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EXPERT OPINION

Bunionectomy as an Acute Postoperative Pain Model: Overview of Common Experimental Methods, and Insights from Past Clinical Trials

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Abstract: To obtain broad regulatory approval for a new analgesic agent in acute postoperative pain, US and European regulatory authorities require pivotal studies in both hard (bony) tissue pain and soft tissue pain. Bunionectomy is by far the most common hard tissue pivotal trial model, in spite of the fact that the model has limited relevance to clinicians prescribing pain drugs (pain from bunionectomy is not extreme or long-lasting, and is adequately treated by existing drugs). The authors outline the experimental characteristics that make bunionectomy an appealing study model for researchers despite its lack of clinical relevance compared to larger surgeries. These include bunionectomy's high signal-to-noise ratio (secondary to the ability to standardize surgical procedures, anesthesia and perioperative care) and relative operational simplicity (including relatively easy subject enrollment). They present an overview of the surgical and anesthetic protocols typical to modern bunionectomy studies, as well as common design paradigms, common endpoints, and other key design features of bunionectomy trials. They also provide an informal qualitative review of bunionectomy acute pain studies performed in the past 15 years, and a master table of acute pain bunionectomy trials performed from 2006–2023. Drawing from their informal review of past studies, the authors discuss trends in rescue medication, study enrollment rates, subject demographics, and the advantages and disadvantages of bunionectomy compared with another common acute pain model, dental impaction pain (third molar extraction).

Keywords: bunionectomy, acute pain clinical trials, acute postoperative pain

Introduction

Bunionectomy is the most common acute postoperative pain model used in pain drug development programs geared at US and/or European regulatory approval (see Table 1 below). Since 2008, 12 drugs have been approved for acute pain (in either the US or EU). 10 out of 12 of these drugs utilized bunionectomy in their development programs (9 in Phase 3, and 1 exclusively in Phase 2) (Table 1).

Despite the prevalence and importance of the bunionectomy pain model, the authors are not aware of any existing review article or meta-analysis that specifically addresses the topic. As such, researchers who wish to utilize bunionectomy as an experimental model are forced to cobble together information from disparate sources. In this paper we will present a comprehensive table of bunionectomy acute pain studies performed or published in the past 15 years, identifying the key outcome measures and experimental features that were employed in each study. Additionally, we will provide an overview of the surgical, anesthetic, and perioperative analgesic techniques typical to a modern bunionectomy acute pain study. We will outline common design paradigms, inclusion/ exclusion criteria, assessments and endpoints, rescue medications, and other key clinical and operational details of bunionectomy trials.

Acute Postoperative Pain Models: Clinical Relevance vs Experimental Quality

Postoperative pain after bunionectomy can in most cases be treated adequately with existing therapies.[13,14] In contrast, pain from larger and more complex hard tissue surgical procedures (eg, total knee arthroplasty, total hip arthroplasty,

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Table 1 Postoperative Acute Pain Drug Approvals Since 2008 (US and/or EU)

Drug Trade Name	Generic Name	Year Approved	US Approval	EU Approval
Bunionectomy model used in Phase 3 pivotal trial(s)				
Nucynta IR	Tapentadol immediate release	2008	Yes	Yes
Exparel	Bupivacaine	2011	Yes	Yes
Tivorbex	Indomethacin	2014	Yes	Yes
Xartemis XR	Oxycodone/ acetaminophen	2014	Yes	No
Dyloject	Diclofenac	2014	Yes	Yes
Anjeso	Meloxicam	2020	Yes	No
Olinvyk	Oliceridine	2020	Yes	No
Zynrelef	Bupivacaine/ meloxicam	2021	Yes	Yes
Seglentis	Celecoxib/ tramadol	2021	Yes	Yes
Bunionectomy model used in Phase 2 trial(s), not Phase 3				
Dsuvia	Sufentanil	2018	Yes	Yes
Bunionectomy model not used				
Xaracoll	Bupivacaine	2020	Yes	No
Posimir	Bupivacaine	2021	Yes	No

Notes: Gathered via online search, including review of drug labels[1–12] and correspondence with regulatory personnel and pharmaceutical sponsors.

major spine surgeries, thoracotomies, etc.) is inadequately addressed by existing analgesic drugs.[15] There is a clinical need to develop novel analgesics to treat pain generated by these larger surgeries. Therefore, clinicians reviewing data on novel analgesics would be best informed by data from studies performed in these larger models, where the study population's pain syndrome most closely resembles that of the patient in need of new therapies. However, larger and more complicated surgical models can give rise to an increased chance of a false negative outcome as the assay sensitivity of experiments performed in these models is relatively low.[16]

Of the larger surgeries listed above, the most popular and well-understood choice as a clinical trial model is total knee arthroplasty (TKA).[17] However, TKA is not frequently employed as a pivotal model for efficacy because it has certain characteristics that can negatively impact assay sensitivity,[18] including the following:

- Patients undergoing TKA have significant comorbidities that can necessitate modifications to protocol-mandated anesthetic and surgical procedures (giving rise to increased variability).[19]
- Surgical and anesthetic capabilities (eg, robotic surgery, ultrasound-guided nerve blocks) differ significantly between hospitals.
- Multiple doctors and caregivers are involved with the perioperative care of TKA patients. The resultant increased number of clinical touch points with the study subject can increase variability and placebo response.
- Slower recruitment rates for TKA studies can result in the need to increase the number of study sites, which can erode assay sensitivity in pain studies.[20]

In contrast, bunionectomy is a relatively simple procedure typically performed on younger, healthier patients, and bunionectomy trials are often performed by actively recruiting patients into a small number of specialized surgery

centers where care is highly standardized (see Recruited vs Non-Recruited Surgeries below). While the Dental Impaction Pain Model (DIPM, ie wisdom tooth extraction) offers similar benefits, it is no longer accepted by regulatory agencies as a pivotal model.[18]

The prevalence of bunionectomy in pivotal clinical trials represents a compromise. Studies in more clinically relevant models are more likely to fail, and so researchers who select bunionectomy trade off some clinical relevance of their study data for a lower likelihood of a Type 2 error.

Recruited vs Non-Recruited Surgeries

A key component of bunionectomy's strength as a model for clinical experiments lies in its origins as an actively recruited study model. Prior to the development of bunionectomy, pivotal postoperative pain studies generally enrolled patients who were scheduled for surgery independently of the research project (the subject's surgery was not predicated on study participation). Actively recruited models like bunionectomy introduced a new paradigm.[18] Researchers recruit subjects through advertising and patient databases. Surgical costs are generally paid by the study sponsor, rather than by the subject or insurance. This paradigm allows researchers to enroll subjects quickly into a small number of research centers where surgery, anesthesia and perioperative care are strictly standardized and can be tailored to the needs of study protocols.[21] Subjects can also be domiciled longer than typical clinical care standards would dictate (eg, a 72-hour inpatient stay for a bunionectomy), enabling:

1. Study assessments to be performed by study staff who are expert in analgesic assessments.
2. Control and verification of investigational product and rescue medication administration.
3. Control and verification of efficacy and safety assessment time points.
4. Control of activities that would likely confound efficacy assessments (such as subject ambulation).

Diagnosis

In an actively recruited surgical study model, fast, simple, unambiguous diagnosis of the underlying condition requiring surgery is key to rapid enrollment. Bunions requiring surgery of the type used in clinical trials (type 2 hallux valgus deformity) are relatively simple to diagnose.[22] Generally, clinical presentation involves pain, difficulty with ambulation and improper fit of the shoe. A clinical examination and plain film X-ray are adequate for confirmation of the diagnosis in most cases.

Surgical Procedure

Postoperative pain after bunionectomy largely arises from the osteotomy (cutting of bone) required for the procedure, and to a lesser degree from the damage to surrounding soft tissues required for surgical exposure. Therefore, standardization of the surgical osteotomy is paramount to ensure experimental homogeneity.

The Austin/ Chevron bunionectomy procedure used in most bunionectomy pain trials is performed entirely on the first metatarsal head and provides correction for moderate Type 2 hallux valgus deformity. Subjects requiring alternate types of metatarsal head osteotomy, as well as base wedge osteotomies (in which the base of the first metatarsal is cut to correct severe deformities), are excluded. Collateral procedures, including hammertoe repair, are generally not allowed. Only subjects undergoing primary unilateral surgeries are included. Total length of convalescence is approximately 8 weeks or more postoperatively, with approximately 4 weeks spent in a surgical shoe.[23]

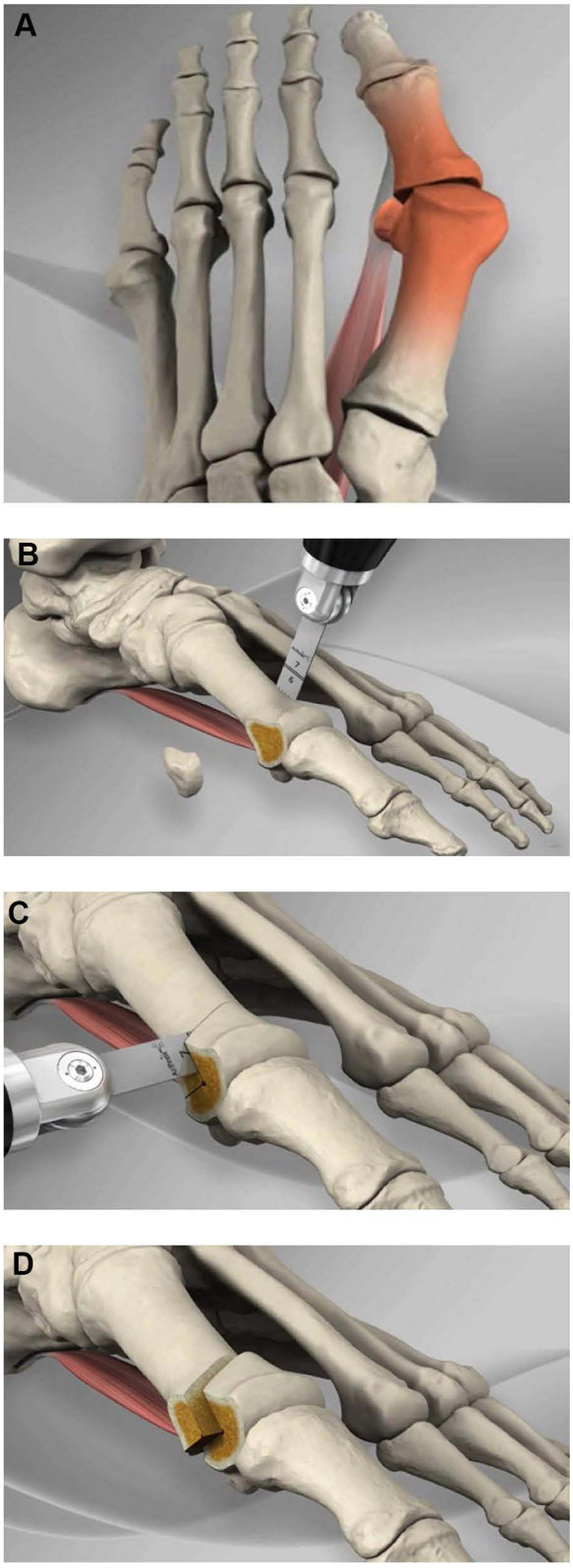
An illustrated outline of a typical Austin procedure is below (Figure 1):

Study Design Paradigms: Timing of First Study Treatment Dose

In bunionectomy studies, the most critical design consideration centers around the timing of the first dose of investigational product relative to the time of the surgery. There are 4 paradigms:

A. Preoperative Dosing

- First dose of study drug is given before surgery (study drug is administered prior to the patient entering the operating room).



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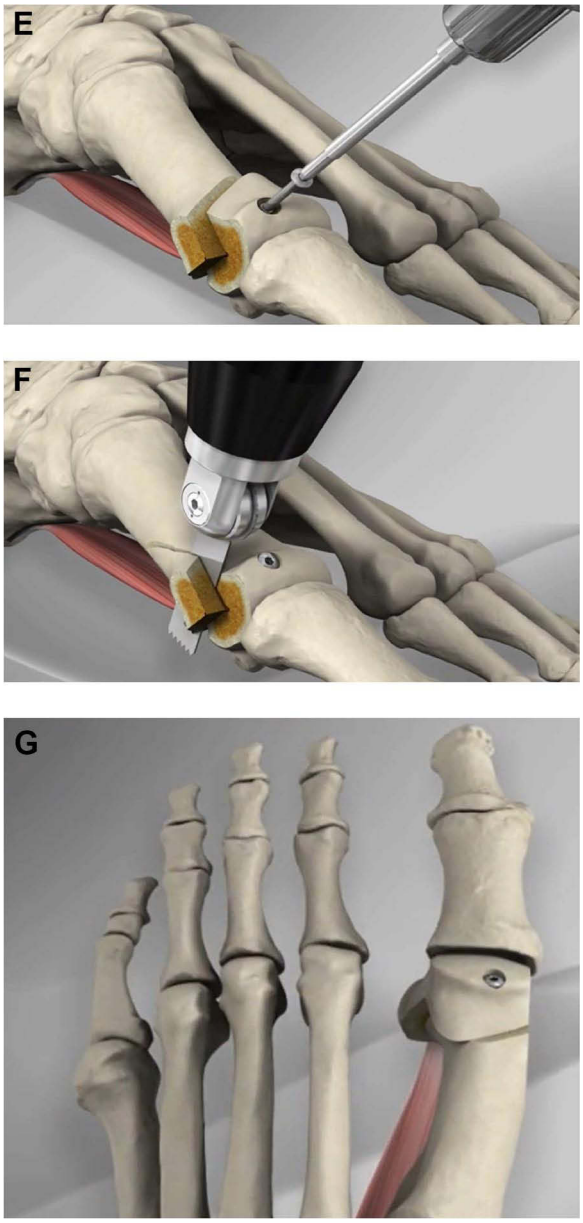

Figure 1 Illustration of Austin bunionectomy surgery. A video demonstration of the Austin procedure is available online: https://www.arthrex.com/resources/PAN1-00010-EN/first-metatarsal-distal-chevron-osteotomy-with-lps-screw.[24] (**A**) Hallux valgus deformity of first metatarsal head. (**B**) An osteotomy is performed to remove the Prominent bump from the first metatarsal head. (**C**) A V-shaped osteotomy is performed on the first metatarsal head. (**D**) The first toe is shifted laterally, which corrects the deformity. (**E**) A screw or pin is placed to provide external fixation. (**F**) An osteotomy is performed to trim the remaining lateral bone fragment. (**G**) The result is a smooth edge on the first metatarsal head. These images provided courtesy of Arthrex, Inc.

- Since subjects are not yet experiencing postsurgical pain when the first dose is administered, a pre-dose baseline pain measurement will not be available for endpoint calculations. Preoperative designs therefore cannot use summed pain intensity difference (SPID) endpoints and must employ an area under the curve (AUC)/ summed pain intensity (SPI) methodology (see Endpoints).
- Speed of onset measures such as the 2-stopwatch technique cannot be employed.

A preoperative design is typically utilized when the IP has a delayed onset of action (>90-120 minutes). For example, for an oral drug that takes 4 hours to reach an efficacious blood level, one might administer the drug 2 hours prior to surgery. By the time the patient wakes up from anesthesia and is ready for postsurgical efficacy assessments, the drug is able to provide analgesic relief.

B. Intraoperative Dosing

- First dose of study drug is given during surgery (study drug is administered while the patient is under anesthesia and surgery is ongoing).
- Because the patient is heavily sedated, a baseline pain measurement cannot be provided. Intraoperative designs must employ an AUC/ SPI methodology (see Endpoints).
- Speed of onset measures such as the 2-stopwatch technique cannot be employed.

This paradigm is required for infiltration analgesics (drugs that are injected into an open surgical wound, such as local anesthetics and injectable capsaicin). It can also be used for intravenous analgesics administered while the subject is under anesthesia.

C. Postoperative Dosing, Day 0

- First dose of study drug is administered on the day of surgery, approximately 1–4 hours postoperatively.
- Generally, subjects are pain free for about an hour after surgery secondary to the intraoperative Mayo block (see Mayo Block). The block will begin to wear off 1–4 hours after surgery.
- Subjects must report adequate pain for randomization postoperatively (see Postoperative Inclusion Criteria). The qualifying pain score is considered to be the subject's baseline. A baseline pain score allows use of SPID as a primary endpoint (see Endpoints).
- Speed of onset measures such as the 2-stopwatch technique can be employed.

The immediate postoperative pain signal from bunionectomy is intense on the day of surgery. As such the Postoperative Day 0 design should only be used for drugs with high potency and rapid onset. It is important to match the pain trajectory of the experimental model to the characteristics of the investigational product (see Figure 2).

D. Postoperative Dosing, Day 1

- First dose of study drug is given the morning after the day of surgery.
- A popliteal catheter is inserted during surgery to continuously numb the foot (see Popliteal Block). On the morning after surgery, the catheter is removed and the numbness recedes.

- Subjects must then report adequate pain for randomization postoperatively (see Postoperative Inclusion Criteria). The qualifying pain score is considered to be the subject's baseline pain. A baseline pain score allows use of SPID as a primary endpoint (see Endpoints).
- Speed of onset measures such as the 2-stopwatch technique can be employed.

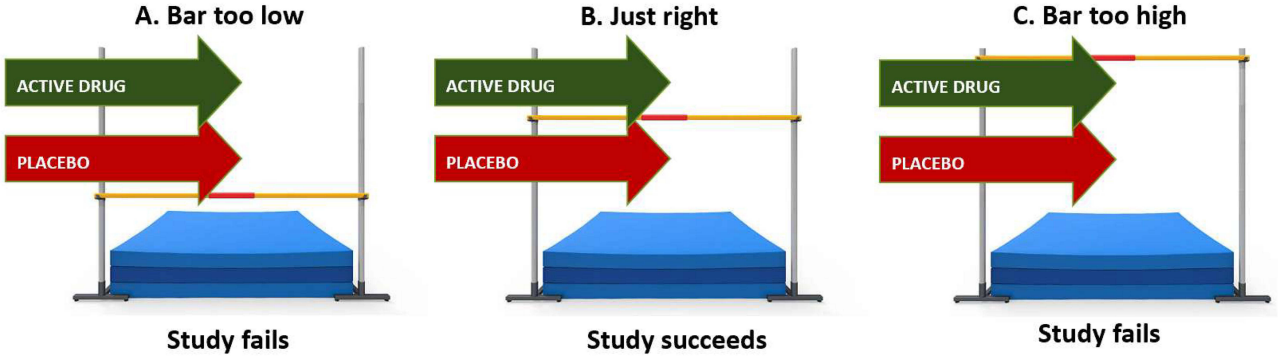

Figure 2 Matching experimental pain signal to study drug potency. Cooper (1983)[25] compared designing an analgesic study to setting the height of an Olympic high jump bar. Assuming the study drug is efficacious, a study should be designed so the "bar" (pain intensity during the treatment period) is at the correct level where active drug can clear it but placebo cannot (**B** above). If the bar is too low (not enough pain **A**), both placebo and study drug will clear the bar, and the study will fail. If the bar is too high (too much pain **C**), neither study drug nor placebo can clear the bar, and the study will fail. To separate an efficacious treatment from placebo, one must design the study to tailor the expected pain signal with the expected potency and onset characteristics of the study drug.

The Postoperative Day 1 design is by far the most common in bunionectomy clinical trials (see Summary Table of Bunionectomy Acute Pain Clinical Trials). The use of a popliteal catheter on the day of surgery allows pain from the surgical insult to partially recede overnight, such that when the patient is ready for randomization on the day after surgery, their pain trajectory is not as severe as it would have been on the day of surgery. This pain signal is an appropriate match for intermediate potency oral analgesics (investigational agents with potency similar to ibuprofen, hydrocodone, or acetaminophen). See Figure 2 re: matching the experimental pain signal to the study drug.

Figure 3 provides a timeline of key events for each dosing approach.

Sedation and Anesthesia

Anesthetic protocols can vary depending on the needs of a given study. One key asset of the bunionectomy model in clinical trials is the ability to adjust anesthesia and immediate postoperative analgesia to influence the onset and duration of a subject's pain trajectory (see Popliteal Block for one example). From an experimental viewpoint, the ideal anesthetic regimen utilizes short-acting drugs that dissipate quickly and as such do not have carryover effects that would confound the efficacy evaluation period. The following anesthetic protocol is typical of modern bunionectomy studies:

- Propofol at approximately 50–150 µg per kilogram per minute is titrated to achieve light sedation appropriate for monitored anesthesia care (MAC).
- 1–2 mg of midazolam may be given for preoperative sedation.
- Muscle relaxants are not used.
- Surgical anesthesia is generally achieved with a Mayo block (see Mayo Block below).
- 50–100 ug of fentanyl is allowed for intraoperative analgesia.

Mayo Block

The Mayo block is a field block around the base of the first metatarsal.[26] Local anesthetic is infiltrated proximal to the surgical site in a ring-type fashion. The block is performed after the patient is sedated but before surgery is initiated. The patient generally experiences dense anesthesia and near-complete numbness of the surgical area. The onset and duration of the block will vary depending on the local anesthetic employed (see Table 2). In bunionectomy trials, all subjects

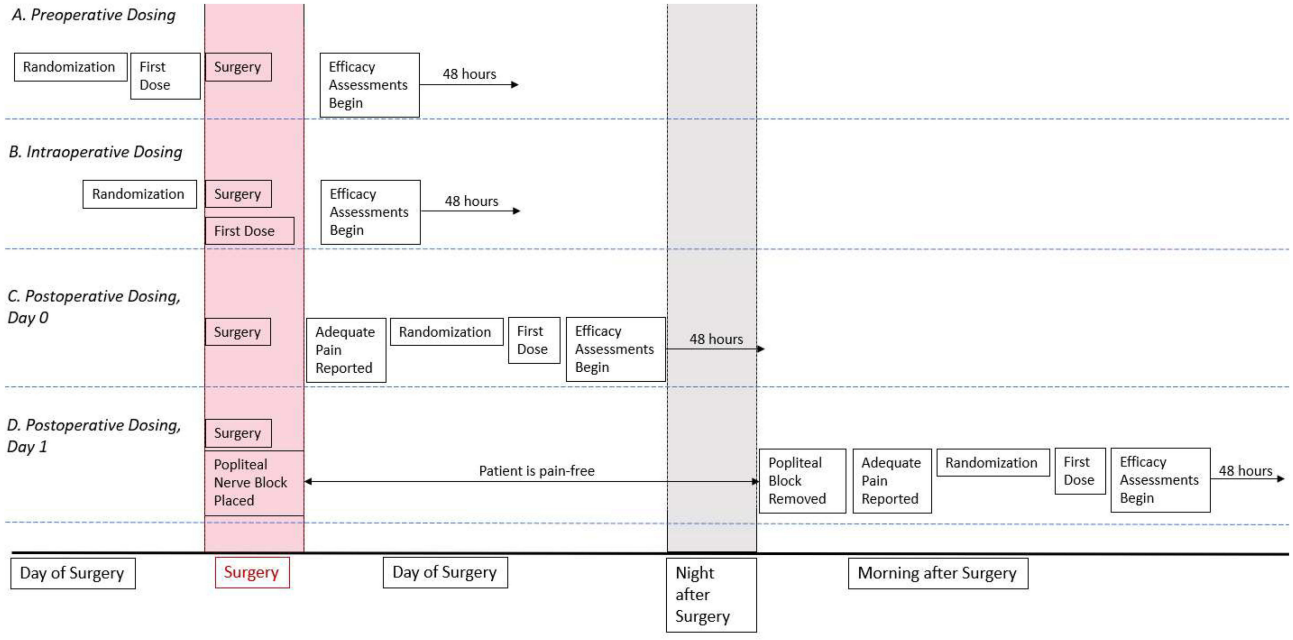

Figure 3 Timelines for each dosing paradigm.

Table 2 Example Mayo Block Specifications

Drug	Concentration	Dose	Onset	Duration
Bupivacaine*	0.25%	15–20 mL	15 m	6 hr
Lidocaine*	1% or 2%	15–20 mL	5 m	2.5 hr

Note: *Without epinephrine.

(regardless of the dosing paradigm) will receive a Mayo block. Subjects in Postoperative Dosing, Day 1 studies will also receive a popliteal block.

Popliteal Block

In Postoperative Day 1 studies (Paradigm D), a popliteal sciatic nerve catheter is placed in the popliteal fossa (the diamond-shaped space behind the knee joint) under ultrasound guidance. The catheter is used to infuse an intermediate-duration local anesthetic giving rise to a numb foot in most subjects.

Administration of local anesthetic for the popliteal block involves a loading dose followed by a continuous infusion and optional bolus doses. A variety of local anesthetics can be used. Examples of typical infusion protocols are presented in Table 3.

Example popliteal block specifications can be found in Table 3. The popliteal block is typically removed early in the morning on the day after surgery (at/around 4am). Numbness in the foot recedes over the next 8 hours. When the patient develops adequate pain (see Postoperative Inclusion Criteria), they are randomized into the study and administered their first dose of study treatment.

Typical Inclusion/ Exclusion Criteria

Preoperative Inclusion/ Exclusion (I/E) Criteria

Bunionectomy programs seek to enroll subjects who are:

1. Relatively healthy
2. Appropriate candidates for surgery (unilateral Austin bunionectomy) and anesthesia
3. Unlikely to be allergic or intolerant to the investigational product or the protocol-mandated rescue medications, and
4. Likely to provide non-confounded analgesic assessments.

In order to achieve point 4, subjects are excluded if they (1) have additional underlying painful conditions beyond bunion pain or (2) are currently taking opioids (eg >15 mg hydrocodone on any single day in the 2 months prior to surgery and any opioid within 10 days of surgery).

Postoperative Inclusion Criteria

In addition to the I/E criteria performed at the screening visit, studies using a postoperative dosing paradigm must specify a set of postoperative criteria to be assessed after the subject wakes up from surgery and begins experiencing pain. Namely, subjects must report postoperative pain that is: A) moderate or severe on a 4-point categorical scale (none, mild, moderate, or severe) and B) ≥4 or 5 on an 11-point NPRS (see Efficacy Assessments).

Table 3 Example Popliteal Block Specifications

Drug	Concentration	Loading Dose	Infusion Rate	Bolus Dose
Ropivacaine	0.2%	10–20 mL	4–12 mL/hr	7 mL
Bupivacaine	0.25%	10–20 mL	4–6 mL/hr	4 mL

Efficacy Assessments

The most common efficacy assessments used in bunionectomy studies are as follows:

NPRS

The numeric pain rating scale (NPRS) is an 11-point scale that requires the subject to select a whole number (between 0 and 10) that best reflects their current pain intensity. A 0 represents "no pain" and a 10 represents "the worst pain imaginable".

Assessment schedules in bunionectomy studies typically call for a scheduled NPRS to be captured at the following time points (in hours): 0.25, 0.50, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and then every 4 hours until Hour 48 (or end of study). In addition to scheduled NPRS assessments captured at specified time points, unscheduled NPRS assessments are also recorded A) immediately prior to use of any analgesic rescue medication and B) prior to subject discontinuation if it occurs before the end of the treatment period. Unscheduled NPRS assessments allow imputation of data that is confounded due to rescue or missing due to early discontinuation.

VAS

The visual analog scale (VAS) is a 100 mm line that the subject is asked to mark in a location that best reflects their current pain intensity. Multiple studies have shown that the NPRS and VAS are comparable in regards to assay sensitivity.[27,28] However, use of VAS in bunionectomy trials has largely fallen out of favor, due to complexities caused by errant marking of the diary by study subjects.

Patient Global Assessment of Pain Control (PGA)

The PGA is a 4- or 5-point scale that asks the subject to "rate how well your pain has been controlled since you received study medication" (there are varying versions with slightly different language). Allowed responses for the 5-point version are Poor, Fair, Good, Very Good or Excellent.

2-Stopwatch Assessments

Studies using postoperative dosing paradigms typically assess speed of onset using the 2-stopwatch technique. When a subject receives their initial dose of study drug, two stopwatches are simultaneously started. One stopwatch is labeled "Perceptible Relief" and the other is labeled "Meaningful Relief". The study coordinator provides the Perceptible Relief stopwatch to the subject and places the Meaningful Relief stopwatch near the bedside.

The subject is instructed to press the Perceptible Relief stopwatch when they feel "any pain relief at all". After the study subject achieves Perceptible Relief, the study coordinator provides the subject with the Meaningful Relief stopwatch. The subject is instructed to press the Meaningful Relief stopwatch when "they experience pain relief that is meaningful to them".

Pain Relief Assessments

Assessments of pain relief (eg, TOTPAR) ask the subject to rate "how much pain relief they have had since the first dose of study medication". Allowed responses are None, A Little, Some, A Lot and Complete. In multidose trials, pain relief assessments can confuse study subjects and as such they have not been included in most modern bunionectomy trials.

Rescue Medication

Time to first use of rescue, and amount of rescue used over various time intervals, are commonly recorded (see Measurement of Rescue Analgesics).

Endpoints

Typical Primary endpoints

SPID

Summed Pain Intensity Difference (SPID), used in Postoperative Dosing, Day 0 and Day 1 paradigms, is the most common primary endpoint utilized for bunionectomy studies. SPID measures how a subject's pain intensity changes over time in relation to the baseline pain score assessed at randomization (Figure 4). Only subjects who are dosed after surgery

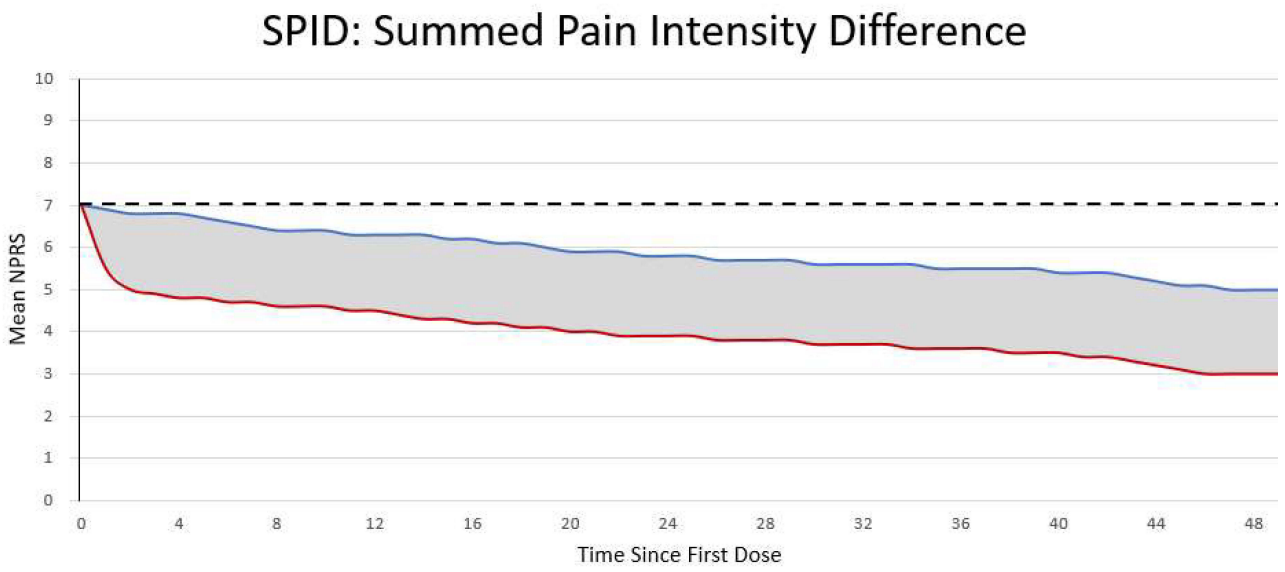

Figure 4 Summed Pain Intensity Difference (SPID). A: Dotted black line represents the mean baseline pain intensity, against which future measurements will be compared. B: Blue line represents mean pain intensity reported by the placebo arm. C: Red line represents mean pain intensity reported by the active arm. D: Gray area represents treatment effect (mean active change from baseline – mean placebo change from baseline).

(Postoperative Day 1 and Postoperative Day 0 designs) can record a baseline pain intensity, and therefore only postoperative dosing designs can utilize SPID as an endpoint. SPID is calculated utilizing a time-weighted average of NPRS scores.

SPI (Auc)

Summed Pain Intensity (SPI), (often called Area under the Curve [AUC]) is utilized for Pre- and Intra-operative dosing paradigms. Like SPID, SPI is a time-weighted average of NPRS scores. However, because there is no baseline pain intensity, the active and placebo arms may have differing baseline values (Figure 5).

Table 4 presents a summary of available endpoints for pre/intra-operative dosing and postoperative dosing paradigms.

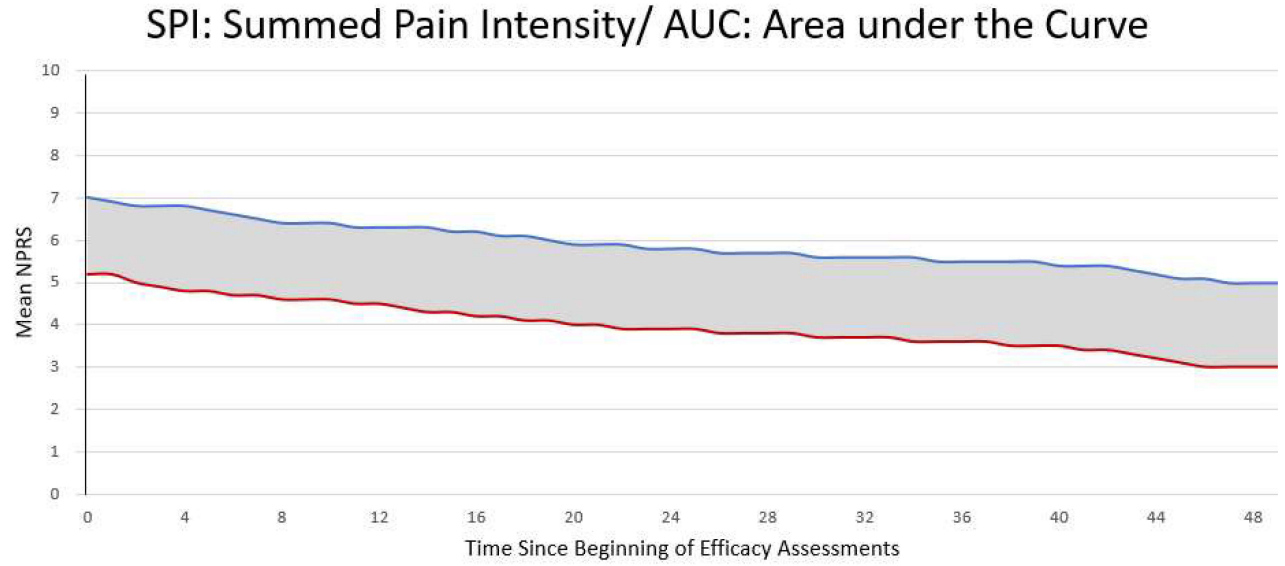

Figure 5 Summed Pain Intensity (SPI)/ Area under the Curve (AUC). A: Blue line represents pain intensity reported by the placebo arm. B: Red line represents pain intensity reported by the active arm. C: Gray area represents treatment effect (mean placebo NPRS - mean active NPRS).

Table 4 Pre-/ Intra-Operative Dosing Vs Postoperative Dosing

	Pre / Intra-operative Dosing	Postoperative Dosing
Postoperative inclusion/ exclusion criteria	No	Yes
Baseline pain measurement	No	Yes
Primary endpoint	SPI, often referred to as AUC	SPID
Drug speed of onset measurable	No	Yes

Typical Secondary Endpoints

Measures of Analgesic Onset

A Kaplan-Meier methodology is utilized to analyze the following endpoints that are derived from 2-stopwatch data:[29]

- Time to Perceptible Pain Relief: an endpoint derived from the median time at which study subjects stop the first stopwatch (which is labeled "Perceptible Relief").
- Time to Meaningful Pain Relief: an endpoint derived from the median time at which study subjects stop the second stopwatch (which is labeled "Meaningful Relief"). Subjects are considered to have achieved meaningful pain relief only if they hit the meaningful pain relief stopwatch before (1) receiving any dose of rescue analgesic or (2) receiving their 2nd scheduled dose of study drug.
- Time to Onset, also known as Time to Confirmed Perceptible Pain Relief: a derived endpoint that considers the time to perceptible pain relief only among subjects who also eventually achieve meaningful pain relief.

An additional method of analyzing analgesic onset is to determine the first time point at which the NPRS scores begin to diverge by a prespecified amount between treatment arms (generally referred to as time-specific pain intensity differences).

Measurement of Rescue Analgesics

Rescue analgesics are provided to study subjects only when needed/requested. As such, the amount of rescue analgesics consumed by the study subject can serve as a surrogate measure for how much pain that subject is experiencing.[30] It is therefore common to tabulate and compare the total number of doses of rescue drug received in each study arm and report rescue-related efficacy endpoints.[31,32] If the rescue analgesic regimen involves multiple opioids, an opioid equivalence chart can be used to facilitate the analysis.[33]

The time elapsed between the administration of the first dose of study drug and the request/receipt of the first dose of rescue drug is commonly calculated and compared between treatment groups. This measure can provide information about analgesic offset.

Summary Table of Bunionectomy Acute Pain Clinical Trials Since 2008

Methods

Data Sources Searched and Criteria for Inclusion/ Exclusion of Publications and Studies

Summary Table of Bunionectomy Studies (Table 5)

MEDLINE/ PubMed was searched for all relevant studies published between January 1, 2008 and December 5th, 2023. Relevant studies included any randomized, double-blind, controlled clinical trial in adults ≥18 years old, that tested a pharmacologic analgesic agent in a bunionectomy acute pain trial. The search was performed for "bunionectomy" and the advanced search option limited results to "clinical trial", "clinical trial, Phase II", "clinical trial, Phase III", "clinical trial, Phase IV", in Humans, and in Adults. Search: ("bunionectomies"[All Fields] OR "bunionectomy"[All Fields]) AND ((clinicaltrial[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter])

Table 5 Bunionectomy Studies

Enroll-ment Start Date (per CTG)	Enroll-ment End Date	Study Drug	Sponsor	CTG Identifier/ Publication	Drug Class (MOA)	Route of Admin-istration	Study Phase	n	# of Arms	Active Comp-Arator (s)	First-Line Rescue	# of Sites	Dosing Paradigm	Mean Base-line Pain (if Post-op Dosing)	Primary Endpoint	Primary Endpoint p-value	Primary Endpoint SES
~1/06*		Nucynta (tapentadol) [CG5503]	Grunenthal	Stegmann 2008[34]	Opioid/ NRI	Oral	2	269	4	Oxycodone	APAP	–	POD1	6.3	SPI24	0.0001	0.77
~1/06*		Dynastat (parecoxib)	Pfizer	Apfelbaum 2008[35]	NSAID	Intravenous		368	3	None	Hydrocodone + APAP	–	POD0	7.3	SPID24	<0.05	–
08/06	10/06	Zipsor (diclofenac) [XP21L]	Xanodyne	NCT00366444/ Riff 2009[36]	NSAID	Oral	3	201	2	None	None	6	POD1	7.1	SPID48	<0.001	0.801
09/06	01/07	Zipsor (diclofenac) [XP21L]	Xanodyne	NCT00375934/ Daniels 2010[37]	NSAID	Oral	3	200	2	None	Hydrocodone + APAP	4	POD1	7.5	–	<0.001	–
~1/07*	05/07	Nucynta (tapentadol) [CG5503]	Johnson & Johnson	NCT00364247/ Daniels 2009[38]	Opioid/ NRI	Oral	3	603	5	Oxycodone	None	–	POD1	–	SPID48	<0.001	1.291
09/07	02/08	Acurox (oxycodone + niacin)	Acura	NCT00654069/ Daniels 2011[39]	Opioid	Oral	3	405	3	None	ketorolac	–	POD0	6.4	SPID48	<0.0001	–
09/07	02/08	Nucynta (tapentadol) [CG5503]	Grunenthal	NCT00609466	Opioid/ NRI	Oral	3	285	3	morphine	–	6	POD1	–	SPID48	<0.0001	0.525
02/08	10/08	Nucynta (tapentadol) [CG5503]	Johnson & Johnson	NCT00613938/ Daniels, Casson 2009[40]	Opioid/ NRI	Oral	3	901	4	oxycodone	APAP	7	POD1	7.1	SPID48	<0.001	0.961
03/08	08/08	(capsaicin) [4975]	Anesiva	NCT00656578	TRPV1	Infiltration	3	–	–	None	–	6	Intra-op	–	–	–	–
12/08	01/09	MoxDuo (morphine + oxycodone) [Q8003]	QRxPharma	NCT00831051	Opioid	Oral	2	197	–	Morphine and oxycodone	–	6	–	–	SPID48	–	–
03/09	08/09	(cebranopadol) [GRT6005]	Grunenthal	NCT00872885/ Scholz 2018[41]	Opioid/ NOP	Oral	2	258	5	Morphine CR	APAP	1	POD1	4.9	SPID 2–10	0.0042	0.575
04/09	11/09	Exparel (bupivacaine) [SKY0402]	Pacira	NCT00890682/ Golf 2011[42]	Local anesthetic	Infiltration	3	193	2	None	Oxycodone + APAP	1	Intra-op	–	AUC0-24	0.0005	0.471
12/09	05/10	(hydrocodone + APAP ER)	Abbvie	NCT01038609	Opioid + APAP	Oral	2	250	5	APAP & morphine	–	4	–	–	SPID48	–	0.461
12/09	03/10	MoxDuo (morphine + oxycodone) [Q8003]	QRxPharma	NCT01016808/ Richards 2013[43]	Opioid	Oral	3	522	3	Morphine and oxycodone	Ibuprofen	5	POD0	–	SPID24	–	–

01/11	04/11	MoxDuo (morphine + oxycodone) [Q8003]	QRxPharma	NCT01280331	Opioid	Oral	3	375	–	Morphine and oxycodone	–	4	–	–	SPID48	–	–
04/11	06/11	(hydrocodone + APAP ER)	Abbvie	NCT01333722	Opioid + APAP	Oral	2	100	2	None	–	3	–	–	SPID12	–	0.822
09/11	02/12	Nucynta (tapentadol) [CG5503]	Grunenthal	NCT01435577	Opioid/ NRI	Intravenous	2	129	2	None	Ibuprofen	1	POD0	7.2	SPID24	–	–
10/11	02/12	Zorvolex (diclofenac) [SoluMatrix diclofenac]	Iroko	NCT01462435/ Argoff 2016[44]	NSAID	Oral	3	428	4	Celecoxib	Hydrocodone + APAP	4	POD1	–	SPID48	<0.001	0.501
11/11	08/12	Xartemis XR (oxycodone + APAP) [MNK-795]	Mallinckrodt	NCT01484652/ Singla 2014[45]	Opioid	Oral	3	303	2	None	ibuprofen	5	POD1	6.1	SPID48	<0.001	0.513
01/12	02/13	Nucynta (tapentadol) [CG5503]	Janssen	NCT01516008	Opioid/ NRI	Oral	3	352	3	Celecoxib	–	7	POD1	–	SPID48	<0.001	0.728
02/12	06/12	Tivorbex (indomethacin) [SoluMatrix indomethacin]	Iroko	NCT01543685/ Altman 2013[46]	NSAID	Oral	3	462	5	None	Hydrocodone + APAP	4	POD1	–	SPID48	<0.001	0.499
05/12	08/12	Tivorbex (indomethacin) [SoluMatrix indomethacin]	Iroko	NCT01626118	NSAID	Oral	3	373	4	None	–	4	–	7.2	SPID48	0.034	0.315
10/12	02/13	Dsuvia (sufentanil) [NanoTab]	AcelRx	NCT01710345/ Singla, Muse 2014[47]	Opioid	Sublingual	3	100	3	None	Hydrocodone + APAP	2	POD0	–	SPID12	0.003	0.191
11/12	05/13	(hydrocodone + APAP) [MNK-155]	Mallinckrodt	NCT01743625/ Singla 2015[48]	Opioid	Oral	2	402	2	None	ibuprofen	5	POD1	7.2	SPID48	<0.001	–
05/13	08/13	Korsuva (difelikefalin) [CR845]	Cara	NCT01789476	Opioid	Intravenous	2	51	2	None	–	1	–	–	SPID24	<0.05	0.613
02/14	11/15	[MDT-10013]	Medtronic	NCT02077140	Unknown	Implant	2	144	4	None	Opioid	2	Intra-op	–	SPI48	–	0.308
04/14	10/14	Olynvik (oliceridine) [TRV130]	Trevena	NCT02100748	Opioid	Intravenous	2	333	–	Morphine	–	4	POD1	–	SPID48	–	–
10/14	06/15	(dexmedetomidine) [DEX-IN]	Baudax	NCT02284243	Alpha-2 agonist	Intranasal	2	168	2	None	Oxycodone	3	POD1	6.5	SPID48	0.018	0.301

(*Continued*)

Table 5 (Continued).

Enroll-ment Start Date (per CTG)	Enroll-ment End Date	Study Drug	Sponsor	CTG Identifier/ Publication	Drug Class (MOA)	Route of Admin-istration	Study Phase	n	# of Arms	Active Comp-Arator (s)	First-Line Rescue	# of Sites	Dosing Paradigm	Mean Base-line Pain (if Post-op Dosing)	Primary Endpoint	Primary Endpoint p-value	Primary Endpoint SES
06/15	09/15	Zynrelef (bupivacaine) [HTX-011]	Heron	NCT02471898	Local anesthetic	Infiltration	2	71	–	None	–	1	Intra-op	–	SPI24	–	–
06/15	07/15	Troxyca ER (oxycodone + naltrexone)	Elite	NCT02401750	Opioid	Oral	3	163	–	Oxycodone + naltrexone	–	5	POD1	–	SPID48	–	–
08/15	11/15	Anjeso (meloxicam) [N1539]	Baudax	NCT02540265	NSAID	Intravenous	2	59	3	None	opioid	1	POD1	7.6	SPID48	–	1.007
08/15	03/16	(hydrocodone + APAP IR) [TV-46763]	Teva	NCT02487108	Opioid	Oral	3	567	4	None	Ibuprofen	8	POD1	–	SPID48	<0.001	0.649
01/16	07/16	Anjeso (meloxicam) [N1539]	Baudax	NCT02675907/ Pollak 2018[32]	NSAID	Intravenous	3	201	2	None	Oxycodone	4	POD1	6.9	SPID48	0.0034	0.407
01/16	06/16	Buvaya (buprenorphine)	INSYS	NCT02634788	Opioid	Sublingual	3	299	4	None	–	4	–	–	SPID48	<0.0001	0.936
05/16	02/17	Zynrelef (bupivacaine) [HTX-011]	Heron	NCT02762929	Local anesthetic	Infiltration	2	429	11	bupivacaine	–	5	Intra-op	–	SPI24	–	1.736
05/16	12/16	Olynvik (oliceridine) [TRV130]	Trevena	NCT02815709	Opioid	Intravenous	3	418	–	Morphine	–	7	POD1	–	% responder	–	–
10/16	06/17	Maxigesic (ibuprofen + APAP)	AFT	NCT02689063/ Daniels 2019[49]	NSAID + APAP	Intravenous	3	276	4	Ibuprofen and APAP	Oxycodone	2	POD1	6.7	SPID48	<0.0001	1.133
01/17	07/17	(dexmedetomidine) [TPU-006]	Teikoku	NCT02953054	Alpha-2 agonist	Transdermal	2	88	–	None	–	2	–	–	SPI 4–24	–	–
03/17	11/17	Seglentis (celecoxib + tramadol) [E-58425]	Esteve	NCT03108482/ Viscusi 2023[50]	NSAID + Opioid/ NRI	Oral	3	637	4	Celecoxib and tramadol	APAP	5	POD1	–	SPID48	<0.001	0.762
06/17	12/17	[VX-150]	Vertex	NCT03206749	Nav1.8 inhibitor	Oral	2	243	3	Hydrocodone + APAP	Ibuprofen	4	POD1	6.3	SPID24	<0.0001	0.643
09/17	04/18	(tramadol) [AVE-901]	Avenue	NCT03290378	Opioid/ NRI	Intravenous	3	409	3	None	Ibuprofen	5	POD1	6.8	SPID48	<0.005	–
10/17	01/18	Zynrelef (bupivacaine) [HTX-011]	Heron	NCT03295721/ Viscusi 2019[31]	Local anesthetic	Infiltration	3	412	3	Bupivacaine	Opioid	15	Intra-op	–	SPI72	<0.001	0.719
07/18	10/18	(Vocacapsaicin) [CA-008]	Concentric	NCT03599089	TRPV1	Infiltration	2	147	4	None	Oxycodone	3	Intra-op	–	SPI96	0.005	0.613

10/18	02/19	Zynrelef (bupivacaine) [HTX-011]	Heron	NCT03718039	Local anesthetic	Infiltration	2	78	3	None	Opioid	1	Intra-op	–	SPI72	No placebo	No placebo
12/18	01/19	(VX-150)	Vertex	NCT03764072	Nav1.8 inhibitor	Oral	2	250	6	None	–	6	POD1	6.6	SPID24	–	0.382
03/19	03/20	(ropivacaine) [TLC590]	Taiwan Liposome Company	NCT03838133	Local anesthetic	Infiltration	2	150	–	Bupivacaine and ropivacaine	–	5	Intra-op	–	SPI24	–	–
05/19	08/19	[VVZ-149]	Vivozon	NCT03997812	Glycine + 5HT inhibitor	Intravenous	2	60	–	None	opioid	2	–	–	SPI12	–	–
05/20	07/21	(bupivacaine + meloxicam + aprepitant) [HTX-034]	Heron	NCT04398329	Local anesthetic	Infiltration	2	73	–	Bupivacaine	–	4	Intra-op	–	SPI72	–	–
07/20	11/20	(pregabalin + APAP) [NVK099]	Nevakar	NCT04495283	Gabapentanoid + APAP	Intravenous	2	87	2	APAP	Opioid	2	Pre-op	–	SPI48	<0.001	1.27
03/21	02/22	(ebaresdax) [ACP-044]	Acadia	NCT04855240	Redox modulator	Oral	2	237	3	None	Opioid	4	POD1	–	AUC0-24	0.1683	0.212
07/21	02/22	[VX-548]	Vertex	NCT04977336	Nav1.8 inhibitor	Oral	2	274	–	Hydrocodone + APAP	–	12	POD1	–	SPID48	–	–
02/22	08/22	Exparel (bupivacaine)	Pacira	NCT05157841	Local anesthetic	Nerve block	3	185	–	Bupivacaine	–	7	Intra-op	–	SPI96	–	–
06/22	09/22	(ropivacaine) [CPL-01]	Cali	NCT05411861	Local anesthetic	Infiltration	2	73	–	None	–	3	Intra-op	–	SPI72	–	–

Notes: *Start date is an estimate. "—" indicates information not presented in sources, not applicable or not calculable based on source data. Baseline pain reported on a VAS scale was converted to NRS (ie, results were divided by 10); additionally, some studies reported that an opioid rescue was used but not the specific opioid. In this situation "opioid" was presented for the rescue.

Abbreviations: APAP, acetaminophen; BID, twice a day; CR, controlled-release; HCl, hydrochloric acid; HC; hydrocodone; IBU, ibuprofen; IR, immediate release; IV, intravenous; mg, milligram; N/A, not applicable; N/R, not reported; NPRS, numerical pain rating scale; OC, oxycodone; PBO, placebo; POD0, post-operative day 0 (ie, day of surgery); POD1, post-operative day 1 (ie, day after surgery); S{I; SPID, sum of the pain intensity difference; TID, three times a day; QID, four times a day; 5HT, serotonin receptor.

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AND (humans[Filter]) AND (2008/1/1:2023/10/1[pdat]) AND (alladult[Filter])). A total of 38 publications were identified in the search. The authors reviewed each abstract and publication to determine if the publication met the criteria for our narrative review.

Additionally, clinicaltrials.gov was searched for unpublished bunionectomy studies using the following criteria: (1) Condition/disease: bunionectomy and then further limited to (2) completed studies, (3) Phase II or III, (4) interventional studies, (5) industry sponsored, and (6) had a primary completion date between January 1st, 2008 and December 5th, 2023.

FDA Summary Basis of Approval documents were reviewed for any additional information missing from publications and/or clincialtrials.gov.

All studies that were identified either through a publication or a clinicaltrials.gov search were included in the table, regardless of availability of data. Dashes in the table represent missing data that the authors were unable to find in public sources.

Rescue Table (Table 6)

All studies from the main search for which sufficient information related to rescue medication was available are included in Table 6. These studies had Studies publicly-available details on A) protocol-allowed rescue medication and B) the rate of early terminations due to lack of efficacy in the placebo arm.

Table 6 Placebo Arm Rescue Use and Efficacy Terminations in Bunionectomy Studies

Study	Rescue Regimen	% of Placebo-Arm Subjects Terminating Early Due to Lack of Efficacy
POSTOPERATIVE DOSING, DAY 1 *(lower pain trajectory than other paradigms)*		
Nucynta (Daniels Upmalis 2009)[38]	No Rescue	48.8
Nucynta (Daniels Casson 2009)[40]	Up to 2g APAP (in first 12 hrs, divided)	23.2
MNK-155 (Singla 2015)[48]	400mg ibuprofen Q6	15.8
Xartemis (Singla Barrett 2014)[45]	400mg ibuprofen Q4	9.8
Anjeso (Pollak 2018)[32]	5mg OC Q2	4.0
Zorvolex (Argoff 2016)[44]	10mg HC/ 325mg APAP Q4h or 7.5mg OC/ 325 APAP Q6h	2.8
Tivorbex (Altman 2013)[46]	1st: 5mg HC/ 500mg APAP Q4h 2nd: 7.5mg OC/ 325mg APAP	2.1
Zipsor (Daniels 2010)[37]	5mg HC/ 500mg APAP 1–2 tablets Q4	2.0
Seglentis (Viscusi 2023)[50]	1st: 1g APAP IV Q4h (up to 4g per day) 2nd: 5mg OC Q4h	1.1
Cebranopadol (Scholz 2018)[41]	1st: up to 3g APAP per day 2nd: up to 150 mg diclofenac per day	0
Combogesic (Daniels 2019)[49]	1st: 5–10 mg OC 2nd: 2–4 mg IV morphine	0

(*Continued*)

Table 6 (Continued).

Study	Rescue Regimen	% of Placebo-Arm Subjects Terminating Early Due to Lack of Efficacy
PRE- or INTRA-OPERATIVE DOSING, or POSTOPERATIVE DOSING, DAY 0 *(higher pain trajectory than Postop Day 1)*		
Dynastat (Apfelbaum 2008)[35]	5mg HC/ 500mg APAP	16.1
Dsuvia (Singla Muse 2014)[47]	5mg HC/ 500mg APAP Q4h	5.0
Oxycodone/ Niacin (Daniels 2011)[39]	IV ketorolac	2
Exparel (Golf 2011)[42]	1st: 5mg OC/ 325mg APAP 1–2 tablets Q4h 2nd: 15–30mg IV ketorolac (single dose)	0
Zynrelef (Viscusi 2019)[31]	1st: 10 mg IV morphine (within 2h period as needed) 2nd: 10mg OC Q4h 3rd: 1g APAP Q6h	0

Demographics Table (Table 7)

The 5 most recent publications were reviewed and common demographic data was compiled in a table Weighted averages were obtained within an individual study and then a weighted average was calculated across all studies. A limited number of recent studies were reviewed for Table 7 as the table is simply meant to provide a brief qualitative

Table 7 Demographic Characteristics of Bunionectomy Subjects

Key Demographics	Weighted Average
Age (Average y)	44.5
Gender (%)^	
Female	85.5
Male	14.5
Race (%)	
White	70.6
Black or African American	20.6
Asian	2.9
Native Hawaiian/ Pacific Islander	0.7
American Indian/ Alaska Native	0.4
Other/ Multiple	5.3
Ethnicity (%)*	
Not Hispanic/ Latino	72.1
Hispanic/ Latino	27.9
BMI (Average kg/m^2)	27.6

Notes: Studies included: Seglentis (Viscusi 2023),[50] Combogesic (Daniels 2019),[49] Zynrelef (Viscusi 2019),[31] Anjeso (Pollak 2018),[32] cebranopadol (Scholz 2018).[41] ^Gender data was not included in the Pollak 2018 publication and therefore is excluded from this assessment. *Ethnicity data was not included in the Viscusi 2023 publication and therefore is excluded from this assessment.

overview of demographic data. Additionally, data from recent available manuscripts may better reflect current demographic patterns in bunionectomy trials than data from older studies.

Analysis

Rescue Medication

Rescue analgesics are ethically required in acute pain studies, but they confound experimental data. In bunionectomy studies rescue is frequent in both the placebo arm (≈95% of placebo subjects receive at least one dose of rescue) and the active arm (≈85% of active subjects receive at least one dose of rescue).[51] As such, the choice of rescue is an important study design element. An ideal rescue regimen is a balance between:

1. Strict rescue, which can give rise to unacceptably high terminations due to lack of efficacy (resulting in a high degree of missing data), and
2. Liberal rescue, which can excessively confound study data (Figure 6).

The optimal way to interrogate a rescue regimen is to examine the placebo arm of past bunionectomy studies and calculate the rate of early terminations due to lack of efficacy. If a rate is too high (greater than ≈20%) then the experiment used too strict a rescue regimen (ie, not enough rescue). On the other hand, if there were very few efficacy terminations in the placebo arm (less than ≈2%), then the experiment likely used too liberal a rescue regimen (ie, too much rescue).

Table 6 shows rescue regimens and placebo dropout rates due to lack of efficacy in bunionectomy studies.

Enrollment Rates

To estimate the average enrollment rate (subjects enrolled per site per month) for bunionectomy acute pain trials, we examined enrollment data from clinicaltrials.gov (CTG). Adequate data was available for 47 of the 53 studies in Table 5. The remaining 6 studies did not have all necessary data to calculate an enrollment rate listed on CTG.[34,35,38,39,41,42] Enrollment rate was calculated with the following formula:

Total study n ÷ number of study centers ÷ enrollment period in months

The enrollment period was considered to be the time from the "Study Start Date" to the "Primary Completion Date".

For these 47 studies, the unweighted mean enrollment rate was 15.2 subjects per site per month.

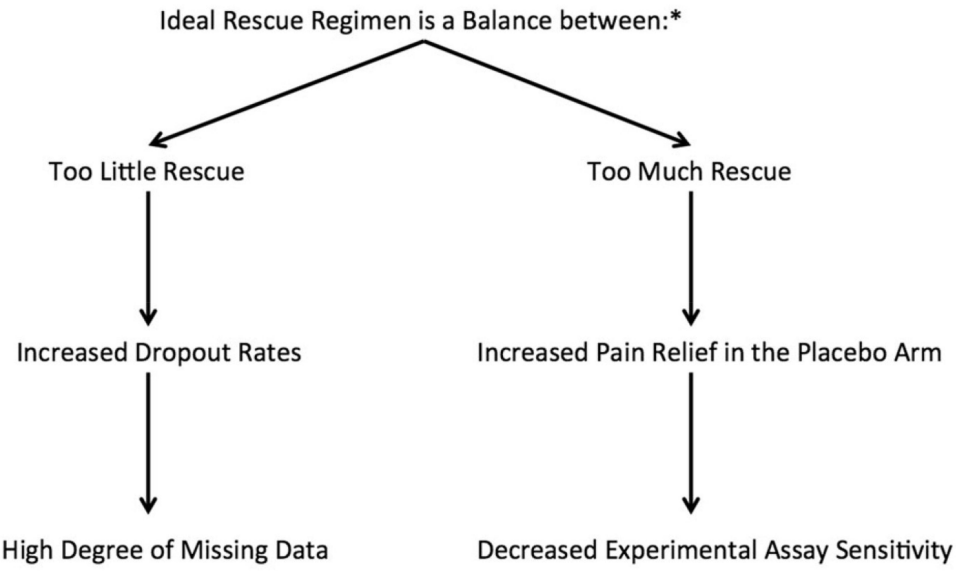

Figure 6 Balancing rescue regimens *Ethical considerations around rescue medication are important, and are discussed in other sources.[51]

Reported enrollment periods derived from CTG data are sometimes longer than the actual active enrollment time of the study. This is because a CTG enrollment period may include pauses during which a study was not actively enrolling. As such the actual mean enrollment rate for these studies may be somewhat higher than 15.2, if only active enrollment time is considered.

Demographics

Table 7 shows a weighted average of demographic information from the 5 most recent bunionectomy publications* as of December 2023:

Dental Impaction Pain Model (DIPM) versus Bunionectomy

DIPM, in which pain is assessed after third molar extraction surgery, is a common and useful hard tissue pain model. Dental studies can be recruited more rapidly (using fewer centers) and more cost-effectively than can bunionectomy studies.[16] The experimental clarity of dental studies is high (higher standardized effect sizes than bunionectomy).[16] As such, dental is an excellent model for:

A. Initial proof of concept
B. Dose ranging, and
C. Exploring PK/PD relationships.

The dental model is generally regarded as a single-dose model that provides assay sensitivity for 6–12 hours after surgery.[52] It has not been accepted by US or European regulators as a pivotal acute pain model in recent years,[18] because it is considered to have low clinical relevance, and does not provide adequate information on efficacy past 6–12 hours (and therefore cannot be used to assess multi-dose efficacy).

Discussion

The three most common hard tissue acute pain models are dental impaction (DIPM), bunionectomy and total knee arthroplasty (TKA). DIPM is a rapidly-recruiting, extremely sensitive model that is considered to have low clinical significance. TKA on the other hand is highly clinically relevant but experimentally confounded. Bunionectomy represents a compromise between these two extremes. It is a model with acceptable assay sensitivity and reasonable clinical relevance (see Figure 7).

Bunionectomy maintains its assay sensitivity for approximately 72–96 hours after surgery.[31,53] As such the model is able to provide information on the multi-dose behavior of an experimental agent. For this reason, regulators in the United States and the European Union have accepted bunionectomy as a pivotal model for putative analgesic candidates.

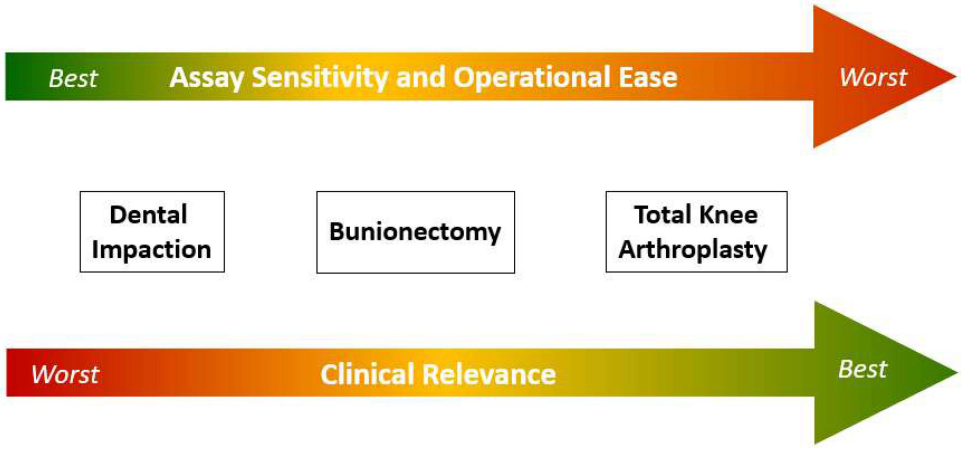

Figure 7 Comparison of common hard tissue acute pain models.

The triad of good assay sensitivity, reasonable clinical relevance and regulatory acceptance explains the popularity of bunionectomy as an acute pain surgical model.

Data Sharing Statement

Data sharing is not applicable to this article, as no new data were created or analyzed for the article.

Disclosure

Neil Singla, MD is the founder of Lotus Clinical Research, a full-service contract research organization, research site network and consulting firm that specializes in analgesic clinical trials. Lotus generates revenue from the performance of studies in acute pain and other therapeutic areas. The authors report no other conflicts of interest in this work.

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