Patel KA, Golden AD, Moric M, Kroin JS. The Incidence and Severity of Postoperative Pain following Inpatient Surgery. *Pain Med*. Dec 2015;16(12):2277-83. doi:10.1111/pme.12751
14. Cordell WH, Keene KK, Giles BK, Jones JB, Jones JH, Brizendine EJ. The high prevalence of pain in emergency medical care. *Am J Emerg Med*. May 2002;20(3):165-9. doi:10.1053/ajem.2002.32643
15. Dix P, Sandhar B, Murdoch J, MacIntyre PA. Pain on medical wards in a district general hospital. *Br J Anaesth*. Feb 2004;92(2):235-7. doi:10.1093/bja/aeh052
16. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *BMJ (Clinical research ed)*. Feb 11 2014;348:g1251. doi:10.1136/bmj.g1251
17. American Society of Addiction Medicine. The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update. *J Addict Med*. Mar/Apr 2020;14(2S Suppl 1):1-91. doi:10.1097/adm.0000000000000633

18. Bertoch. T DDA, Jessica McCoun, Daneshvari Solanki, Louise Taber, Joshua Urban, Jessica Oswald, Matthew Swisher, Simon Tian, Xiaopeng Miao, Darin J Correll, Paul Negulescu, Carmen Bozic, Scott Weiner. Suzetrigine (VX-548) ASA Update. Vertex Pharmaceuticals Incorporated; 2024:
19. Taylor NP. Vertex posts full pain data ahead of FDA ruling, unpacking combo results, Vicodin miss and stellar safety. FIERCE Biotech; 2024. October 21, 2024. https://www.fiercebiotech.com/biotech/vertex-posts-full-pain-data-ahead-fda-ruling-unpacking-combo-results-vicodin-miss-and
20. Agboola FW, AC. A Framework for Evaluating the Diversity of Clinical Trials. *Journal of Clinical Epidemiology*. 2024:111299.
21. Farrar JT, Berlin JA, Strom BL. Clinically Important Changes in Acute Pain Outcome Measures: A Validation Study. *Journal of Pain and Symptom Management*. 2003;doi:10.1016/S0885-3924(03)00162-3
22. Myles PS, Christelis N. Measuring pain and analgesic respons. *European Journal of Anaesthesiology*. 2011;doi:10.1097/EJA.0b013e32834592a8
23. Bjerre E, Damkjær Hansen M, Frahm Olsen M, et al. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC Medicine*. 2017;doi:10.1186/s12916-016-0775-3
24. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 1988.
25. Brasure M. *Treatment for acute pain : an evidence map*. Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services; 2019.
26. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. *Morbidity and Mortality Weekly Report*. 2022;71
27. Goshua A, Craigie S, Guyatt GH, et al. Patient Values and Preferences Regarding Opioids for Chronic Noncancer Pain: A Systematic Review. *Pain Med*. 2018;19(12)doi:https://doi.org/10.1093/pm/pnx274
28. Gazelka HM, Leal JC, Lapid MI, Rummans TA. Opioids in Older Adults: Indications, Prescribing, Complications, and Alternative Therapies for Primary Care. *Concise Review for Clinicians*. 2020;95(4)doi:10.1016/j.mayocp.2020.02.002
29. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. *Biochem Pharmacol*. Oct 2020;180:114147. doi:10.1016/j.bcp.2020.114147
30. Lanza FL, Chan FK, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol*. Mar 2009;104(3):728-38. doi:10.1038/ajg.2009.115
31. Haghbin H, Zakirkhodjaev N, Husain FF, Lee-Smith W, Aziz M. Risk of Gastrointestinal Bleeding with Concurrent Use of NSAID and SSRI: A Systematic Review and Network Meta-Analysis. *Dig Dis Sci*. May 2023;68(5):1975-1982. doi:10.1007/s10620-022-07788-y
32. Nash DM, Markle-Reid M, Brimble KS, et al. Nonsteroidal anti-inflammatory drug use and risk of acute kidney injury and hyperkalemia in older adults: a population-based study. *Nephrol Dial Transplant*. Jul 1 2019;34(7):1145-1154. doi:10.1093/ndt/gfz062
33. Wei L, MacDonald TM, Jennings C, Sheng X, Flynn RW, Murphy MJ. Estimated GFR reporting is associated with decreased nonsteroidal anti-inflammatory drug prescribing and increased renal function. *Kidney Int*. Jul 2013;84(1):174-8. doi:10.1038/ki.2013.76
34. Chan AT, Manson JE, Albert CM, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. *Circulation*. Mar 28 2006;113(12):1578-87. doi:10.1161/circulationaha.105.595793
35. Rind DM, Safran C, Phillips RS, et al. Effect of computer-based alerts on the treatment and outcomes of hospitalized patients. *Archives of internal medicine*. Jul 11 1994;154(13):1511-7.

36. Leth MF, Bukhari S, Laursen CCW, et al. Risk of serious adverse events associated with non-steroidal anti-inflammatory drugs in orthopaedic surgery. A protocol for a systematic review. *Acta Anaesthesiol Scand*. Nov 2022;66(10):1257-1265. doi:10.1111/aas.14140
37. Pollak RA, Gottlieb IJ, Hakakian F, et al. Efficacy and Safety of Intravenous Meloxicam in Patients With Moderate-to-Severe Pain Following Bunionectomy: A Randomized, Double-Blind, Placebo-controlled Trial. *The Clinical journal of pain*. 2018-01-01 2018;34(10)doi:10.1097/ajp.0000000000000609
38. Gan TJ, Daniels SE, Singla N, Hamilton DA, Carr DB. A novel injectable formulation of diclofenac compared with intravenous ketorolac or placebo for acute moderate-to-severe pain after abdominal or pelvic surgery: a multicenter, double-blind, randomized, multiple-dose study. *Anesth Analg*. Nov 2012;115(5):1212-20. doi:10.1213/ANE.0b013e3182691bf9
39. Zhang Y, Alyass A, Vanniyasingam T, et al. A systematic survey of the methods literature on the reporting quality and optimal methods of handling participants with missing outcome data for continuous outcomes in randomized controlled trials. *J Clin Epidemiol*. Aug 2017;88:67-80. doi:10.1016/j.jclinepi.2017.05.016
40. Taylor NP. Vertex posts full pain data ahead of FDA ruling, unpacking combo results, Vicodin miss and stellar safety. https://www.fiercebiotech.com/biotech/vertex-posts-full-pain-data-ahead-fda-ruling-unpacking-combo-results-vicodin-miss-and
41. Downing NS, Shah ND, Aminawung JA, et al. Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010. *Jama*. May 9 2017;317(18):1854-1863. doi:10.1001/jama.2017.5150
42. Puhl HL, 3rd, Ikeda SR. Identification of the sensory neuron specific regulatory region for the mouse gene encoding the voltage-gated sodium channel NaV1.8. *J Neurochem*. Aug 2008;106(3):1209-24. doi:10.1111/j.1471-4159.2008.05466.x
43. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present Status of Brugada Syndrome: JACC State-of-the-Art Review. *J Am Coll Cardiol*. Aug 28 2018;72(9):1046-1059. doi:10.1016/j.jacc.2018.06.037
44. Hu D, Barajas-Martínez H, Pfeiffer R, et al. Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome. *J Am Coll Cardiol*. Jul 8 2014;64(1):66-79. doi:10.1016/j.jacc.2014.04.032
45. Moras E, Gandhi K, Narasimhan B, et al. Genetic and Molecular Mechanisms in Brugada Syndrome. *Cells*. Jul 5 2023;12(13)doi:10.3390/cells12131791
46. Yu SM, Bonventre JV. Acute Kidney Injury and Progression of Diabetic Kidney Disease. *Adv Chronic Kidney Dis*. Mar 2018;25(2):166-180. doi:10.1053/j.ackd.2017.12.005
47. Khanna D, Khanna PP, Furst DE. COX-2 controversy: where are we and where do we go from here? *Inflammopharmacology*. 2005;13(4):395-402. doi:10.1163/156856005774415583
48. Zhu Y, Evans EA, Mooney LJ, et al. Correlates of Long-Term Opioid Abstinence After Randomization to Methadone Versus Buprenorphine/Naloxone in a Multi-Site Trial. *J Neuroimmune Pharmacol*. Dec 2018;13(4):488-497. doi:10.1007/s11481-018-9801-x
49. Hser YI, Evans E, Grella C, Ling W, Anglin D. Long-term course of opioid addiction. *Harv Rev Psychiatry*. Mar-Apr 2015;23(2):76-89. doi:10.1097/hrp.0000000000000052
50. National Center on Substance Abuse and Child Welfare. Medication-assisted treatment: A primer for judicial professionals serving parents and children affected by substance abuse disorders. Accessed 10/2/2024, https://ncsacw.acf.hhs.gov/files/mat-primer-508.pdf
51. Schoenfeld AJ, Jeyakumar S, Geiger JM, et al. An Evaluation of the Incidence of Opioid Use Disorder Among People with Acute and Chronic Pain Managed with Prescription Opioids and the Associated Economic and Societal Burden in the United States. 2024:

52. Dowell D, Brown S, Gyawali S, et al. Treatment for Opioid Use Disorder: Population Estimates - United States, 2022. *MMWR Morb Mortal Wkly Rep*. Jun 27 2024;73(25):567-574. doi:10.15585/mmwr.mm7325a1
53. Larney S, Tran LT, Leung J, et al. All-Cause and Cause-Specific Mortality Among People Using Extramedical Opioids: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2020;77(5):493-502. doi:10.1001/jamapsychiatry.2019.4170
54. Santo T, Jr, Clark B, Hickman M, et al. Association of Opioid Agonist Treatment With All-Cause Mortality and Specific Causes of Death Among People With Opioid Dependence: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2021;78(9):979-993. doi:10.1001/jamapsychiatry.2021.0976
55. Wittenberg E, Bray JW, Aden B, Gebremariam A, Nosyk B, Schackman BR. Measuring benefits of opioid misuse treatment for economic evaluation: health-related quality of life of opioid-dependent individuals and their spouses as assessed by a sample of the US population. *Addiction*. Apr 2016;111(4):675-84. doi:10.1111/add.13219
56. Wu L-T, Zhu H, Swartz MS. Treatment utilization among persons with opioid use disorder in the United States. *Drug and Alcohol Dependence*. 2016/12/01/ 2016;169:117-127. doi:https://doi.org/10.1016/j.drugalcdep.2016.10.015
57. Davenport S, Weaver A, Caverly M. Economic impact of non-medical opioid use in the United States: Annual estimates and projections for 2015 through 2019. *Society of Actuaries Available online: https://www soa org/globalassets/assets/files/resources/research-report/2019/econ-impact-non-medical-opioid-use pdf (accessed on 25 September 2019)*. 2019;
58. Fairley M, Humphreys K, Joyce VR, et al. Cost-effectiveness of Treatments for Opioid Use Disorder. *JAMA Psychiatry*. Jul 1 2021;78(7):767-777. doi:10.1001/jamapsychiatry.2021.0247
59. Vertex. Vertex Announces Positive Results From the VX-548 Phase 3 Program for the Treatment of Moderate-to-Severe Acute Pain. Accessed September 16, 2024, https://news.vrtx.com/news-releases/news-release-details/vertex-announces-positive-results-vx-548-phase-3-program
60. Statistics NCfH. Life Tables. CDC. https://www.cdc.gov/nchs/products/life_tables.htm
61. Dixon S, Poole CD, Odeyemi I, Retsa P, Chambers C, Currie CJ. Deriving health state utilities for the numerical pain rating scale. *Health and quality of life outcomes*. Nov 3 2011;9:96. doi:10.1186/1477-7525-9-96
62. McCarthy DM, Kim HS, Hur SI, et al. Patient-Reported Opioid Pill Consumption After an ED Visit: How Many Pills Are People Using? *Pain Med*. Feb 23 2021;22(2):292-302. doi:10.1093/pm/pnaa048
63. Institute for Clinical and Economic Review. ICER's Reference Case for Economic Evaluations: Elements and Rationale. Accessed 10/8/2024, https://icer.org/wp-content/uploads/2024/02/RefCase_Sep2023_For-Publication_100124.pdf
64. Jiao B, Basu A. Catalog of Age- and Medical Condition-Specific Healthcare Costs in the United States to Inform Future Costs Calculations in Cost-Effectiveness Analysis. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Jul 2021;24(7):957-965. doi:10.1016/j.jval.2021.03.006
65. Brummett CM, Evans-Shields J, England C, et al. Increased health care costs associated with new persistent opioid use after major surgery in opioid-naive patients. *J Manag Care Spec Pharm*. Jun 2021;27(6):760-771. doi:10.18553/jmcp.2021.20507
66. Correll DJ. Chapter 22 - The Measurement of Pain: Objectifying the Subjective. In: Waldman SD, ed. *Pain Management (Second Edition)*. W.B. Saunders; 2011:191-201.
67. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *Journal of Clinical Nursing*. 2005;14(7):798-804. doi:https://doi.org/10.1111/j.1365-2702.2005.01121.x
68. ClinicalTrials.gov. A Single-arm Study to Evaluate Safety and Effectiveness of VX-548 for Acute Pain. https://clinicaltrials.gov/study/NCT05661734?term=NCT05661734&rank=1

69. Ottersen T, Førde R, Kakad M, et al. A new proposal for priority setting in Norway: Open and fair. *Health Policy*. Mar 2016;120(3):246-51. doi:10.1016/j.healthpol.2016.01.012
70. van de Wetering EJ, Stolk EA, van Exel NJ, Brouwer WB. Balancing equity and efficiency in the Dutch basic benefits package using the principle of proportional shortfall. *The European journal of health economics : HEPAC : health economics in prevention and care*. Feb 2013;14(1):107-15. doi:10.1007/s10198-011-0346-7
71. Stolk EA, van Donselaar G, Brouwer WB, Busschbach JJ. Reconciliation of economic concerns and health policy: illustration of an equity adjustment procedure using proportional shortfall. *PharmacoEconomics*. 2004;22(17):1097-107. doi:10.2165/00019053-200422170-00001
72. Mossey JM. Defining Racial and Ethnic Disparities in Pain Management. *Clinical Orthopaedics and Related Research*. 2011;7:1859-70. doi:doi: 10.1007/s11999-011-1770-9
73. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain*. Feb 2016;17(2):131-57. doi:10.1016/j.jpain.2015.12.008
74. Chou R, Wagner J, Ahmed AY, et al. AHRQ Comparative Effectiveness Reviews. *Treatments for Acute Pain: A Systematic Review*. Agency for Healthcare Research and Quality (US); 2020.
75. Herzig SJ, Mosher HJ, Calcaterra SL, Jena AB, Nuckols TK. Improving the Safety of Opioid Use for Acute Noncancer Pain in Hospitalized Adults: A Consensus Statement From the Society of Hospital Medicine. *J Hosp Med*. Apr 2018;13(4):263-271. doi:10.12788/jhm.2980
76. Bova G, Domenichiello A, Letzen JE, et al. Developing consensus on core outcome sets of domains for acute, the transition from acute to chronic, recurrent/episodic, and chronic pain: results of the INTEGRATE-pain Delphi process. *EClinicalMedicine*. 2023;doi:10.1016/j.eclinm.2023.102340
77. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med*. Mar 1 1997;126(5):376-80.
78. Higgins J, Thomas, J, Chandler, J, Cumpston, M, Li, T, Page, MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). https://training.cochrane.org/handbook/current
79. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical research ed)*. Mar 29 2021;372:n71. doi:10.1136/bmj.n71
80. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed)*. 2019;366:l4898. doi:10.1136/bmj.l4898
81. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed)*. 2019;doi:10.1136/bmj.l4898
82. Argoff C, McCarberg B, Gudin J, Nalamachu S, Young C. SoluMatrix R Diclofenac: Sustained Opioid-Sparing Effects in a Phase 3 Study in Patients with Postoperative Pain. *Pain medicine (Malden, Mass)*. 2016-01-01 2016;17(10)doi:10.1093/pm/pnw012
83. Daniels SE, Baum DR, Clark F, Golf MH, McDonnell ME, Boesing SE. Diclofenac potassium liquid-filled soft gelatin capsules for the treatment of postbunionectomy pain. *Current medical research and opinion*. 2010-01-01 2010;26(10)doi:10.1185/03007995.2010.515478
84. Gibofsky A, Silberstein S, Argoff C, Daniels S, Jensen S, Young CL. Lower-dose diclofenac submicron particle capsules provide early and sustained acute patient pain relief in a phase 3 study. *Postgraduate medicine*. 2013-01-01 2013;125(5)doi:10.3810/pgm.2013.09.2693
85. Riff DS, Duckor S, Gottlieb I, et al. Diclofenac potassium liquid-filled soft gelatin capsules in the management of patients with postbunionectomy pain: a Phase III, multicenter, randomized, double-

blind, placebo-controlled study conducted over 5 days. *Clinical therapeutics*. 2009-01-01 2009;31(10)doi:10.1016/j.clinthera.2009.09.011
86. Altman R, Saag K, Daniels S, Young C. Lower-dose indomethacin submicron particle capsules provide effective acute pain relief: Phase 3 study results. *Osteoarthritis Cartilage*. 2013-01-01 2013;21
87. Gharibo CG, Argoff C, Markenson JA, et al. Opioid-sparing Effects of SoluMatrix Indomethacin in a Phase 3 Study in Patients With Acute Postoperative Pain. *The Clinical journal of pain*. 2018-01-01 2018;34(2)doi:10.1097/ajp.0000000000000525
88. ClinicalTrials.gov. Study of Indomethacin Capsules to Treat Pain Following Bunionectomy. https://clinicaltrials.gov/study/NCT01626118?term=NCT01626118&rank=1
89. Viscusi ER, de Leon-Casasola O, Cebrecos J, et al. Celecoxib-tramadol co-crystal in patients with moderate-to-severe pain following bunionectomy with osteotomy: A phase 3, randomized, double-blind, factorial, active- and placebo-controlled trial. *Pain practice : the official journal of World Institute of Pain*. 2023-01-01 2023;23(1)doi:10.1111/papr.13136
90. Singla N, Margulis R, Kostenbader K, et al. Randomized, double-blind, placebo-controlled, phase 3 study of the safety and analgesic efficacy of MNK-155 extended-release hydrocodone bitartrate/acetaminophen tablets (HB/APAP ER) in an acute pain model. *J Pain*. 2014-01-01 2014;15(4)doi:10.1016/j.jpain.2014.01.340
91. Singla N, Margulis R, Kostenbader K, et al. Randomized, double-blind, placebo-controlled study of the efficacy and safety of biphasic immediate-release/extended-release hydrocodone bitartrate/acetaminophen tablets for acute postoperative pain. *The Physician and Sportsmedicine*. 2015/04/03 2015;43(2):126-137. doi:10.1080/00913847.2015.1025029
92. ClinicalTrials.gov. Hydrocodone/Acetaminophen for Acute Pain Following Bunionectomy. https://clinicaltrials.gov/study/NCT01038609?intr=NCT01038609&rank=1&tab=results
93. AbbVie Inc. *Hydrocodone/Acetaminophen Extended Release Tablets M12-058 Clinical Study Report*. 2011. https://www.abbvie.com/content/dam/abbvie-dotcom/clinical-trials/hydrocodone_M12-058.pdf
94. ClinicalTrials.gov. Study to Evaluate the Analgesic Efficacy and Safety of Hydrocodone Bitartrate/ Acetaminophen Immediate-Release Tablets in Participants With Moderate to Severe Pain Following Bunionectomy. https://clinicaltrials.gov/study/NCT02487108?term=NCT02487108&rank=1
95. Teva Pharmaceuticals. IR Hydrocodone Commercial Kickoff All Hands Meeting. https://files.cand.uscourts.gov/files/18-CV-07591_CCSF_v_Purdue/2022.05.17%20The%20Peoples%20Exhibits/P-22527_00001.pdf
96. Daniels SE, Casson E, Stegmann J-U, et al. A randomized, double-blind, placebo-controlled phase 3 study of the relative efficacy and tolerability of tapentadol IR and oxycodone IR for acute pain. *Current Medical Research and Opinion*. 2009;25(6)doi:10.1185/03007990902952825
97. Daniels SE, Upmalis D, Okamoto A, Lange C, Häeussler J. A randomized, double-blind, phase III study comparing multiple doses of tapentadol IR, oxycodone IR, and placebo for postoperative (bunionectomy) pain. *CURRENT MEDICAL RESEARCH AND OPINION*. 2009;25doi:10.1185/03007990902728183
98. Singla N, Barrett T, Sisk L, Kostenbader K, Young J, Giuliani M. A randomized, double-blind, placebo-controlled study of the efficacy and safety of MNK-795, a dual-layer, biphasic, immediate-release and extended-release combination analgesic for acute pain. *Current medical research and opinion*. 2014-01-01 2014;30(3)doi:10.1185/03007995.2013.876979
99. United States Census Bureau. United States Census Bureau Quick Facts. https://www.census.gov/quickfacts/

100. Cai Y, Song Y, He M, et al. Global prevalence and incidence of hallux valgus: a systematic review and meta-analysis. *Journal of foot and ankle research*. 2023;16(1):1-n/a. doi:10.1186/s13047-023-00661-9
101. American Society of Plastic Surgeons. PLASTIC SURGERY STATISTICS REPORT. 2020;
102. American Society of Plastic Surgeons. 2023 Plastic Surgery Statistics Report. https://www.plasticsurgery.org/documents/news/statistics/2022/plastic-surgery-statistics-report-2022.pdf
103. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. Updated January 31, 2020. https://icer.org/evidence-rating-matrix/
104. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Med Care*. Jun 2010;48(6 Suppl):S145-52. doi:10.1097/MLR.0b013e3181d9913b
105. Singla N, Rogier T. Abdominoplasty as an acute postoperative pain model: insights from 8 years of clinical trials. *Pain*. 2022;doi:10.1097/j.pain.0000000000002736
106. Singla N, Meske DS, Desjardins P. Exploring the Interplay between Rescue Drugs, Data Imputation, and Study Outcomes: Conceptual Review and Qualitative Analysis of an Acute Pain Data Set. *Pain Ther*. 2017;doi:10.1007/s40122-017-0074-5
107. Olsen M, Bjerre E, Hansen M, et al. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. BMC Med;doi:10.1186/s12916-016-0775-3
108. Joshi GP, Van de Velde M, Kehlet H. Development of evidence-based recommendations for procedure-specific pain management: PROSPECT methodology. *Anaesthesia*. 2019;doi:10.1111/anae.14776.
109. Moore RA, Derry S, Aldington D, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. *The Cochrane database of systematic reviews*. 2015;doi:10.1002/14651858.CD008659.pub3.
110. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama*. Sep 13 2016;316(10):1093-103. doi:10.1001/jama.2016.12195
111. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Aug 2019;22(8):931-941. doi:10.1016/j.jval.2019.02.009
112. Vertex. Suzetrigine (VX-548) ASA Update. Accessed November 12, 2024, https://investors.vrtx.com/static-files/39514f75-f903-4a34-a729-7b1646b4b0f9
113. Murphy SM. The cost of opioid use disorder and the value of aversion. *Drug Alcohol Depend*. Dec 1 2020;217:108382. doi:10.1016/j.drugalcdep.2020.108382
114. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. https://icer.org/our-approach/methods-process/value-assessment-framework/
115. Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Mar 2018;21(3):258-265. doi:10.1016/j.jval.2017.12.017

Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Numeric Pain Rating Scale (NPRS): A scale for self-report of pain, with the respondent selecting a number that best reflects the intensity of their pain using a 0–10 scale, with zero meaning "no pain" and 10 meaning "the worst pain imaginable".[66]

Sum of the Pain Intensity Difference (SPID): A measure derived from the NPRS that summarizes treatment response over a clinically relevant period (e.g., SPID-48 hours). Higher SPID values represent greater reduction in pain.[10]

Verbal Categorical Rating Scale (VRS): A four-level scale that ranges from no pain to severe pain.[67]

Patient Global Assessment (PGA): A measurement of pain treatment effectiveness, where patients rate their experience as poor, fair, good, very good, or excellent.[68]

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[69] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[70,71] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4% = 2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above one suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

We chose not to calculate the HIDI due to a lack of sufficient data of acute pain rates in racial and ethnic minority populations. There is a trend for people from racial and ethnic minority populations to underreport pain intensity, contributing to disparities in pain management.[72] Thus, we are unable to confidently provide a racial and ethnic breakdown of the US population who experience acute pain as cases in these subgroups are likely to go unreported.

A2. Potential Cost-Saving Measures in Acute Pain

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for acute pain (e.g., need for treatment of opioid overdose), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of acute pain beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with acute pain that could be reduced, eliminated, or made more efficient. No suggestions were received.

We received a suggestion from a clinician that there should be a reduction in the use of opioids, benzodiazepines, gabapentinoids, and muscle relaxants in patients who present with acute back pain in an acute care setting.

A3. Patient Input on Clinical Trial Design

Manufacturers were asked to submit a written explanation of how they engaged patients in the design of their clinical trials, including the methods used to gather patient experience data and how they determined the outcomes that matter most to patients. ICER did not receive any feedback on this specific inquiry.

B. Patient Perspectives : Supplemental Information

B1. Methods

As part of our review, we spoke to two individual patients and three patient groups (Patient Mind, US Pain Foundation, and Voices for Non-Opioid choices) and with a bioethicist who has experienced and written about acute pain.

The individual patients both experienced acute pain in the setting of chronic pain; we had difficulty finding individual patients to speak with who were only experiencing acute pain. These two patients were unaware of suzetrigine.

Apart from informing Section 2 of this report, the input we received contributed to our deciding not to focus on chronic use of non-opioid medications as a comparative outcome in this review and to perform network meta-analyses comparing suzetrigine with NSAIDs and higher dose opioids.

C. Clinical Guidelines

American Pain Society, American Society of Regional Anesthesia, and American Society of Anesthesiologists

This 2016 guideline for postoperative pain management makes recommendations that are broad and focused on good practice.[73] Recommendations include tailored education around treatment options; documentation of plans and goals; teaching caregivers how to assess pain in children; assessing patients for a history of psychiatric comorbidities, chronic pain, substance abuse, and prior postoperative treatment regimens and responses; and adjustment of the pain management plan based on adequacy of pain relief and the occurrence of adverse events.

Centers for Disease Control and Prevention

This 2022 guideline for prescribing opioids for pain shares a senior/first author with the above 2016 guideline but is much more directive in its recommendations.[26] It relies on a number of evidence reviews by the Agency for Healthcare Research and Quality (AHRQ) including a 2020 AHRQ review of treatments for acute pain.[74]

Recommendations for acute pain include maximizing the use of nonpharmacologic and nonopioid therapies; discuss risks and benefits before prescribing opioids; prescribe immediate-release opioids rather than more extended-release forms; prescribe the lowest effective dose and be cautious about increasing the dose; and limit the quantity of prescribed opioids to the expected duration of need.

The first recommendation in the guideline states, “Nonopioid therapies are at least as effective as opioids for many common types of acute pain.” Although this is consistent with the AHRQ review mentioned above that found this to be the case even for nonopioid pharmacologic therapies, we note that we heard from a number of clinical experts who disagree with this with regard to pharmacologic therapies.

Society of Hospital Medicine

This 2018 consensus guideline makes recommendations for the use of opioids for treating noncancer pain in hospitalized adults.[75] Recommendations include limiting the use of opioids to patients with severe pain, moderate pain that has not responded to nonopioid therapy, or when nonopioid therapy is contraindicated; use caution when administering opioids to patients at increased risk for adverse events; educate patients and caregivers about risks and side effects of opioids; use the lowest effective opioid dose for the shortest possible duration; use immediate release formulations of opioids; and use the oral route of administration of opioids whenever possible.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of focus for the review is adult patients with acute pain that is not adequately controlled with non-systemic therapies.

Interventions

The full list of interventions is as follows:

- Suzetrigine in addition to non-systemic therapies, if any

Comparators

Data permitting, we intend to compare all the agents to each other and to the following comparators:

- No systemic therapy for pain
- Non-opioid analgesics including NSAIDs, acetaminophen, and the combination of NSAIDs and acetaminophen
- Opioid analgesics alone or in combination with acetaminophen

Outcomes

A 2023 consensus core outcome set for acute pain recommended outcomes of pain (including pain intensity and pain interference with the patient's life), physical function, and quality of life.[76]

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Pain control
    - Pain interference in daily life (including activities of daily living)
    - Time to clinically important reduction in pain
    - Time until pain medication is no longer needed

    - Quality of life
    - Physical functioning
    - Short-term adverse events, including:
        - Undesired sedation
        - Gastrointestinal side effects including nausea, abdominal pain, constipation
        - Headache
        - Confusion
        - Clinically-important renal dysfunction
        - Gastrointestinal bleeding
    - Long-term adverse events, including:
        - Chronic pain
        - Need for chronic pain medication
        - Opioid use disorder and/or opioid misuse
- Other Outcomes
    - Adverse events including:
        - Laboratory evidence of renal dysfunction

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on settings where concerns around acute pain are likely to arise, including post-surgical, medical inpatient, emergency department, urgent care, and primary care settings in the United States.

Study Design

Randomized controlled trials and non-randomized controlled trials with any sample size will be included. Comparative observational studies will also be included.

Table D1.1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.

Section and Topic	Item #	Checklist Item
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.

Section and Topic	Item #	Checklist Item
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on suzetrigine for acute pain, as well as opioids and NSAIDs for post-operative abdominoplasty or bunionectomy acute pain, followed established best research methods.[77,78] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[79] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews.

Table D1.2. Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews Search Strategy for Suzetrigine

#	Search Term
1	exp acute pain/
2	('Acute Pain*' or 'Pain, Acute' or 'Pains, Acute' or 'Pain' or 'Pain management').ti,ab.
3	1 or 2
4	('Suzetrigine' or 'VX-548' or 'VX548').ti,ab.
5	3 and 4
6	(animals not (humans and animals)).sh.
7	5 NOT 6
8	(addresses OR autobiography OR bibliography OR biography OR comment OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR guideline OR interactive tutorial).pt
9	7 NOT 8
10	limit 9 to English language
11	Remove duplicates from 10

Table D1.3. EMBASE Search Strategy for Suzetrigine

#	Search Term
1	'pain'/exp
2	('acute pain' OR 'deep pain' OR 'lightning pain' OR 'nocturnal pain' OR 'pain response' OR 'pain syndrome' OR 'treatment related pain' OR 'pain' or 'pain management'):ti,ab
3	#1 OR #2
4	('Suzetrigine' OR 'VX-548’ OR 'VX548’ OR 'NaV1.8 inhibitor’):ti,ab
5	#3 and #4
6	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
7	#5 NOT #6
8	#7 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
9	#8 AND [english]/lim

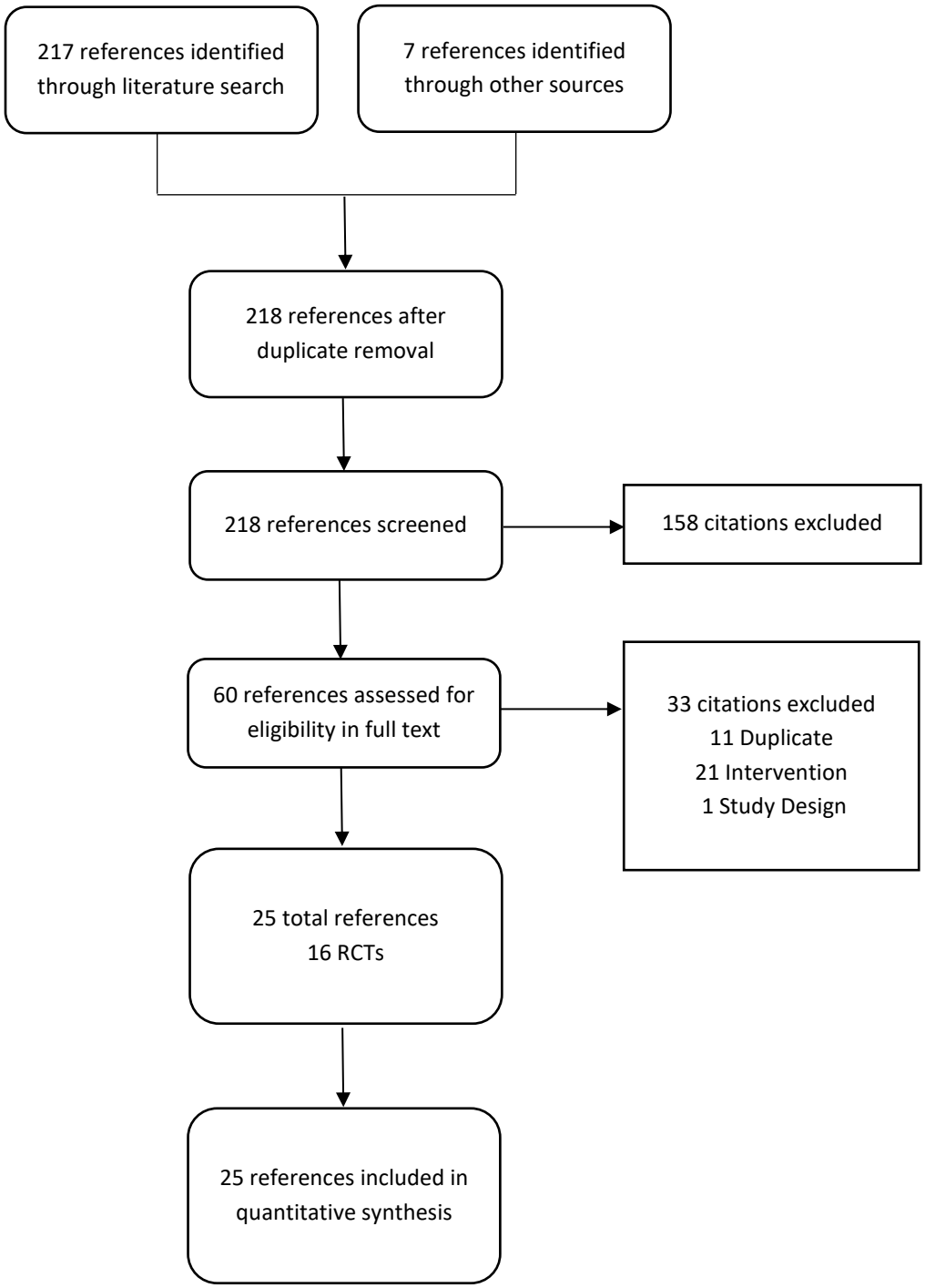
Table D1.4. Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews Search Strategy for Comparators

#	Search Term
1	('bunion' or 'bunionectomy').ti,ab.
2	('abdominoplasty').ti,ab.
3	1 or 2
4	3 AND (clinical trial, phase iii or randomized controlled trial).pt.
5	4 NOT (addresses or autobiography or bibliography or biography or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt
6	(animals not (humans and animals)).sh.
7	5 NOT 6
8	limit 7 to English language
9	Remove duplicates from 8

Table D1.5. EMBASE Search Strategy for Comparators

#	Search Term
1	'bunionectomy'/exp
2	('bunion surgery' OR 'bunionectomy'):ti,ab
3	#1 OR #2
4	'abdominoplasty'/exp
5	('abdomen plasty' OR 'plastic operation, abdomen' OR 'lipoabdominoplasty' OR 'abdominoplasty'):ti,ab
6	#3 OR #4 OR #5
7	#6 AND ('phase 3 clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de)
8	#7 NOT ('addresses' OR 'autobiography' OR 'bibliography' OR 'biography' OR 'case report' OR 'cohort analysis' OR 'comment' OR 'congresses' OR 'consensus development conference' OR 'cross-sectional study' OR 'duplicate publication' OR 'editorial' OR 'guideline' OR 'in vitro' OR 'interview' OR 'lecture' OR 'legal cases' OR 'legislation' OR 'letter' OR 'news' OR 'newspaper article' OR 'note' OR 'observational study' OR 'patient education handout' OR 'periodical index' OR 'personal narratives' OR 'portraits' OR 'practice guideline' OR 'review' OR 'retrospective study' OR 'short survey' OR 'video audio media')/it
9	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
10	#8 NOT #9
11	#10 AND [english]/lim
12	#11 NOT [medline]/lim

Figure D1.1. PRISMA flow Chart Showing Results of Literature Search for Suzetrigine and Comparators



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, Minnesota);a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

Data Extraction

Data were extracted into Microsoft Word and Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[78,80] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. Clinical trials that did not have a corresponding peer-reviewed journal article were assessed on their publicly available sources of information, such as ClinicalTrials.gov record and statistical analysis plan.[81]

To assess the risk of bias in trials, we rated the categories as: “low risk of bias,” “some concerns,” or “high risk of bias.” Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias*: The study is judged to be at low risk of bias for all domains for this result.*

Some concerns*: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

High risk of bias*: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the outcome of SPID48. See Table D1.6.

Table D1.6. Risk of Bias Assessment for SPID-48 Outcome

Study (NCT, study label)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Suzetrigine[10,18]						
NCT05553366 NAVIGATE-1	Low Risk	Low Risk	Some Concerns	Low Risk	Some Concerns	Some Concern
	Notes: During this assessment, the NAVIGATE-1 study design, and results had not been formally published in a research protocol or peer-reviewed journal and were instead shared via a slide-deck presentation. Study design was assumed to be identical to previous bunionectomy Phase II trial (NCT04977336). Rescue medication (ibuprofen) was used, but the proportion of participants per study arm was not reported. Missing data from use of rescue medication were imputed using a 6-hour windowed Last Observation Carried Forward (LOCF) method. An ad hoc sensitivity analysis showed different results when rescue imputation was not applied. The difference in SPID48 between suzetrigine and HB5/APAP325 was no longer significant.					
NCT05558410 NAVIGATE-2	Low Risk	Low Risk	Some Concern	Low Risk	Some Concern	Some Concern
	Notes: During this assessment, the NAVIGATE-2 study design and results had not been formally published in a research protocol or peer-reviewed journal and were instead shared via a slide-deck presentation. Study design was assumed to be identical to previous abdominoplasty Phase II trial (NCT05034952). Rescue medication (ibuprofen) was used, but the proportion of participants per study arm was not reported. Missing data from use of rescue medication were imputed using a 6-hour windowed LOCF method. An ad hoc sensitivity analysis showed similar results when rescue imputation was not applied. The difference in SPID48 between suzetrigine and HB5/APAP325 was no longer significant.					
NCT05034952	Low Risk	Low Risk	Some Concern	Low Risk	Low Risk	Some Concern
	Notes: To address rescue medication's potential impact, researchers used a 6-hour windowed LOCF method for pain intensity analysis. LOCF was applied to 26% of NPRS scores in the suzetrigine group and 34% in the placebo group. The Cochrane Risk of Bias 2 tool considers these imputed data as missing data, suggesting potential bias. A post-hoc sensitivity analyses of SPID48 using multiple imputation of the last observation found similar benefit of treatment versus placebo.					

Study (NCT, study label)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
NCT04977336	Low Risk	Low Risk	Some Concern	Low Risk	Low Risk	Some Concern
	Notes: To address rescue medication's potential impact, researchers used a 6-hour windowed LOCF method for pain intensity analysis. LOCF was applied to 28% of NPRS scores in the suzetrigine group and 30% in the placebo group. The Cochrane Risk of Bias 2 tool considers these imputed data as missing data, suggesting potential bias. A post-hoc sensitivity analyses of SPID48 using multiple imputation of the last observation found similar benefit of treatment versus placebo.					
Diclofenac[82-85]						
NCT00366444	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk
	Notes: After rescue medication (hydrocodone/APAP [5 mg/500 mg]), pain assessments for the subsequent six hours were considered missing, with the pain assessment at rescue medication time carried forward (LOCF). A significantly greater proportion of participants in the placebo arm utilized rescue medication than those in the diclofenac arm (91% vs 43%). The substantial difference in missing/imputed data between study groups indicates a high risk of bias in outcome data. For patients who discontinued the study, the worst-observation-carried-forward (WOCF) approach was used for the remainder of the 48-hour multiple-dose period. However, few patients in each arm discontinued the trial: 1% diclofenac and 2% placebo.					
NCT00375934	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk
	Notes: SPID48 was a secondary outcome in this study. After rescue medication (hydrocodone/APAP [5 mg/500 mg]), pain assessments for the subsequent six hours were considered missing, with the pain assessment at rescue medication time carried forward (LOCF). A significantly greater proportion of participants in the placebo arm utilized rescue medication than those in the diclofenac arm (92% vs 58%). The substantial difference in missing/imputed data between study groups indicates a high risk of bias in outcome data. For patients who discontinued the study, the WOCF approach was used for the remainder of the 48-hour multiple-dose period. However, few patients in each arm discontinued the trial: 3% diclofenac and 6% placebo.					
NCT01462435	Low Risk	Low Risk	Some Concern	Low Risk	Low Risk	Some Concern
	Notes: The imputation method used BOCF (Baseline Observation Carried Forward) when subjects used rescue medication, withdrew due to lack of efficacy, or experienced adverse events. LOCF was used for withdrawals due to other reasons. High rescue medication rates (82-85% in treatment arms, 97% in placebo) resulted in substantial missing data. FDA sensitivity analyses using no imputation and 6-hour windowed LOCF confirmed the primary analysis showing treatment groups superior to placebo, though standardized mean differences were notably higher.					
Indomethacin[86-88]						

Study (NCT, study label)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
NCT01543685	Low Risk	Low Risk	Some Concern	Low Risk	Some Concern	Some Concern
	Notes: Missing pain assessments were imputed using different methods: BOCF for early discontinuation due to lack of efficacy, adverse events, or intolerance; LOCF for other reasons; and linear interpolation for intermittent missing assessments. Pain assessments after the first dose of rescue medications were disregarded and imputed using BOCF. High rescue medication rates (82-90% in treatment arms, 97% in placebo) resulted in substantial missing data. Trial participants in placebo arm had median of 5 uses of rescue medication versus 2 and 3 in the treatment arms. FDA sensitivity analyses using a 4 and 6-hour windowed BOCF imputation confirmed the primary analysis showing treatment groups superior to placebo, though standardized mean differences were notably higher.					
NCT01626118	Low Risk	Low Risk	Some Concern	Low Risk	Some Concern	Some Concern
	Notes: Missing pain assessments were imputed using different methods: BOCF for early discontinuation due to lack of efficacy, adverse events, or intolerance; LOCF for other reasons; and linear interpolation for intermittent missing assessments. Pain assessments after the first dose of rescue medications were disregarded and imputed using BOCF. High rescue medication rates (76-87% in treatment arms, 89% in placebo) resulted in substantial missing data. FDA sensitivity analyses using a 4 and 6-hour windowed BOCF imputation confirmed the primary analysis showing treatment groups superior to placebo, though standardized mean differences were notably higher.					
Celecoxib[89]						
NCT03108482	Low Risk	Low Risk	Some Concern	Low Risk	Some Concern	Some concern
	Notes: Missing pain intensity scores due to discontinuation from related AEs or lack of efficacy were imputed using the WOCF. Scores missing due to other reasons for discontinuation used the LOCF. When rescue medication was taken within the 48 hours, the prerescue pain intensity score was used to impute all scores within four hours post-medication, even if another dose of study medication was administered within this period. There were similar rates of rescue mediation (acetaminophen or oxycodone HCl) use between the celecoxib and placebo study arms (88.4 and 88.8%, respectively). Sensitivity analyses around different styles of imputation (e.g., no imputation, WOCF for all missing data) were largely supportive of the main analysis, with the exception of adjusted analysis for rescue medication use, which did not find a statistically significant difference between treatment and placebo.					
Opioid/APAP[90-95]						

Study (NCT, study label)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
NCT01743625	Low Risk	Low Risk	Some Concern	Low Risk	Low Risk	Some Concern
	Notes: Both the treatment and placebo study arms had high proportions of rescue medication use (81.1 and 93.1%, respectively). As a result, pain scores were censored within six hours of rescue medication. Study withdrawals stemmed from adverse events, lack of efficacy, or other reasons, and were categorized as "missing-not-at-random" with the model addressing distinct missingness patterns. In the treatment arm, 12 of 203 participants discontinued due to lack of efficacy, compared to 32 of 203 in the placebo arm.					
NCT01038609	Low	No Information	Some Concern	No Information	Some Concern	Some Concern
	Notes: Clinical trial information is limited, sourced only from a clinicaltrials.gov listing and one clinical study report. The study was single-blinded. Rescue medication usage in the 48-hour treatment period differed statistically significantly between treatment and placebo arms. Within the first 12 hours, placebo subjects had a higher rescue medication rate (80%) compared to HB10/APAP650 subjects (63%). The study did not report: Methods for handling missing scores due to rescue medication. Impact of sensitivity analyses using different imputation methods on overall findings.					
NCT02487108	Low Risk	Low Risk	High Risk	Low Risk	High Risk	High Risk
	Notes: The imputation method used for when subjects used rescue medication is unknown. We were unable to find any peer-reviewed publication for this study and were limited to the clinicaltrials.gov listing. High rescue medication rates (69.7-78% in treatment arms, 93% in placebo) resulted in substantial missing data. It is unknown whether any sensitivity analyses would support primary efficacy findings.					
Oxycodone[96-98]						
NCT00613938	Low Risk	Low Risk	Some Concern	Low Risk	Some Concern	Some Concern
	Notes: Missing pain intensity scores due to discontinuation were imputed using the LOCF method. A greater proportion of participants in the placebo arm utilized rescue medication than those in the oxycodone HCl IR arm (23.2% vs 3.2%). Sensitivity analyses using BOCF and WOCF for imputation were said to be consistent with primary efficacy results but not reported.					
NCT00364247	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk
	Notes: A significantly greater proportion of participants in the placebo arm utilized rescue medication than those in the oxycodone HCl IR 15-mg arm (49% vs 9%). Participants who utilized rescue medication were discontinued from the study due to lack of efficacy; LOCF was applied for the remainder of the study. The substantial difference in missing/imputed data between study groups indicates a high risk of bias in outcome data. Permitted rescue medications included acetaminophen, ketorolac, and/or hydrocodone/ acetaminophen combination, which can vary in the magnitude and duration of analgesic relief provided.					

Study (NCT, study label)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
NCT01484652	Low Risk	Low Risk	Some Concern	Low Risk	Low Risk	Some Concern
	Notes: Both the treatment and placebo study arms had high proportions of rescue medication use (85.8 and 99.3%, respectively). As a result, pain intensity scores were censored for six hours after supplemental medication use. Multiple imputation with Markov chain Monte Carlo (MCMC) method replaced censored or missing pain intensity data for both patients using and not using supplemental medication. Multiple sensitivity analyses for SPID48 were conducted by the FDA to explore various multiple imputation techniques (BOCF/LOCF, 6-8 hour windows for rescue) and confirmed initial reporting of treatment benefit over placebo.					

AEs: adverse events, NPRS: Numeric Pain Rating Scale, SPID-48: Summed Pain Intensity Difference Score Calculated Over the First 48 Hour

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[20] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.5. Representation for each demographic category was evaluated by quantitatively comparing clinical trial participants with disease-specific prevalence estimates, using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Next, a representation score between 0 to 3 was assigned based on the PDRR estimate (See Table D1.6 for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.7.

Prevalence estimates of moderate to severe acute pain stratified by race/ethnicity, sex, and age were not available. Instead, we compared the demographic characteristics of the participants in the two pivotal suzetrigine trials, NAVIGATE-1 and NAVIGATE-2, to three reference populations: the overall United States population, and patients who have undergone the same surgical procedures as in the trials, specifically abdominoplasty and bunionectomy.

Table D1.7. Demographic Characteristics and Categories

Demographic Characteristics	Categories
1. Race and Ethnicity*	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
2. Sex	• Female • Male
3. Age	• Older adults (≥65 years)

*Multinational trials: For multinational clinical trials, our approach is to evaluate only the subpopulation of patients enrolled from the US on racial and ethnic diversity

Table D1.8. Representation Score

PDRR	Score
0	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.9. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black or African American, White, and Hispanic or Latino	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

*American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

Results United States Population

Table D1.10. Race and Ethnicity

	White	Black/African American	Asian	Hispanic/ Latino	Total score	Diversity Rating	AIAN	NHPI
Prevalence[99]	75.50%	13.60%	6.30%	19.10%	-	-	-	-
NAVIGATE-1[18]	70.70%	24.20%	NR	NR	-	-	NR	NR
PDRR	0.94	1.78	NC	NC	-	-	NC	NC
Score	3	3	0	0	6	Poor	NC	NC
NAVIGATE-2[18]	69.60%	26.70%	NR	NR	-	-	NR	NR
PDRR	0.92	1.96	NC	NC	-	-	NC	NC
Score	3	3	0	0	6	Poor	NC	NC

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.11. Sex and Age

	Sex				Age		
	Male	Female	Score	Rating	Older Adults (≥65 years)	Score	Rating
Prevalence[99]	49.50%	50.50%	-	-	-	-	-
NAVIGATE-1[18]	15.00%	85.00%	-	-	NR	NR	NR
PDRR	0.30	1.68	-	-	NC	NC	NC
Score	1	3	4	Poor	NC	NC	NC
NAVIGATE-2[18]	1.80%	98.20%	-	-	NR	NR	NR
PDRR	0.04	1.94	-	-	NC	NC	NC
Score	1	3	4	Poor	NC	NC	NC

NC: Not Calculated, PDRR: Participant to Disease-prevalence Representation Ratio

Results: Bunionectomy

A Diversity Rating for race and ethnicity was not calculated for the NAVIGATE-1 trial because we were unable to obtain data on the prevalence or incidence of bunionectomy procedures by race and ethnicity.

Table D1.12. Sex and Age

	Sex				Age		
	Male	Female	Score	Rating	Older Adults (≥65 years)	Score	Rating
Prevalence[100]	13.70%	86.39%	-	-	-	-	-
NAVIGATE-1[18]	15.00%	85.00%	-	-	NR	-	-
PDRR	1.09	0.98	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC

NC: Not Calculated, PDRR: Participant to Disease-prevalence Representation Ratio

Results: Abdominoplasty

Table D1.13. Race and Ethnicity

	White	Black/African American	Asian	Hispanic/ Latino	Total score	Diversity Rating	AIAN	NHPI
Prevalence[101]	74.00%	7.00%	5.00%	12.00%	-	-	-	-
NAVIGATE-1[18]	69.60%	26.70%	NR	NR	-	-	NR	NR
PDRR	0.94	3.81	NC	NC	-	-		
Score	3	3	0	0	6	Poor	NC	NC

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.14. Sex and Age

	Sex				Age		
	Male	**Female**	**Score**	**Rating**	**Older Adults (≥65 years)**	**Score**	**Rating**
Prevalence[102]	2.00%	98.00%	-	-	-	-	-
NAVIGATE-2[102]	1.80%	98.20%	-	-	NR	-	-
PDRR	0.90	1.00	-	-	NC	-	-
Score	3	3	6	Good	NC	NC	NC

NC: Not Calculated, PDRR: Participant to Disease-prevalence Representation Ratio

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[103,104]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, as well as the large number of investigated therapies for acute pain, particularly in our two acute pain models of abdominoplasty and bunionectomy, we performed an assessment of publication bias for suzetrigine and other therapies in our network meta-analysis using ClinicalTrials.gov. Search terms included “VX-548", "suzetrigine”, “abdominoplasty”, and “bunionectomy”.

We identified two studies that were conducted and posted study results to ClinicalTrials.gov, but did not produce a peer-reviewed publication: StudyB15 (NCT01038609) and Study 16 (NCT02487108), two bunionectomy trials that evaluated several combinations of hydrocodone/acetaminophen versus placebo.

D2. Network Meta-Analysis Methodology and Results

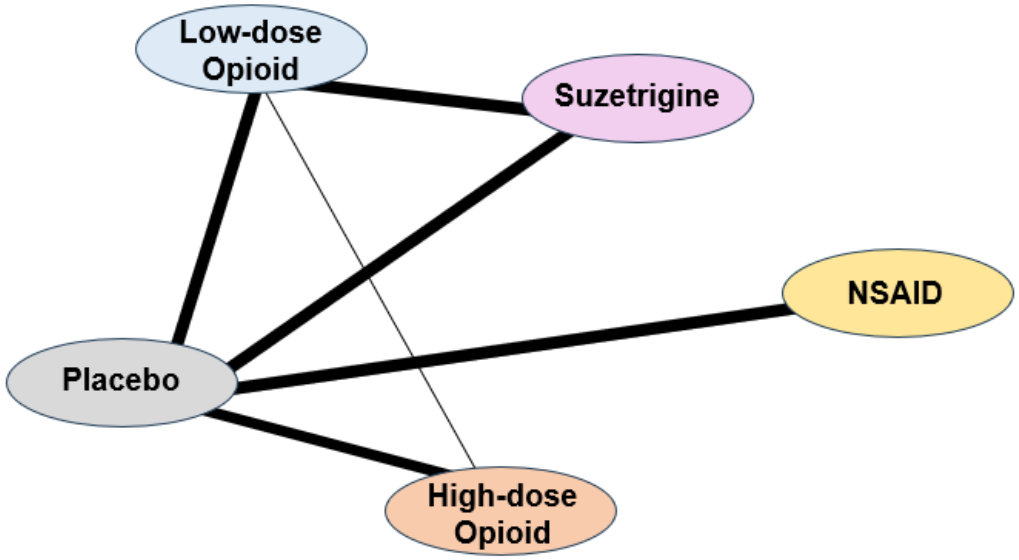
Feasibility of Conducting Indirect Comparison / Network Meta-Analysis (NMA)

We examined the feasibility of conducting indirect comparisons or an NMA because direct evidence for the comparative efficacy of suzetrigine versus high-dose opioids and suzetrigine versus NSAIDs for acute pain was not available. We examined whether there were notable differences in study populations, study design, intervention type, outcome definition and measurement, and analytic methods, as well as quality of these studies.

Sixteen trials met the criteria for inclusion in the NMA, demonstrating sufficient similarity across critical study parameters, including population characteristics, experimental design, intervention

approaches, outcome definitions, and analytical methodologies (detailed in Table D2.3 and D3.1). Most of the trials focused on post-surgical pain following bunionectomy procedures. The study populations were predominantly female, with participants typically in their early to mid-40s, and characterized by a baseline pain intensity averaging around 6 on a 10-point scale.

Figure D2.1. Network Diagram (16 Trials)



Treatments with direct comparisons are linked with a line. The thickness of the line corresponds to the number of trials in the comparison.

NMA Methods

The pivotal trials of suzetrigine provided a direct comparison versus no systematic therapy (represented by placebo arms) and HB5/APAP325 every six hours, which we deemed to be a low-dose opioid analgesic in typical clinical practice given the strength of hydrocodone and frequency of treatment. As there were no direct evidence for the comparative efficacy of suzetrigine against two additional classes of analgesics: high-dose oral opioids (therapies with greater dose and frequency of opioid use than HB5/APAP325) and NSAIDs, both with and without acetaminophen, we conducted a network meta-analysis.

We restricted our systematic literature search to the study population of patients with acute pain following abdominoplasty and bunionectomy procedures to align with the studied population of the suzetrigine clinical trials. These procedures represent validated pain models for soft-tissue and hard-tissue pain, respectively, and are recognized by regulatory authorities as benchmark models for analgesic drug approval.[105]

Our outcome of interest was the SPID48, a time-weighted sum of the pain-intensity difference over the 48-hour period. This is a common primary endpoint in acute pain trials and was evaluated as a continuous outcome. Table D2.4 provides an overview of each study arm's SPID48 mean scores and respective standard error and standard deviation. Because there are differences in how the SPID48 was measured (using the Numerical Pain Rating Scale or Visual Analog Scale) and reported (positive or negative least squares mean) across the trials in our network, we calculated the standardized mean difference between the active treatment and placebo arms for each study (Table D2.4). We explored the feasibility of assessing suzetrigine and other analgesics on safety and tolerability outcomes but found inconsistent durations of follow-up across our trials and did not proceed with the analysis.

A full list of included therapies and their dosages are outlined in Table D2.1. We categorized the interventions into classes, which included low-dose and high-dose opioids, NSAIDs, suzetrigine, and placebo (Figure D2.1). We excluded intravenous formulations of NSAID and opioid analgesics for two reasons: first, their rapid onset of action would likely distort SPID48 values (as earlier pain reduction would yield higher scores compared to equivalent oral doses); and second, we aimed to compare therapies typically used in outpatient care. We excluded tapentadol and tramadol from our analysis based on specific clinical factors. Tapentadol was excluded due to its limited use in clinical practice and absence of a generic equivalent. Tramadol was omitted because it is believed to present comparable side effects and addiction risks to other opioids while providing less effective pain management, rendering it less meaningful as a clinical comparator.

The NMA used a Bayesian random-effects approach using normal likelihood with identity link. Noninformative prior distributions were applied to all model parameters, and each analysis was conducted using 100,000 iterations, after discarding the first 5,000 burn-in iterations. The input was standardized mean differences between active treatment and placebo in SPID48 (using the Numerical Pain Rating Scale or Visual Analog Scale) and standard error. For one study (NCT01743625), we imputed the unknown standard error value for both study arms by calculating the mean standard error scores from comparable trials within the network. We evaluated model fit for all outcomes and ran both random and fixed-effects models for comparison (Table D2.2). Due to the heterogeneity among the included trials in our network (Table D2.3), we focused on the results of the random-effects NMA results described in the main report.

Table D2.1. Model Fit for Random-Effects and Fixed-Effects Model

Model	Outcome	Dbar	DIC	Unconstrained Datapoints	I^2
Random-Effects	SPID48	16.430616	25.276728	17	3%
Fixed-Effects	SPID48	21.432956	25.439833	17	25%

Dbar: posterior distribution for the deviance, DIC: deviance information criterion, I^2: fraction of variance due to heterogeneity, SPID48: Sum of the pain-intensity difference over 48 hours.

Our base-case analysis consisted of 12 trials, 10 of which were bunionectomy trials. We conducted a sensitivity analysis that included only on bunionectomy trials and found the results to be consistent with the base case (Table D2.6). We identified several studies in our network that had significantly greater SMD/effect size values (e.g., SMD of 1.4 of diclofenac 25 mg versus placebo) that we believe may be due to different rates of use of rescue medication between study arms and subsequent imputation of SPID48 scores. We considered these studies to be at high risk of bias due to their treatment of missing data (see Table D1.6) and excluded them from the base-case analysis. A sensitivity analysis that included all relevant trials, irrespective of their risk of bias, demonstrated no change in the statistical significance of any point estimates. However, the point estimates for higher-dose opioids and NSAIDs versus placebo were higher than those reported in the base-case analysis (Table D2.7).

Table D2.2. Included Interventions in the Network

Intervention	Detail
Suzetrigine	The dosing of the suzetrigine monotherapy arm was 100-mg loading dose with a subsequent 50 mg dose every 12 hours. Two other dosing strategies of suzetrigine were studied in earlier Phase II trials: 60-mg loading dose, then 30 mg every 12 hours and 20-mg loading dose, then 10 mg every 12 hours. These dosages were not studied in later Phase III trials and were not included in the model.
Placebo	The placebo arm of each trial.
Low-dose Opioid	The low-dose opioid in the network included pooled estimates from the HB/APAP(5/325 mg) Q6H use of HB/APAP(5/325 mg) every six hours.
High-dose Opioid	The high-dose opioid class in the network included pooled estimates from the following interventions: Oxycodone HCL IR [15 mg Q4-6H] Xartemis [oxycodone 15/APAP 650 mg] Q12H HB/APAP [7.5/325 mg Q12H] HB/APAP ER [10/650 mg Q12H] HB/APAP IR [7.5/325 mg Q4-6H] HB/APAP IR [10/325 mg Q4-6H]

Intervention	Detail
NSAID	The NSAID class in the network included pooled estimates from the following interventions: Zipsor [Diclofenac 25 mg Q6H] Celebrex [Celecoxib 200 mg BID] Celebrex [Celecoxib 100 mg Q12H] Zorvolex [Diclofenac 18 mg TID] Zorvolex [Diclofenac 35 mg TID] Tivorbex [Indomethacin 20 mg TID] Tivorbex [Indomethacin 40 mg BID] Tivorbex [Indomethacin 40 mg TID]

BID: twice a day, HB/APAP: Hydrocodone bitartrate-acetaminophen, HCL: hydrochloride, IR: immediate release, mg: milligram, NSAID: Nonsteroidal anti-inflammatory drugs, Q6H: every six hours, Q12H: every twelve hours, TID: three times a day

NMA Baseline Characteristics

Table D2.3. NMA Trial Baseline Characteristics[10,82,83,85-87,90-97]

Trial	Arm	Treatment Class	N	Age, Mean (SD)	Female, n (%)	Pain at Baseline, Mean (SD)
NCT05558410	Suzetrigine 50 mg Q12H	Suzetrigine	447	41.5 (9.1)	437 (97.8)	NPRS: 7.3 (1.7)
	HB/APAP 5/325 mg Q6H	Low-dose Opioid	448	42.1 (8.7)	441 (98.4)	NPRS: 7.4 (1.7)
	Placebo	Placebo	223	41.5 (8.5)	220 (98.7)	NPRS: 7.5 (1.7)
NCT05553366	Suzetrigine 50 mg Q12H	Suzetrigine	426	47.7 (13.3)	366 (85.9)	NPRS: 6.7 (1.8)
	HB/APAP 5/325 mg Q6H	Low-dose Opioid	431	48.3 (12.6)	359 (83.3)	NPRS: 6.8 (1.9)
	Placebo	Placebo	216	48.1 (13.5)	187 (86.6)	NPRS: 6.8 (1.8)
NCT04977336	Suzetrigine 50 mg Q12H	Suzetrigine	60	47.6 (13.7)	53 (88)	NPRS: 6.7 (1.7)
	HB/APAP 5/325 mg Q6H	Low-dose Opioid	60	50.0 (12.5)	50 (83)	NPRS: 6.9 (1.9)
	Placebo	Placebo	59	47.8 (13.6)	49 (83)	NPRS: 6.9 (1.7)
NCT05034952	Suzetrigine 50 mg Q12H	Suzetrigine	76	43.1 (9.7)	75 (99)	NPRS: 7.2 (1.7)
	HB/APAP 5/325 mg Q6H	Low-dose Opioid	76	45.4 (10.7)	73 (96)	NPRS: 7.3 (1.8)
	Placebo	Placebo	77	42.6 (9.5)	76 (99)	NPRS: 7.4 (1.6)
NCT00375934	DPSGC 25 mg Q6H	NSAID	99	42 (18-65)*	86 (87)	NPRS: 7.52 (1.56)
	Placebo	Placebo	101	42 (18-63)*	86 (85)	NPRS: 7.44 (1.42)
NCT00366444	DPSGC 25 mg Q6H	NSAID	102	45 (11.2)	88 (86.3)	NPRS: 6.9 (NR)
	Placebo	Placebo	99	45.4 (11.8)	86 (86.9)	NPRS: 7.3 (NR)
NCT01462435	Diclofenac 35 mg TID	NSAID	107	39.2 (11.8)	89 (83.2)	VAS: 74.1 (16.1)
	Diclofenac 18 mg TID	NSAID	109	39.4 (11.7)	94 (86.2)	VAS: 76.7 (15.9)
	Celecoxib 200 mg BID	NSAID	106	40.3 (11.9)	96 (90.6)	VAS: 74.2 (16.8)
	Placebo	Placebo	106	39.9 (12.6)	92 (86.8)	VAS: 76.3 (16.3)
NCT01543685	Indomethacin 40 mg TID	NSAID	93	41.5 (11.4)	79 (84.9)	VAS: 72.8 (17.4)
	Indomethacin 40 mg BID	NSAID	91	41.4 (12.4)	72 (79.1)	VAS: 73.7 (17.0)
	Indomethacin 20 mg TID	NSAID	91	41.5 (13.4)	79 (86.8)	VAS: 72.2 (16.8)
	Celecoxib 200 mg BID	NSAID	93	41.0 (12.3)	77 (82.8)	VAS: 73.5 (17.0)
	Placebo	Placebo	94	40.4 (13.3)	77 (81.9)	VAS: 73.7 (16.2)

Trial	Arm	Treatment Class	N	Age, Mean (SD)	Female, n (%)	Pain at Baseline, Mean (SD)
NCT01626118	Indomethacin 40 mg TID	NSAID	94	40.2 (12.27)	80 (85.1)	VAS: 71 (16.33)
	Indomethacin 40 mg BID	NSAID	93	38.9 (12.50)	77 (82.8)	VAS: 71.2 (16.11)
	Indomethacin 20 mg TID	NSAID	92	41.3 (12.57)	77 (83.7)	VAS: 72.3 (15.90)
	Placebo	Placebo	94	40.7 (11.32)	83 (88.3)	VAS: 73.9 (16.60)
NCT03108482	Celecoxib 100 mg Q12H	NSAID	181	45.1 (13.0)	160 (88.4)	NPRS: 6.7 (1.4)
	Placebo	Placebo	89	46.1 (14.9)	75 (84.3)	NPRS: 6.8 (1.3)
NCT01484652	Oxycodone/APAP (15/650 mg) Q12H	High-dose Opioid	150	41.9 (13.1)	131 (87.3)	NPRS: 6.2 (1.7)
	Placebo	Placebo	153	44.1 (14.0)	127 (83.0)	NPRS: 6.0 (1.5)
NCT01743625	HB/APAP (7.5/325 mg) Q12H	High-dose Opioid	201	42.5 (13.4)	168 (83.6)	NPRS: 7.4 (NR)
	Placebo	Placebo	202	44.3 (13.7)	185 (91.6)	NPRS: 7 (NR)
NCT02487108	HB/APAP IR (5/325 mg) Q4-6H	Low-dose Opioid	142	47.5 (14.39)	124 (87.3)	NR
	HB/APAP IR (7.5/325 mg) Q4-6H	High-dose Opioid	143	45.8 (14.45)	125 (87.4)	NR
	HB/APAP IR (10/325 mg) Q4-6H	High-dose Opioid	142	44.9 (13.87)	113 (79.6)	NR
	Placebo	Placebo	142	46.2 (18.94)	119 (83.8)	NR
NCT01038609	HB/APAP ER (10/650 mg) Q12H	High-dose Opioid	48	40.4 (13.16)	41 (85.4)	NR
	Placebo	Placebo	51	45.2 (12.47)	45 (88.2)	NR
NCT00364247	Oxycodone HCl IR 15 mg Q4-6H	High-dose Opioid	125	46.4 (13.02)	110 (88)	NR†
	Placebo	Placebo	120	44.3 (14.45)	108 (90)	
NCT00613938	Oxycodone IR 10 mg Q4-6H	High-dose Opioid	278	43.4 (13.25)	233 (84)	NPRS: 7.1 (1.84)
	Placebo	Placebo	69	42.8 (13.65)	64 (93)	NPRS: 6.8 (1.90)

APAP: acetaminophen, BID: twice a day, DPSGC: Diclofenac Potassium liquid filled Soft Gelatin Capsule, ER: extended release, HB: hydrocodone bitartrate, HCl: hydrochloride, IR: immediate release, mg: milligram, N: number of participants, NPRS: Numeric Pain Rating Scale, NR: not reported, NSAID: Nonsteroidal anti-inflammatory drugs, SD: standard deviation, TID: three times a day, VAS: visual Analog Scale, Q6H: every six hours, Q4-6h: every four to six hours, Q12H: every 12 hours, Q24H: every 24 hours

*Age, mean (range)

†The majority of patients (74% to 78%) reported severe pain at the baseline pain assessment

Table D2.4 SPID48 Measurements[10,82,83,85-87,90-97]

Study & Procedure	Treatment Arm & Class	N	LS Mean SPID48	SPID48 SE	SPID48 SD
NCT05558410 (Phase III Abdominoplasty)	Low-dose Opioid: HB/APAP(5/325 mg) Q6H	448	111.8	4.3	91.0
NCT05558410 (Phase III Abdominoplasty)	Placebo	223	70.1	6.1	91.1
NCT05558410 (Phase III Abdominoplasty)	Suzetrigine (100 mg loading dose, then 50 mg Q12H)	447	118.4	4.3	90.9
NCT05034952 (Phase II Abdominoplasty)	Low-dose Opioid: HB/APAP(5/325 mg) Q6H	76	85.2	10.3	89.8
NCT05034952 (Phase II Abdominoplasty)	Placebo	77	72.7	10.2	89.5
NCT05034952 (Phase II Abdominoplasty)	Suzetrigine (100 mg loading dose, then 50 mg Q12H)	76	110.5	10.3	89.8
NCT05553366 (Phase III Bunionectomy)	Low-dose Opioid: HB/APAP(5/325 mg) Q6H	431	120.1	4.5	93.4
NCT05553366 (Phase III Bunionectomy)	Placebo	216	70.6	6.3	92.6
NCT05553366 (Phase III Bunionectomy)	Suzetrigine (100 mg loading dose, then 50 mg Q12H)	426	99.9	4.5	92.9
NCT04977336 (Phase II Bunionectomy)	Low-dose Opioid: HB/APAP(5/325 mg) Q6H	60	115.6	11.5	89.1
NCT04977336 (Phase II Bunionectomy)	Placebo	59	101	11.6	89.1
NCT04977336 (Phase II Bunionectomy)	Suzetrigine (100 mg loading dose, then 50 mg Q12H)	60	137.8	11.5	89.1
NCT01484652 (Phase III Bunionectomy)	High-dose Opioid: Xartemis [oxycodone 15/APAP 650 mg] Q12H	150	114.9	7.6	93.6
NCT01484652 (Phase III Bunionectomy)	Placebo	153	66.9	7.6	94.0
NCT01743625 (Phase III Bunionectomy)	High-dose Opioid: HB/APAP (7.5/325 mg) Q12H	201	144.2	7.0*	98.5*
NCT01743625 (Phase III Bunionectomy)	Placebo	202	101.8	7.0*	98.8*
NCT00366444 (Phase III Bunionectomy)	NSAID: Zipsor [Diclofenac (25 mg)] Q6H	102	210	8.1	81.8
NCT00366444 (Phase III Bunionectomy)	Placebo	99	90.3	9.1	90.8
NCT00375934 (Phase III Bunionectomy)	NSAID: Zipsor [Diclofenac (25 mg)] Q6H	99	203.1	9.5	94.8
NCT00375934 (Phase III Bunionectomy)	Placebo	101	86.6	9.5	95.2
NCT01462435 (Phase III Bunionectomy)	NSAID: Celebrex [celecoxib 200 mg BID]	106	390.22	86.6	891.9
NCT01462435 (Phase III Bunionectomy)	NSAID: Zorvolex [Diclofenac 18 mg TID]	109	393.25	85.5	892.1
NCT01462435 (Phase III Bunionectomy)	NSAID: Zorvolex [Diclofenac 35 mg TID]	107	524.05	86.2	892.0
NCT01462435 (Phase III Bunionectomy)	NSAID: Zorvolex [Diclofenac 18 and 35 mg TID; POOLED]	216	458.04	60.7	892.4

Study & Procedure	Treatment Arm & Class	N	LS Mean SPID48	SPID48 SE	SPID48 SD
NCT01462435 (Phase III Bunionectomy)	Placebo	106	77.1	86.6	891.8
NCT01462435 (Phase III Bunionectomy)	NSAID: Celebrex and Zorvolex Pooled for Class Effect	322	435.7	49.7	891.4
NCT01543685 (Phase III Bunionectomy)	NSAID: Celebrex [celecoxib 200 mg BID]	93	279.4	91.9	886.3
NCT01543685 (Phase III Bunionectomy)	NSAID: Tivorbex [Indomethacin 20 mg TID]	91	380.5	92.9	886.2
NCT01543685 (Phase III Bunionectomy)	NSAID: Tivorbex [Indomethacin 40 mg BID]	91	328	92.9	886.2
NCT01543685 (Phase III Bunionectomy)	NSAID: Tivorbex [Indomethacin 40 mg TID]	93	509.6	91.9	886.3
NCT01543685 (Phase III Bunionectomy)	NSAID: Tivorbex [Indomethacin 20 TID, 40 BID, POOLED]	182	354.3	65.5	884.1
NCT01543685 (Phase III Bunionectomy)	NSAID: Tivorbex [Indomethacin 20 TID, 40 BID, 40 TID, POOLED]	275	406.8	53.4	886.3
NCT01543685 (Phase III Bunionectomy)	Placebo	94	67.8	91.4	886.2
NCT01626118 (Phase III Bunionectomy)	NSAID: Tivorbex [Indomethacin 20 mg TID]	92	342.8	89.5	858.6
NCT01626118 (Phase III Bunionectomy)	NSAID: Tivorbex [Indomethacin 40 mg BID]	93	623.2	122.6	1182.1
NCT01626118 (Phase III Bunionectomy)	NSAID: Tivorbex [Indomethacin 40 mg TID]	94	598.7	121.1	1173.8
NCT01626118 (Phase III Bunionectomy)	NSAID: Tivorbex [Indomethacin 20 TID, 40 BID, POOLED]	185	483.8	76.5	1040.7
NCT01626118 (Phase III Bunionectomy)	NSAID: Tivorbex [Indomethacin 20 TID, 40 BID, 40 TID, POOLED]	279	522.5	65.1	1086.6
NCT01626118 (Phase III Bunionectomy)	Placebo	94	280.5	84.3	817.6
NCT03108482 (Phase III Bunionectomy)	NSAID: Celebrex [celecoxib 100 mg Q12H]	181	103.7	6.5	87.2
NCT03108482 (Phase III Bunionectomy)	Placebo	89	74.6	9.2	86.4
NCT00613938 (Phase III Bunionectomy)	High-dose Opioid: Oxycodone IR [10 mg Q4-6H]	278	140.3	6.0	99.5
NCT00613938 (Phase III Bunionectomy)	Placebo	69	54.1	12.7	105.7
NCT01038609 (Phase II Bunionectomy)	High-dose Opioid: HB/APAP ER [10/50 Q12H]	48	450.8	159.6	1105.9
NCT01038609 (Phase II Bunionectomy)	Placebo	51	-57.6	154.0	1099.7
NCT02487108 (Phase III Bunionectomy)	Low-dose Opioid: HB/APAP IR [5/325 mg Q4-6H]	142	115.4	6.9	82.5
NCT02487108 (Phase III Bunionectomy)	High-dose Opioid: HB/APAP IR [7.5/325 mg Q4-6H]	141	120.5	6.9	82.1
NCT02487108 (Phase III Bunionectomy)	High-dose Opioid: HB/APAP IR [10/325 mg Q4-6H]	142	129.9	6.9	82.0
NCT02487108 (Phase III Bunionectomy)	Placebo	142	76.5	6.9	82.5
NCT02487108 (Phase III Bunionectomy)	High-dose Opioid: HB/APAP IR [7.5 and 10/APAP325 Q4-6H] POOLED	283	125.2	4.9	82.0

Study & Procedure	Treatment Arm & Class	N	LS Mean SPID48	SPID48 SE	SPID48 SD
NCT00364247 (Phase III Bunionectomy)	High-dose Opioid: Oxycodone HCL IR [15 mg Q4-6H]	125	172.3	9.9	110.9
NCT00364247 (Phase III Bunionectomy)	Placebo	120	24.5	11.0	120.9

APAP: acetaminophen, BID: twice a day, DPSGC: Diclofenac Potassium liquid filled Soft Gelatin Capsule, ER: extended release, HB: hydrocodone bitartrate, HCl: hydrochloride, IR: immediate release, LS: least standard, mg: milligram, N: number of participants, NPRS: Numeric Pain Rating Scale, NR: not reported, NSAID: Nonsteroidal anti-inflammatory drugs, Q6H: every six hours, Q4-6h: every four to six hours, Q12H: every 12 hours, Q24H: every 24 hours, SD: standard deviation, SE: standard error, SPID48: Summed Pain Intensity Difference Score Calculated Over the First 48 Hours, TID: three times a day, VAS: visual Analog Scale

*Imputed values

Table D2.5 NMA Inputs (Standardized Mean Difference and Standard Error)

Study	Included in Base Case	SMD	Standard Error	Treatment
NCT05558410	Yes	0.5317	0.0833	Suzetrigine
		0.4587	0.0829	Low-dose opioid
		NA	0.0588	Placebo
NCT05034952	Yes	0.4244	0.1635	Suzetrigine
		0.1404	0.1619	Low-dose opioid
		NA	0.115	Placebo
NCT05553366	Yes	0.3163	0.084	Suzetrigine
		0.5322	0.0847	Low-dose opioid
		NA	0.0596	Placebo
NCT04977336	Yes	0.4166	0.1853	Suzetrigine
		0.1653	0.1837	Low-dose opioid
		NA	0.1305	Placebo
NCT01484652	Yes	0.5135	0.1168	High-dose opioid
		NA	NA	Placebo
NCT01743625	Yes	0.4308	0.1008	High-dose opioid
		NA	NA	Placebo
NCT00366444	No	1.3953	0.1573	NSAID
		NA	NA	Placebo
NCT00375934	No	1.2324	0.1543	NSAID
		NA	NA	Placebo
NCT01462435	Yes	0.4032	0.1128	NSAID
		NA	NA	Placebo
NCT01543685	Yes	0.3838	0.1203	NSAID
		NA	NA	Placebo
NCT01626118	Yes	0.2363	0.1196	NSAID
		NA	NA	Placebo
NCT00613938	Yes	0.8548	0.1384	High-dose opioid
		NA	NA	Placebo
NCT03108482	Yes	0.3348	0.1303	NSAID
		NA	NA	Placebo
NCT01038609	Yes	0.4658	0.2038	High-dose opioid
		NA	NA	Placebo
NCT02487108	No	0.4748	0.1203	Low-dose opioid
		0.5927	0.1048	High-dose opioid
		NA	0.0794	Placebo

Study	Included in Base Case	SMD	Standard Error	Treatment
NCT00364247	No	1.2839	0.1403	High-dose opioid
		NA	NA	Placebo

SMD: Standardized Mean Difference or Effect Size, NA: Not Applicable, NSAID: Nonsteroidal anti-inflammatory drugs.

Sensitivity Analyses

Table D2.6. NMA Results for Bunionectomy Only Studies (Relative Treatment Effect Size on SPID48 Outcome)

High-Dose Opioid				
0.17 (-0.07, 0.4)	**Suzetrigine**			
0.07 (-0.12, 0.27)	-0.11 (-0.29, 0.12)	**Low-Dose Opioid**		
0.17 (-0.04, 0.37)	-0.01 (-0.24, 0.25)	0.1 (-0.13, 0.31)	**NSAID**	
0.51 (0.36, 0.65)	**0.33 (0.15, 0.54)**	**0.44 (0.26, 0.59)**	**0.34 (0.19, 0.49)**	**Placebo**

NSAID: Nonsteroidal anti-inflammatory drugs. Standardized mean differences greater than 0 favor the column-defining treatment. Significant results are in bold.

Table D2.7. NMA Results for All Studies including High Risk of Bias (Relative Treatment Effect Size on SPID48 Outcome)

High-Dose Opioid				
0.23 (-0.23, 0.69)	**Suzetrigine**			
0.29 (-0.12, 0.71)	0.06 (-0.3, 0.43)	**Low-Dose Opioid**		
0.03 (-0.39, 0.45)	-0.2 (-0.68, 0.27)	-0.26 (-0.71, 0.18)	**NSAID**	
0.67 (0.38, 0.97)	**0.44 (0.08, 0.81)**	**0.38 (0.06, 0.71)**	**0.65 (0.34, 0.95)**	**Placebo**

NSAID: Nonsteroidal anti-inflammatory drugs. Standardized mean differences greater than 0 favor the column-defining treatment. Significant results are in bold.

NMA Limitations

There are limitations to our NMA. There is uncertainty surrounding the liberal use of rescue medication in acute pain trials; most study arms saw greater than 80% of patients requesting additional analgesic relief (e.g., ibuprofen or HB/APAP) over the 48 hour-follow-up period. This high use of rescue medication can distort the measured treatment difference between an active treatment and placebo. Additionally, there was variability in how missing data was imputed (e.g., last observation) and it is likely to have had an impact on the calculation of pain intensity via SPID48 and comparative effectiveness. Clinical trials are increasingly using windowed imputation approaches to account for the analgesic relief provided within a four-to-six-hour period after rescue medication. However, an analysis of several bunionectomy trials found that even use of windowed imputation can produce findings that appear counterintuitive, such as resulting in higher SPID48 values in the placebo arm.[106]

Suzetrigine was evaluated as a monotherapy against therapies which are combination drugs (e.g., hydrocodone/ acetaminophen), which are more in line with real-world practice. An ad hoc analysis was performed in the Phase III suzetrigine trials that assessed the effect of ibuprofen rescue medication added on to suzetrigine and placebo arms without imputing NPRS scores; the calculated effect sizes between the therapies were slightly lower in this real-world multimodal treatment comparison.

Due to the different scales used to assess pain intensity, we opted to use standardized mean differences as our model output. While these may not offer immediately clear interpretation, raw SPID48 scores similarly lack straightforward clinical meaning, as the field has not established a consensus regarding a clinically significant change threshold for acute pain outcomes.[107]

The pooling of medications within the NSAID and high-dose opioids may obscure unique treatment effects specific to individual medications. In a related issue, the NSAIDs used in the network are newer reformulations of drugs that have been in common use for decades, which may impact the generalizability of study results. These reformulations are typically created to increase faster onset of analgesic activity and reduce side effects. However, the extent to which these interventions represent the current analgesic market is unclear.

The NMA provided insight on analgesics' ability to reduce pain intensity, but this represents only one dimension of the decision-making process. Other critical factors, such as safety and tolerability, particularly regarding opioid-related adverse events and addiction potential, were not available for analysis. Our review qualitatively addressed known harms of short-term opioid and NSAID use in the Harms section of the report.

D3. Evidence Tables

Table D3.1. Study Design

Trial (NCT)	Study Design	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Primary Outcomes
Suzetrigine				
NAVIGATE-1[18] **NCT05553366**	Phase III, interventional, randomized, parallel assignment, quadruple, treatment N = 1075 Duration: 14 days	-SUZ orally (100 mg followed by 50 mg every 12 hours) -HB/APAP orally (5 mg/325 mg every six hours) -Placebo orally	**Inclusion:** -All analgesic guidelines were followed during and after the bunionectomy **Exclusion:** -Prior history of bunionectomy -History of cardiac dysrhythmias within the last 2 years requiring anti-arrhythmia treatment(s) -Any prior surgery within 1 month before the first study drug dose -Participant had a type 3 deformity requiring a base wedge osteotomy, concomitant surgery such as hammertoe repair; or experienced medical complications during the bunionectomy	Time-weighted sum of the SPID as recorded on the NPRS from 0 to 48 hours

Trial (NCT)	Study Design	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Primary Outcomes
NAVIGATE-2[18] **NCT05558410**	Phase III, interventional, randomized, parallel assignment, quadruple, treatment N = 1118 Duration: 14 days	-SUZ orally (100 mg followed by 50 mg every 12 hours) -HB/APAP orally (5 mg/325 mg every six hours) -Placebo orally	**Inclusion:** -All analgesic guidelines were followed during and after the abdominoplasty -Abdominoplasty procedure duration less than or equal to (≤3) hours **Exclusion:** -Prior history of abdominoplasty -Any prior surgery within 1 month before the first study drug dose -Participant had a non-standard abdominoplasty, collateral procedures during the abdominoplasty or any surgical complications during the abdominoplasty	Time-weighted sum of the SPID as recorded on the NPRS from 0 to 48 hours

Trial (NCT)	Study Design	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Primary Outcomes
Mod-Sev Acute Pain[18] **NCT05661734**	Phase III, interventional, single group assignment, open label, treatment N = 258 Duration: 28 days	-SUZ orally, every 12 hours up to 14 days	**Inclusion:** -Non-surgical participants with pain of new origin that is moderate or severe on the VRS and ≥4 on the NPRS -Surgical participants reporting pain at the surgical site that is moderate or severe on the VRS and ≥4 on the NPRS Key **Exclusion:** -History of previous surgery due to the same condition, except for procedures for which a previous surgery on the contra-lateral limb or organ is allowed -History of a prior surgical procedure in the same region of the body that resulted in any perioperative complications	Safety and tolerability as assessed by number of participants with AEs and SAEs (Day 1 up to Day 28)

Trial (NCT)	Study Design	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Primary Outcomes
Abdominoplasty Surgery Pain (MAD)[10] **NCT05034952**	Phase II, interventional, randomized, parallel assignment, quadruple blind, treatment N = 303 Duration: 14 days	-SUZ orally (100 mg dose followed by a 50 mg every 12 hours) -SUZ orally (60 mg dose followed by a 30 mg every 12 hours) -HB/APAP orally (5 mg hydrocodone bitartrate and 325 mg acetaminophen every six hours) -Placebo orally every six hours	**Inclusion:** -Abdominoplasty procedure duration ≤3 hours without collateral procedures **Exclusion:** -Prior history of abdominoplasty, intra-abdominal and/or pelvic surgery	Time-weighted sum of the SPID as recorded on the NPRS from 0 to 48 hours
PoC (Post Bunionectomy Surgery)[10] **NCT04977336**	Phase II, interventional, randomized, parallel assignment, quadruple blind, treatment N = 274 Duration: 14 days	-SUZ orally (100 mg dose followed by 50 mg every 12 hours) -SUZ orally (60 mg dose followed by 30 mg every 12 hours) -SUZ orally (20 mg dose followed by 10 mg every 12 hours) -HB/APAP orally (5 mg hydrocodone bitartrate and 325 mg acetaminophen every six hours) -Placebo orally every six hours	**Inclusion:** -All analgesic guidelines were followed during and after the bunionectomy **Exclusion:** -Prior history of bunionectomy -History of cardiac dysrhythmias requiring anti-arrhythmia treatment(s) -Any prior surgery within 1 month before the first study drug dose -Participant had a type 3 deformity requiring a base wedge osteotomy, concomitant surgery such as hammertoe repair; or experienced medical complications during the bunionectomy	Time-weighted sum of the SPID as recorded on the NPRS from 0 to 48 hours

NSAIDs				
Trial (NCT)	**Study Design**	**Arms & Dosing Regimen**	**Inclusion / Exclusion Criteria**	**Primary Outcomes**
NCT00366444[85]	Phase III, randomized, parallel assignment, double blind study N = 201 Duration: Five days	-diclofenac potassium 25 mg oral capsule every six hours -Placebo oral capsule every six hours	**Inclusion:** -18-65 years of age -Have undergone bunionectomy surgery -Have achieved adequate post-surgical pain **Exclusion:** -Confounding medical conditions which preclude study participation	Average Numeric NPRS Over 48 Hours After Bunionectomy
NCT00375934[83]	Phase III, randomized, parallel assignment, double blind study N = 200 Duration: Five days	-diclofenac potassium 25 mg oral capsule every six hours -Placebo oral capsule every six hours	**Inclusion:** -18-65 years of age -Have undergone bunionectomy surgery -Have achieved adequate post-surgical pain **Exclusion:** -Confounding medical conditions which preclude study participation	Average Numeric NPRS Over 48 Hours After Bunionectomy
NCT01462435[82]	Phase III, randomized, double-blind, multiple-dose, parallel-group, active- and placebo-controlled study N = 428	-diclofenac 35 mg oral capsule TID -diclofenac 18 mg oral capsule TID -placebo oral capsule -celecoxib 200 mg oral capsule BID	**Inclusion:** -Undergone primary, unilateral, first metatarsal bunionectomy with no additional collateral procedures -Patient must be willing to stay at the study site ≥ 72 hour	The Time-Weighted Summed Pain Intensity Difference Measured Using the VAS From 0 to 48 Hours After Trial Entry

	Duration: Five to nine days			
Trial (NCT)	**Study Design**	**Arms & Dosing Regimen**	**Inclusion / Exclusion Criteria**	**Primary Outcomes**
NCT01543685[86]	Phase III, randomized, double-blind, multiple-dose, parallel-group, active- and placebo-controlled study N = 462 Duration: Two days	-indomethacin 40 mg oral capsule TID -indomethacin 40 mg oral capsule BID -indomethacin 20 mg oral capsule TID -celecoxib 200 mg oral capsule BID -placebo oral capsule	**Inclusion:** -Undergone primary, unilateral, first metatarsal bunionectomy with no additional collateral procedures -Patient must be willing to stay at the study site ≥72 hour	The Time-Weighted Summed Pain Intensity Difference Measured Using the VAS From 0 to 48 Hours After Trial Entry

NCT01626118[88]	Phase III, randomized, double-blind, multiple-dose, parallel-group, placebo-controlled study N = 373 Duration: Two days	-indomethacin 40 mg oral capsule TID -indomethacin 40 mg oral capsule BID -indomethacin 20 mg oral capsule TID -placebo oral capsule	**Inclusion** - Undergone primary, unilateral, first metatarsal bunionectomy with no additional collateral procedures - Patient must be willing to stay at the study site ≥ 72 hours	The Time-Weighted Summed Pain Intensity Difference Measured Using the VAS From 0 to 48 Hours After Trial Entry
Trial (NCT)	**Study Design**	**Arms & Dosing Regimen**	**Inclusion / Exclusion Criteria**	**Primary Outcomes**

NCT03108482[89]	Phase III multicenter, randomized, double-blind, parallel-group, placebo-controlled study N = 637 Duration: Two days	- Celecoxib 100 mg every 12 hours -Co-crystal E-58425 (Tramadol/Celecoxib, 100 mg), two tablets orally every 12 hours -Tramadol 50 mg orally every six hours - Placebo, one or two tablets orally every six hours	**Inclusion:** - Subject must be at least 18 years old, scheduled to undergo primary unilateral first metatarsal osteotomy with internal fixation with no additional collateral procedure.	Time-weighted sum of the SPID as recorded on the NPRS from 0 to 48 hours
Opioids				

Trial (NCT)	Study Design	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Primary Outcomes
NCT01484652[91]	Phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group study N = 329 Duration: Three days	-Oxycodone/acetaminophen (15 mg /650 mg), two tablets orally every 12 hours -Placebo, two tablets orally every 12 hours	**Inclusion:** -Be scheduled for a primary unilateral first metatarsal bunionectomy (with no collateral procedures) -Be classified as Physical status 1 to 2 by the American Society of Anesthetists Physical Status Classification System **Exclusion:** -Have previous abdominal surgery within the past year or history of abdominal adhesions, known or suspected paralytic ileus.	Time-weighted sum of the SPID as recorded on the NPRS from 0 to 48 hours
NCT01743625[90]	Phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group study N = 406 Duration: Two days	-Hydrocodone/acetaminophen (7.5 mg /325 mg), loading dose of 3 tablets followed by two tablets orally every 12 hours -Placebo, loading dose of 3 tablets followed by two tablets orally every 12 hours	**Inclusion:** -Be scheduled for a primary unilateral first metatarsal bunionectomy (with no collateral procedures) -Be classified as either Physical status 1 or 2 by the American Society of Anesthetists Physical Status Classification System **Exclusion:** -Have previous abdominal surgery within the past year or history of abdominal adhesions, known or suspected paralytic ileus.	Time-weighted sum of the SPID as recorded on the NPRS from 0 to 48 hours
Trial (NCT)	**Study Design**	**Arms & Dosing Regimen**	**Inclusion / Exclusion Criteria**	**Primary Outcomes**

NCT02487108[94,95]	Phase III multicenter, randomized, double-blind, placebo-controlled study N = 569 Duration: 13 days	-5 mg/325 mg of hydrocodone bitartrate/acetaminophen IR tablets every four to six hours -7.5 mg/325 mg of hydrocodone bitartrate/acetaminophen IR tablets every four to six hours -10 mg/325 mg of hydrocodone bitartrate/acetaminophen IR tablets every four to six hours -Placebo every four to six hours	**Inclusion:** -Scheduled to undergo a primary unilateral first metatarsal Austin bunionectomy with distal osteotomy and internal fixation without any collateral procedures -Pain intensity score of ≥4 on an 11-point NPRS-11 **Exclusion:** -Use of any nonpharmacologic pain management techniques	Summed pain intensity difference score calculated over the first 48 hours after the first dose of study drug on an 11-point numerical pain rating scale
NCT00364247[97]	Phase III randomized, double-blind, active- and placebo-controlled, parallel-group, multicenter study N = 602 Duration: Nine days	-Oxycodone HCL IR 15 mg every four to six hours -Tapentadol IR 50 mg every four to six hours -Tapentadol IR 75 mg every four to six hours -Tapentadol IR 100 mg every four to six hours -Placebo every four to six hours	**Inclusion:** -Patients must undergo primary unilateral first metatarsal bunionectomy -Pain intensity must be moderate to severe following stoppage of a continuous popliteal sciatic block	The sum of pain intensity difference at 48 hours relative to the first dose
Trial (NCT)	**Study Design**	**Arms & Dosing Regimen**	**Inclusion / Exclusion Criteria**	**Primary Outcomes**

NCT00613938[96]	Phase III randomized, double-blind, active- and placebo-controlled, parallel-group, multicenter study N = 901 Duration: Three days	-Oxycodone HCL IR 10 mg every four to six hours -Tapentadol IR 50 mg every four to six hours -Tapentadol IR 75 mg every four to six hours -Placebo every four to six hours	**Inclusion:** -Patients must undergo primary unilateral first metatarsal bunionectomy -Pain intensity must be moderate to severe following stoppage of a continuous popliteal sciatic block	Summed pain intensity difference score calculated over the first 48 hours recorded on the 11-point numerical rating scale (NRS)
NCT01038609[92,93]	Phase II randomized, single-blind, , active- and placebo-controlled, multicenter study N = 250 Duration: Four days	-HB/APAP ER (10/650 mg), ne tablet orally every 12 hours -Morphine ER 10 mg, one tablet orally every 12 hours -Acetaminophen 325 mg every six hours -Morphine 10 mg, one tablet orally every 12 hours, plus Acetaminophen 325 mg, one tablet orally every six hours -Placebo every six hours	**Inclusion:** - Subjects who were in general good health, experiencing moderate to severe pain following bunionectomy surgery and who were willing to remain confined for approximately four days following surgery for study procedures. **Exclusion** -Subjects who underwent Base wedge osteotomy and/or Long-Z hart bunionectomy procedures	The Time-Weighted Summed Pain Intensity Difference Measured Using the VAS From 0 to 48 Hours After the First Dose

AEs: adverse events, BID: twice a day, HB/APAP: Hydrocodone bitartrate-acetaminophen, HCL: hydrochloride, IR: immediate release, mg: milligram, mL: milliliter, N: number, NPRS: Numeric Pain Rating Scale, NRS: Numerical Rating Scale, VAS: Visual Analog Scale, SAEs: serious adverse events, SPID: Sum of the pain-intensity difference, TID: three times a day, VRS: Verbal Categorical Rating Scale

Table D3.2. NAVIGATE 1 & 2 Baseline Characteristics[18]

Trial		NAVIGATE-1			NAVIGATE-2		
		Bunionectomy			Abdominoplasty		
Arms		SUZ	HB-APAP	Placebo	SUZ	HB-APAP	Placebo
N		426	431	216	447	448	223
Age, years	Mean (SD)	47.7 (13.3)	48.3 (12.6)	48.1 (13.5)	41.5 (9.1)	42.1 (8.7)	41.5 (8.5)
Sex, n (%)	Male	60 (14.1)	72 (16.7)	29 (13.4)	10 (2.2)	7 (1.6)	3 (1.3)
	Female	366 (85.9)	359 (83.3)	187 (86.6)	437 (97.8)	441 (98.4)	220 (98.7)
Race, n (%)	White	285 (66.9)	314 (72.9)	160 (74.1)	307 (68.7)	316 (70.5)	155 (69.5)
	Black	116 (27.2)	96 (22.3)	48 (22.2)	123 (27.5)	114 (25.4)	62 (27.8)
	Other*	25 (5.9)	21 (4.9)	8 (3.7)	17 (3.8)	18 (4.0)	6 (2.7)
BMI	Mean (SD)	28.10 (4.93)	28.07 (4.82)	28.29 (4.77)	29.21 (4.06)	29.38 (4.37)	29.58 (4.20)
NPRS	Mean (SD)	6.7 (1.8)	6.8 (1.9)	6.8 (1.8)	7.3 (1.7)	7.4 (1.7)	7.5 (1.7)
NPRS category, n (%)	<8	274 (64.3)	274 (63.6)	143 (66.2)	227 (50.8)	229 (51.1)	111 (49.8)
	≥8	152 (35.7)	157 (36.4)	73 (33.8)	220 (49.2)	219 (48.9)	112 (50.2)
VRS, n (%)	Moderate	291 (68.3)	279 (64.7)	147 (68.1)	266 (59.5)	262 (58.5)	127 (57.0)
	Severe	135 (31.7)	152 (35.3)	69 (31.9)	181 (40.5)	186 (41.5)	96 (43.0)

BMI: Body Mass Index, HB/APAP: hydrocodone bitartrate/acetaminophen, N: number of participants, NPRS: Numeric Pain Rating Scale, SD: standard deviation, VRS: Verbal Categorical Rating Scale

*Other includes Asian, American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, Other, Multiracial, or Missing.

D4. Ongoing Studies

Table D4.1. Ongoing Studies

NCT/Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
NCT06176196 **Vertex**	Phase II, randomized, double-blind, placebo-controlled, parallel-design study of the efficacy and safety of SUZ. N = 218	-Suzetrigine -Placebo, administered orally for up to 12 weeks	**Inclusion** -Patients with diagnosis of Painful Lumbosacral Radiculopathy for greater than 3 months as per criteria pre-specified in the protocol. -Weekly average of daily Numeric Pain Rating Scale score ≥4 and <10 with limited variation in the 7-day Run-in Period.	Change From Baseline in the Weekly Average of Daily leg Pain Intensity on the NPRS.	April 2025

NCT/Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
NCT06628908 **Vertex**	Phase III, randomized, double-blind, placebo- and active-controlled study of the efficacy and safety of SUZ. N = 1100	-Suzetrigine, administered orally -Pregabalin, administered orally -Placebo, administered orally	**Inclusion** -Patients with diagnosis of diabetes mellitus type 1 or type 2 by glycosylated hemoglobin A1c ≤9% and the presence of bilateral pain in lower extremities due to Diabetic Peripheral Neuropathy. -Weekly average of daily NPRS score ≥4 and less than or equal to (≤) 9 with limited variation in the 7-day Baseline Period.	Change From Baseline in the Weekly Average of Daily Pain Intensity on the Numeric Pain Rating Scale at Week 12 Compared to Placebo.	May 2027

Source: www.ClinicalTrials.gov

N: number of participants, NPRS: Numeric Pain Rating Scale

D5. Previous Systematic Reviews and Technology Assessments

Our review found no ongoing health technology assessments for suzetrigine. While analgesics for acute pain are typically evaluated within specific surgical contexts, we identified no procedure-specific recommendations for post-operative pain management in either abdominoplasty or bunionectomy procedures.[108] Although several systematic reviews examine analgesics for postoperative pain, these analyses face important limitations. The studies often aggregate data from diverse surgical procedures that differ substantially in their pain characteristics (e.g., type [somatic versus visceral], location, intensity, and duration) and in how inadequate pain relief affects postoperative organ function. Moreover, analgesic efficacy can vary significantly depending on the specific surgical procedure, making broad generalizations challenging.

Cochrane Review: Single Dose Analgesics for Acute Postoperative Pain in Adults

The study reviewed 39 Cochrane Reviews analyzing single-dose oral analgesics for acute postoperative pain, encompassing around 50,000 participants across approximately 460 studies.[109] It focused on high-quality trials with standardized methods and outcomes, without performing statistical comparisons.

The Number Needed to Treat (NNT) for achieving at least 50% maximum pain relief over four to six hours compared with placebo ranged from 1.5 to 20. For example:

Ibuprofen 200 mg + Paracetamol 500 mg: NNT of 1.6

Ibuprofen Fast Acting 200 mg: NNT of 2.1

Diclofenac Potassium 50 mg: NNT of 2.1

Etoricoxib 120 mg: NNT of 1.8

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	¨	¨	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	¨	
	Unpaid caregiver-time costs	NA	¨	
	Transportation costs	NA	¨	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	¨	
Consumption	Future consumption unrelated to health	NA	¨	
Social Services	Cost of social services as part of intervention	NA	¨	
Legal/Criminal Justice	Number of crimes related to intervention	NA	¨	
	Cost of crimes related to intervention	NA	X	
Education	Impact of intervention on educational achievement of population	NA	¨	
Housing	Cost of home improvements, remediation	NA	¨	

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Environment	Production of toxic waste pollution by intervention	NA	¨	
Other	Other impacts (if relevant)	NA	¨	

NA: not applicable

Adapted from Sanders et al[110]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[111]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The population of focus for the economic evaluation included adult patients with moderate-to-severe acute pain not adequately controlled with non-systemic therapies. We defined the characteristics of this population using evidence from an evaluation of the incidence of OUD among people with acute pain. Although these population characteristics differed from those in the Phase III suzetrigine trials, they better reflect those who are at risk of moderate-to-severe acute pain.

Table E1.2. Base-Case Model Cohort Characteristics

	Value	Source
Mean Age	45.3 years	Schoenfeld et al., 2024[51]
Male	45.5%	Schoenfeld et al., 2024[51]

Treatment Strategies

The model compared suzetrigine to HB/APAP. HB/APAP is commonly prescribed for short-term pain management after surgery or injury but carries a risk of dependency due to the opioid component.

Model Structure

The model structure is depicted in Figure 4.1. Health outcomes and costs depended on time spent in each health state and related and unrelated direct and indirect health care costs. Health outcomes included life years gained, quality-adjusted life years (QALYs) gained, and equal value of life years (evLY) gained. Mortality was a function of all-cause mortality using US life tables for patients without OUD and OUD-specific mortality for patients with OUD. Quality of life weights were applied to each health state and derived from publicly available sources. The up-front decision tree captured differences in quality of life from acute pain interventions using an EQ-5D mapping instrument to the numeric pain rating scale (NPRS).[61] Productivity changes and other indirect costs (e.g., non-health related costs such as criminal justice system costs) were included in a separate modified societal perspective analysis. All costs were inflated to 2024 US dollars using the medical care component of the consumer price index (CPI) for health care costs and all items of the CPI for other costs. Costs and outcomes were discounted at 3% per year. Results were expressed in terms of incremental cost per QALY gained, cost per evLYG, cost per life year gained, and cost per OUD case averted.

E2. Model Inputs and Assumptions

Model Inputs

Key model assumptions can be found in Table 4.1. Key model inputs can be found in Table 4.2.

Clinical Inputs

Clinical Probabilities/Response to Treatment

Baseline NPRS scores and reductions in pain following treatment were reported for two trials (abdominoplasty and bunionectomy).[59] Using both trials, we calculated a weighted average baseline NPRS score and an on-treatment NPRS score for both treatment arms (measured at 48 hours). The time in each NPRS state was used to estimate utility scores and improvements in pain in both arms of the model.

Transition Probabilities

In addition to the probability of transitioning to OUD, we calculated the probability of transitioning from OUD to sustained abstinence. Among those with OUD, 25.1% receive MAT and sustained five-year abstinence from all opioids is achieved by 20.7% of those receiving MAT.[48,52] Combining these two estimates resulted in a five-year proportion of patients with OUD achieving abstinence of 0.052. We calibrated the model for both the three-year incidence of OUD (i.e., 0.43%) and for the 0.052 who transitioned to the abstinence state by five years following transition to OUD.

Utilities

We derived a baseline utility of 0.57 using a tool for mapping NPRS levels to EQ-5D values.[61] On-treatment utility did not differ between treatment groups (0.88). We truncated post-treatment utility at the average utility of the US adult population (0.851) and applied this utility from one week to three months. Utilities for the OUD and abstinence states were based on a nationally representative survey that used the standard gamble approach to measure health-related quality of life of different opioid misuse and treatment states, including active injection drug misuse, active prescription drug misuse, initiation and stabilization on both methadone and buprenorphine treatment, and remission.[55] Participants in the survey were presented with vignettes describing the different states in terms of impacts on physical and emotional health, employment, family relationships, and criminal justice involvement. For the OUD state, we calculated a weighted average utility based on the reported utilities for active injection and prescription drug misuse and initiation with either methadone or buprenorphine treatment. We assumed that 18% of people with OUD are injection drug users and that an equal number of people receiving MAT (25.1%) receive either methadone or buprenorphine.[56] For the abstinence state, we calculated a weighted average utility based on the reported utilities for being in stable treatment with either methadone or buprenorphine and for remission. We assumed that 20.7% of those receiving MAT experience sustained remission.[48] These utilities were then converted to disutilities. Disutilities were calculated as the difference between the utility of a reference health state (representing the general population in the US) and the utility values assigned to specific disease states, reflecting the decrement in quality of life. A utility score of 0.851 was used for the general population, based on the age- and sex-adjusted utility of individuals in the US.[111] For OUD, the health state-specific disutility was calculated as 0.851-0.62=0.231, and for the abstinence state, it was 0.851-0.77=0.081.

Caregiver disutilities were included in a scenario analysis. The study described above also measured the spillover utility of opioid misuse or MAT on the healthy spouse of someone with OUD.[55] As described above, we calculated a weighted average of spouse utilities for active injection or prescription opioid use and the initiation stage of treatment with methadone or buprenorphine and converted to a disutility. We assumed an average of one caregiver per patient. The disutility (0.064) was applied to the OUD health state.

Adverse Events

Grade 3 or 4 adverse events occurred in 2% or fewer of clinical trial participants prescribed suzetrigine or HB/APAP.[112] Because we have not received data regarding the specific clinical nature of all short-term grade 3 or 4 adverse events, these are not included in the economic model. Long-term adverse events of opioid use, specifically OUD, were included in the model.

Economic Inputs

Drug Costs

Table E2.4. Drug Cost Inputs

Interventions	Route	Dose	Frequency of Administration	Weekly Drug Cost	Source
Suzetrigine	Oral	Initial dose of 100 mg followed by 50 mg	Every 12 hours (at 12, 24 and 36 hours after the first dose)	$420*	IPD Analytics
HB/APAP	Oral	5 mg/325 mg	Every six hours for first 48 hours	$10.64†	US Redbook

HB/APAP: Hydrocodone bitartrate/acetaminophen
*Placeholder price
†WAC as of October, 2024.

Administration and Monitoring Costs

There were no administration and monitoring costs.

Direct Non-Drug Costs

Excess health care costs for people with OUD were identified in a matched case-control study using administrative claims data across private and public payers and adjusted to represent the US population.[57] This estimate includes the excess costs of inpatient, outpatient, and behavioral health care services such as MAT. For individuals in the abstinence state, we assumed ongoing MAT. The costs of treatment with methadone and buprenorphine, inclusive of integrated psychosocial and

medical support, were identified in a recent cost-effectiveness analysis of treatments for OUD.[58] We assumed equal utilization of methadone and buprenorphine when calculating a weighted average cost of MAT. Gender- and age-specific unrelated health care costs were added to health states. [64]

Indirect Costs

We identified the cost of lost productivity due to OUD as well as criminal justice costs associated with OUD. The cost of lost productivity reflects OUD-related absenteeism and decreases in labor force participation. The cost of lost productivity was included for the full lifetime of patients in the model. The criminal justice cost includes four components: police protection, legal and adjudication, correctional facilities, and property lost due to crimes.

Table E2.6. Indirect Costs Associated with OUD

Parameter	Value	Source
Annual Per-Person Productivity Loss due to Non-Medical Opioid Use	$8,857	Davenport et al. 2019[57], Authors' calculation
Annual Per-Person Criminal Justice Costs due to Opioid Misuse and OUD	$5,146	Murphy et al. 2020[113]

OUD: Opioid use disorder

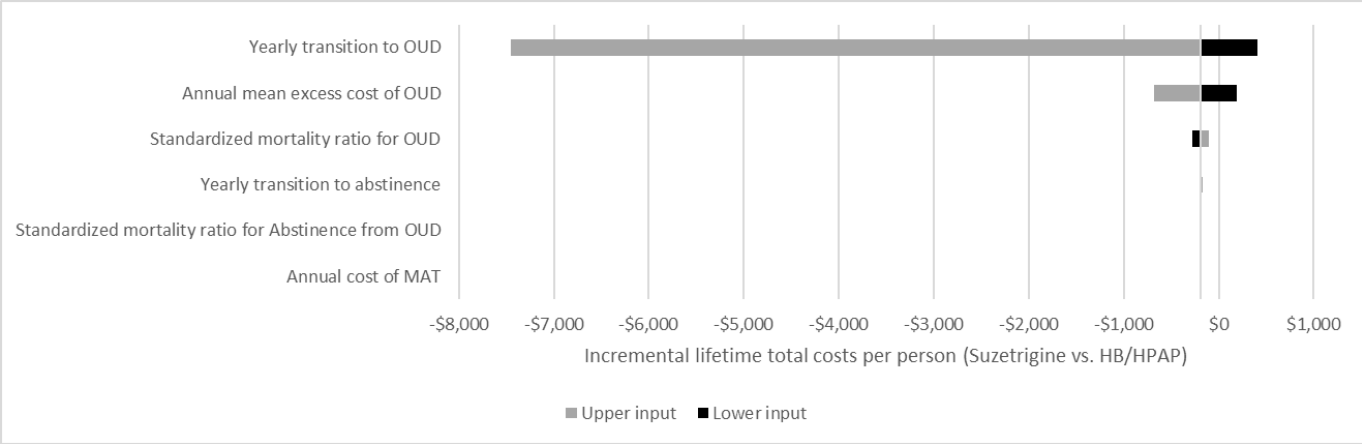
E3. Results

Results are described in Section 4.3 of the report.

E4. Sensitivity Analyses

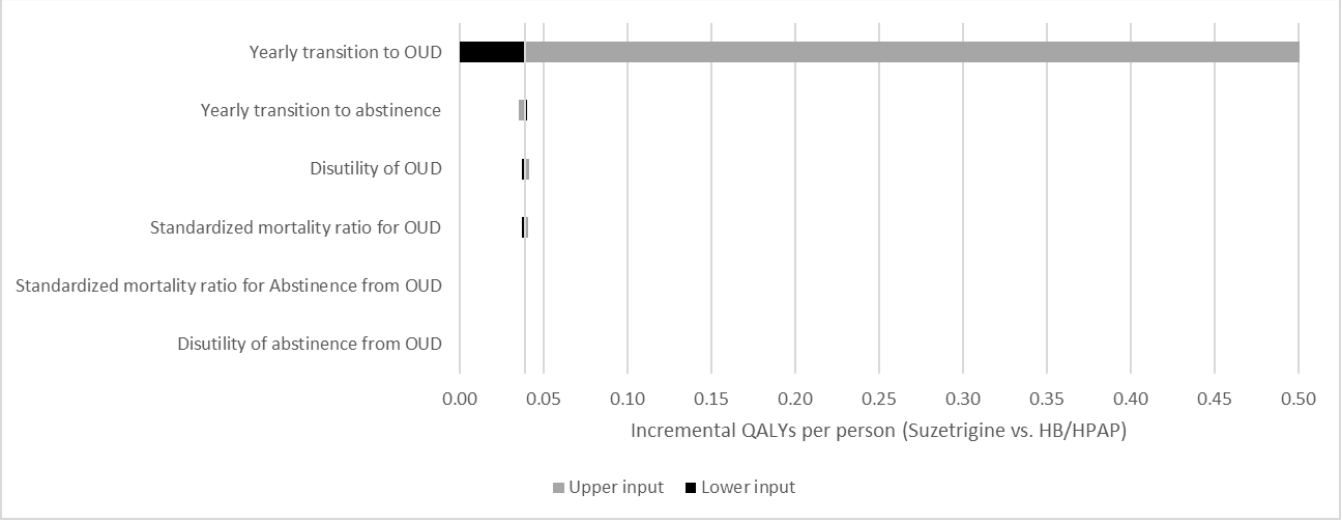
To demonstrate the effects of uncertainty on both costs and health outcomes, we varied input parameters using available estimates of parameter uncertainty (e.g., standard errors or plausible parameter ranges). Because suzetrigine, at the placeholder price, results in dominant (less costly, more effective) scenarios, we present a tornado diagram with incremental per person lifetime costs separate from incremental per person lifetime QALY and evLY estimates. Figures E4.2 and E4.3 present tornado diagrams resulting from the one-way sensitivity analyses for suzetrigine versus HB/APAP. Key drivers of cost-effectiveness estimates include the risk of OUD from a short course of HB/APAP, annual mean excess costs of OUD, and excess mortality related to OUD. Sensitivity analyses are based on the placeholder price for suzetrigine.

Figure E4.2. Tornado Diagram for Incremental Lifetime Costs



HB/APAP: Hydrocodone bitartrate/acetaminophen; MAT: medication-assisted therapy; OUD: opioid use disorder

Figure E4.3. Tornado Diagram for Incremental Quality-Adjusted Life Years Gained



HB/APAP: Hydrocodone bitartrate/acetaminophen; MAT: medication-assisted therapy; OUD: opioid use disorder; QALYs: quality-adjusted life years

Table E4.1. Tornado Diagram Inputs and Results for Suzetrigine versus HB/APAP on Incremental Costs

	Lower Incremental Costs	Upper Incremental Costs	Lower Input*	Upper Input*
Yearly transition to OUD†	$400	-$7,500	0	0.019
Annual mean excess cost of OUD	$200	-$700	$10,134	$27,415
Standardized mortality ratio for OUD	-$300	-$100	4.21	5.98
Yearly transition to abstinence	-$200	-$150	0	0.05
Standardized mortality ratio for Abstinence from OUD	-$200	-$200	1.71	2.31
Annual cost of MAT	-$200	-$200	$6,942	$8,446

CE: cost-effectiveness

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

†The upper bound estimate reflects a cumulative incidence of OUD at year 3 = 5.7%

Table E4.2. Tornado Diagram Inputs and Results for Suzetrigine versus HB/APAP on Incremental QALYs

	Lower Incremental QALYs	Upper Incremental QALYs	Lower Input*	Upper Input*
Yearly transition to OUD†	0.000	0.510	0.000	0.019
Yearly transition to abstinence	0.040	0.035	0.000	0.050
Disutility of OUD	0.037	0.042	0.187	0.278
Standardized mortality ratio for OUD	0.037	0.041	4.210	5.980
Standardized mortality ratio for Abstinence from OUD	0.039	0.039	1.710	2.310
Disutility of abstinence from OUD	0.039	0.039	0.070	0.100

CE: cost-effectiveness

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

†The upper bound estimate reflects a cumulative incidence of OUD at year 3=5.7%

Table E4.3. Results of Probabilistic Sensitivity Analysis for Suzetrigine versus HB/APAP

	Suzetrigine Mean*	HB/APAP Mean	Incremental
Costs	$198,000	$199,000	-$850
QALYs	18.65	18.62	0.03
evLYs	18.65	18.62	0.03
Incremental CE Ratio	Less costly, more effective		

CE: cost-effectiveness, evLYs: equal-value life year, HB/APAP: hydrocodone bitartrate/acetaminophen, QALY: quality-adjusted life year

*Based on placeholder price

E5. Heterogeneity and Subgroups

There were no pre-specified heterogeneity or subgroup analyses.

Prior Economic Models

While prior relevant economic models were designed to estimate the cost effectiveness of medication assisted therapy (MAT) for OUD itself,[58] the focus of this model was to examine the adverse effects of OUD on health outcomes and costs where an alternative therapy is available to HB/APAP or similar opioids. We did not find other acute pain models to compare to this model structure and analysis. However, in our model validation exercises we relied on existing observed longitudinal data sources to confirm transitions between no OUD, OUD, and abstinence from OUD. Health states were similar to other models including OUD, abstinence, and an increased risk of mortality. However, where possible, we collapsed specific health states to include both in and out of treatment and calibrated model inputs to represent the broader OUD population. Our estimates are consistent with other OUD models in that outcomes for persons with OUD have excess costs, excess mortality, and decrements to quality of life.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year-time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for suzetrigine. To estimate the size of the potential candidate population, we used inputs for the US prevalence of acute pain requiring management with prescription medication. A retrospective cross-sectional study using two nationally representative datasets from 2019 estimated that 80.2 million patients in the US annually experience acute pain, defined as requiring prescription pain medication for less than three months.[2] Among all patients with acute pain, 10.9 million patients with both acute and chronic pain were excluded to ensure alignment with the specific population studied in the cost-effectiveness analysis. The prevalence of acute pain (69.3 million) was multiplied by the proportion of acute pain patients who received one or more prescriptions or administrations of opioids (51%) to estimate the number of patients likely to receive opioids for treating acute pain each year. Other types of treatment, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opioid analgesics, were not considered in estimating the number of eligible patients, as suzetrigine is anticipated to primarily displace opioids, which are the main comparator in the cost-effectiveness analysis. Applying these findings results in estimates of 35.3 million eligible patients in the US per year. For the purposes of this analysis, we will assume that 20% of these patients would initiate treatment in each of the five years, or 7.1 million patients per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[114,115] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Once estimates of budget impact are calculated, we compare our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's Methods Presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2023-2024, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $735 million per year for new drugs.