Narrative Review

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Abdominoplasty as an acute postoperative pain model: insights from 8 years of clinical trials

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Abstract

To have a complete understanding of an experimental analgesic's efficacy in treating acute postoperative pain, it is necessary to understand its effect on both hard-tissue pain and soft-tissue pain. For this reason, regulatory bodies including the U.S. Food and Drug Administration and European EMA typically require drug developers to demonstrate efficacy in both hard-tissue and soft-tissue pain to grant a broad approval for an analgesic in acute postoperative pain. Hard-tissue models such as bunionectomy and molar extraction are well-validated and efficient with long histories in clinical trials, but until recently, a similarly well-standardized and fast-enrolling soft-tissue model was not available. Abdominoplasty was developed as an acute postoperative pain model and introduced to the clinical trial marketplace in 2014 to address the need for a viable soft-tissue model. Since then, at least 13 industry-sponsored studies, including multiple pivotal trials, have been conducted, providing a data set that can be used to interrogate the model's strengths and weaknesses. The authors outline the development history of abdominoplasty, discuss key clinical and design characteristics of the model, and review public data from abdominoplasty acute pain studies available to date. The data suggest that abdominoplasty is a well-validated soft-tissue surgical model that provides high-quality experimental outputs, enabling the efficacy of investigational analgesics in soft-tissue pain to be understood successfully.

Keywords: Abdominoplasty, Acute pain, Postoperative pain, Bunionectomy, Clinical trials, Pain research, Clinical trial enrollment, Soft-tissue surgery, Acute pain regulatory pathways, Postsurgical pain, Pain clinical trials

1. Introduction

1.1. Overview

To have a complete understanding of an experimental analgesic agent's efficacy in treating acute postoperative pain, it is necessary to understand its effect on both hard-tissue (bony) pain and soft-tissue pain. Each of these 2 types of pain has different anatomical or neurological origin and can respond differently to the same analgesic agent.[1] For this reason, regulatory bodies including the U.S. Food and Drug Administration (FDA), European Medicines Agency, and others typically require drug developers to demonstrate efficacy in both hard-tissue and soft-tissue pain to grant a broad approval for use of a putative analgesic for acute postoperative pain.

Hard-tissue acute pain experimental models such as bunionectomy and molar extraction are well-validated with long histories in clinical trials and have proven to be reliable and efficient at providing data on an analgesic drug's effectiveness.[17] These models are typically performed in well-controlled study settings (often specialized research centers) on homogenized patient populations, which leads to high experimental assay sensitivity and therefore a strong likelihood of separating a genuinely efficacious drug from placebo. These bony models (bunionectomy and molar extraction) are highly standardized, rapid to enroll, and inexpensive to perform relative to other common surgeries and can therefore accelerate a drug's development pathway.

Before the advent of abdominoplasty, a soft-tissue acute pain experimental model akin to bunionectomy (well-controlled, highly sensitive, and rapidly enrolling) was not available. Therefore, researchers had to rely on imperfect soft-tissue surgery models (eg, hysterectomy, various laparotomies, open colon surgery, etc), which gave rise to multiple failed studies on therapies that were likely efficacious. Beginning in 2007, the authors set out to develop a soft-tissue surgical model with similar experimental characteristics to the 2 well-validated bony models described above (bunionectomy and molar extraction). After extensive review of several soft-tissue surgical models (including but not limited to hernia repair, breast augmentation, breast lift, cholecystectomy, and laparoscopic colectomy) and discussions with multiple general and plastic surgeons (see "Development of Abdominoplasty" below), the authors settled on abdominoplasty as the optimal candidate for a soft-tissue clinical trial model and initiated pilot studies.

Since that time, beginning with smaller proof-of-concept studies and advancing to large Phase 3 pivotal programs, at

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 164 (2023) 258–270

http://dx.doi.org/10.1097/j.pain.0000000000002736

least 13 high-quality randomized, double-blind, placebo-controlled acute pain clinical trials in abdominoplasty have been performed. Abdominoplasty has become an industry standard model for characterizing a drug's effect on acute soft-tissue pain. It has also been validated as a Phase 3 pivotal registration model in the United States, where 2 new analgesic agents that relied on abdominoplasty as the soft-tissue model in pivotal programs have been approved by FDA (Baudax Bio's IV meloxicam [Anjeso], a nonsteroidal anti-inflammatory drug (NSAID), and Trevena Inc.'s IV oliceridine [Olinvyk], a novel opioid). Multiple other drug candidates are currently progressing toward potential U.S. market approval based in part on pivotal trials in abdominoplasty performed under FDA guidance.

This paper will provide a brief summary of the development history of abdominoplasty and outline the clinical and experimental characteristics of abdominoplasty as an acute postoperative pain model. We will review data and design characteristics from acute pain abdominoplasty trials conducted to date, discuss abdominoplasty's safety profile, clinical relevance, and other key characteristics and compare abdominoplasty with other common acute pain models.

1.2. Experimental characteristics of postoperative pain models: standard vs enhanced recruitment

Recruitment of subjects into acute postoperative pain studies falls into 2 main paradigms. There is no widely accepted terminology for the 2 categories; for the purpose of discussion, they will be described as "standard recruitment" and "enhanced recruitment," both defined below. Abdominoplasty is important as the first and most common soft-tissue surgical model allowing enhanced recruitment.

- A study using **standard recruitment** enrolls subjects who are already scheduled for surgery before the study—they would undergo surgery whether or not they participated in the study. Surgical costs are paid by the subject or by insurance. Surgery is typically performed at a hospital or institution dictated by the subject's insurance requirements or personal preference. These institutions are unlikely to have special expertise in analgesic clinical research.
- In studies using **enhanced recruitment**, investigators actively accumulate potential subjects through advertisements and patient databases. Surgical costs are paid by study grant, rather than by the subject or insurance. This structure allows subjects to be funneled into a small number of dedicated research centers.

Table 1 shows the most common acute pain models and the typical recruitment paradigm for each model.

Results from studies in enhanced recruitment models tend to demonstrate better experimental assay sensitivity[17] for the following reasons:

- Fewer, more specialized centers
  - Enhanced recruitment studies can be enrolled more rapidly and can use fewer centers to enroll the required n (generally 3-4 centers for enhanced recruitment vs 10-20 for standard recruitment). Enhanced recruitment studies work within a select few centers that treat high volumes of patients, with surgical or anesthetic protocols and other aspects of patient care tightly standardized per study protocols.
  - In standard recruitment, hospitals may have different standards of care for surgical and anesthetic techniques and other aspects of treatment. These differences can increase variability.

Table 1

Common acute pain models.

Common standard recruitment models	Common enhanced recruitment models
Hard tissue	Hard tissue
Total knee arthroplasty	Third molar extraction
Total hip arthroplasty	Bunionectomy
Shoulder surgery (joint replacement and rotator cuff repair)	
Soft tissue	Soft tissue
Cholecystectomy	(Since 2014) Abdominoplasty
Gynecologic surgery (eg, hysterectomy)	
Ventral hernia repair	

- Healthier subjects
  - Enhanced recruitment enables investigators to use restrictive inclusion or exclusion criteria to minimize confounding comorbidities.
- Subject domiciling
  - Standard recruitment subjects are typically not domiciled at hospitals longer than standard-of-care dictates. Study assessments (eg, pain scores) are often reported by subjects via take-home diaries. Studies using enhanced recruitment typically domicile patients during the entire study treatment period to assess study outcomes using highly trained research staff. Concomitant medications and other potential confounds are carefully controlled.

Given their superior assay sensitivity and reduced enrollment timelines, most pivotal registration programs on acute pain drugs in the past 8 to 10 years have used enhanced recruitment models.[10,12,16,17,19,21] However, before abdominoplasty, there was no soft-tissue enhanced recruitment model to serve as a counterpart to the well-standardized hard-tissue model available in bunionectomy.

1.3. Development of abdominoplasty as an enhanced recruitment soft-tissue surgical model

1.3.1. Creation and validation of abdominoplasty as a pain model

The search for a surgical model to satisfy the scientific and regulatory need for efficacy data in soft-tissue acute pain has an extensive history. Various candidates including hernia repair, gynecologic surgeries, and others have been attempted, mostly without success.[17] Beginning in 2007, the authors conducted a series of interviews with general and plastic surgeons to determine potential soft-tissue procedures that could enable enhanced recruitment. Enhanced recruitment models (bunionectomy and third molar extraction) had become industry standards to characterize hard-tissue acute pain, and pharmaceutical sponsors were receptive to expanding the enhanced recruitment concept into soft-tissue acute pain if a suitable model could be found. For an acute postoperative pain model to be both scientifically viable and compatible with the enhanced recruitment paradigm, it must have the following characteristics:

1. Generates adequate measurable pain
2. Pain signal follows a relatively consistent trajectory over time across subjects
3. Surgery is relatively quick and inexpensive
4. Surgical procedure is low risk or safe

5. Surgical procedure can be easily standardized across surgeons or centers
6. Anesthetic protocol can be controlled according to study specifications
7. Patient population is generally healthy, or surgical procedure is not intended to treat a difficult underlying condition with associated comorbidities
8. Underlying condition is easy to diagnose or does not require extensive diagnostic testing
9. Patients generally do not experience significant postoperative complications, do not require extensive postoperative care, and are generally satisfied with surgical results

Various models were considered; abdominoplasty was the leading candidate based on the above-listed criteria. The authors set out to attain a detailed understanding of the characteristics of abdominoplasty as a research model (including its pain trajectory) by conducting multiple pilot studies. These studies confirmed that the procedure consistently generates significant pain, likely secondary to a relatively large incision dissecting densely innervated tissues.[2,3] The pilot studies also confirmed that abdominoplasty was easy to recruit, enabled careful control of surgical and anesthetic protocols, and involved relatively few postoperative complications.

In 2014, Trevena, Inc., conducted the first Phase 2 efficacy trial in abdominoplasty for acute postoperative pain.[19] The 200-patient study was performed at 2 centers in California and Texas and tested 2 doses of Trevena's novel opioid oliceridine against an active comparator (morphine) and placebo. Both doses of oliceridine achieved the study's primary endpoint vs placebo (model-based, time-weighted average change in NPRS over 24 hours) with *P*-values between 0.0001 and 0.0005.

In 2015, the authors incorporated abdominoplasty into AcelRx's pivotal trial of DSUVIA sublingual sufentanil for the treatment of postoperative pain after abdominal surgery; the outcome of the study was positive.[13]

In 2016, Baudax Bio. (formerly Recro Pharma) designed and conducted the first Phase 3 pivotal registration study entirely in abdominoplasty.[16] This 219-patient trial tested Baudax's intravenous meloxicam formulation (Anjeso) against placebo and achieved statistical significance in its primary and most of its key secondary efficacy endpoints. In 2020, Anjeso became the first novel analgesic approved by FDA based on a soft-tissue pivotal study solely in abdominoplasty (along with companion bunionectomy and open-label safety studies).

Since these early efforts, the abdominoplasty model has been used in at least 10 additional acute postoperative pain trials, including 4 additional pivotal registration studies (see **Table 2** below).

1.4. Clinical characteristics of abdominoplasty as an experimental model

Abdominoplasty requires a larger (and thus more painful) surgical incision compared with other common soft-tissue models (**Fig. 1**).

Abdominoplasty is an elective cosmetic surgery designed to remove excess skin and adipose tissue from the lower abdomen and tighten abdominal muscles and fascia, to give the abdomen an improved appearance. The exact cosmetic issues that abdominoplasty patients present with can be fairly variable in clinical practice. As such, there are multiple forms of abdominoplasty surgery involving varying techniques, including different incision lengths, different incision placements, and different degrees of tissue removal. For an overview of standard surgical techniques used for abdominoplasty in practice, please see Regan (2020).[15]

In clinical practice, secondary or collateral procedures (such as liposuction outside the immediate area of the abdominoplasty incision, breast lift, etc.) are often performed concurrently with abdominoplasty. But most research studies seek to minimize collateral procedures by strict requirements in the study surgical protocol, to guarantee relatively standardized surgeries across subjects. Abdominoplasties performed in acute pain postoperative studies typically fall into 1 of 2 types: partial or "mini" abdominoplasty or full abdominoplasty.

Mini abdominoplasty and full abdominoplasty use different surgical techniques (**Fig. 2**).

1.4.1. Main types of abdominoplasty used in clinical trials

Image: Memorial Plastic Surgery (2019).[11]

1.4.1.1. Mini abdominoplasty

- A 12″ to 16″ incision is made roughly from iliac crest to iliac crest, below the umbilicus
- Skin and fat are removed roughly from the pubic bone to below the umbilicus
- Umbilicus remains in place
- May or may not involve rectus plication, depending on whether or not the patient presents with rectus diastasis (a bulging of the rectus muscle, requiring tightening)
- Minimal to no abdominal liposuction
- Surgery typically takes approximately 90 minutes

1.4.1.2. Full abdominoplasty

- Incision is made from iliac crest to iliac crest; surgical wound encompasses the umbilicus
- Skin can be removed from as far as from the xiphoid to the pubic bone

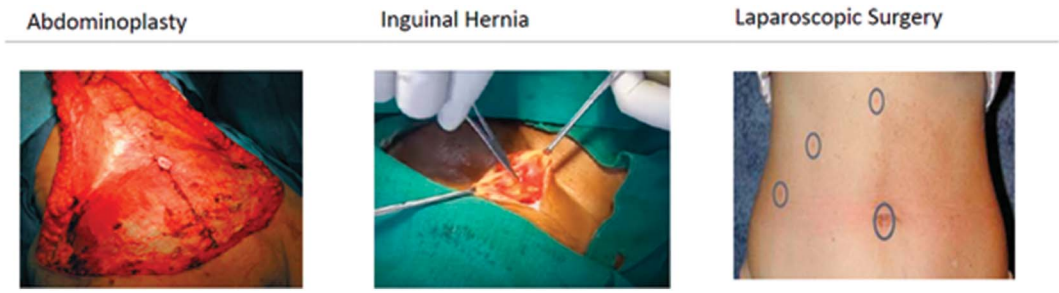

Figure 1. Abdominoplasty incision compared with other common soft-tissue surgeries.

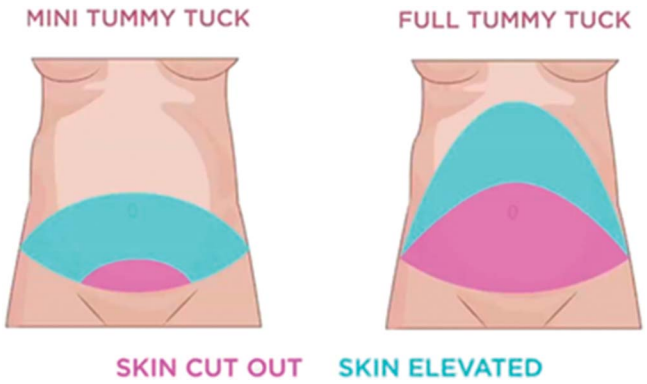

Figure 2. Illustration of mini abdominoplasty vs full abdominoplasty.

- Umbilicus is removed, reconstructed, and repositioned
- Always requires plication of the rectus muscle
- Extensive fascial plication
- Extensive repair and suture of abdominal wall muscle and fascia
- Moderate to extensive abdominal liposuction
- Surgery can take up to 2 1/2 hours or more

Because mini and full abdominoplasties are different surgeries with different degrees of tissue dissection, they have different pain trajectories. In an ideal analgesic study, the pain trajectory associated with the chosen surgical model matches up with the expected onset, potency, and offset of the experimental agent (the model gives rise to the most pain when the drug is most potent). So whether full abdominoplasty or mini abdominoplasty is a better choice for a given study depends in part on the expected characteristics of the study drug.

The ideal model gives rise to a level of postoperative pain where an effective drug provides relief, but placebo does not (**Fig. 3**). Cooper[5] likened an analgesic study to an Olympic high jump bar. Assuming the investigational drug actually works, the goal is to design a study where the "bar" (postoperative pain) is at height where study drug can clear it but placebo cannot (**Fig. 3B**). With a bar that is too low (ie, not enough pain generated by surgery [**Fig. 3A**]), both placebo and study drug will provide relief, and the study fails. With a bar that is too high (too much pain generated by surgery [**Fig. 3C**]), neither study drug nor placebo will provide adequate relief, and the study fails. To best differentiate an effective study drug from placebo, one must match the model and design of a study with the expected characteristics of a drug and choose a model that generates only as much pain as the drug can reliably relieve.

The pain signal from full abdominoplasty is typically of greater intensity than that of mini abdominoplasty, and full abdominoplasty pain lasts longer than mini abdominoplasty pain (approximately 72 vs 48 hours). For a study drug believed to be highly potent (comparable with narcotic analgesia), full abdominoplasty may be the better choice. For a drug believed to have moderate potency (comparable with NSAIDs or acetaminophen), mini abdominoplasty is likely the better choice.

1.4.2. Anesthetic and analgesic procedures

For most studies, the goal of the anesthetic regimen is for subjects to wake up in the recovery room shortly after surgery presenting as alert, capable of answering questions or following instructions, and either experiencing moderate pain or on the verge of doing so. In general, abdominoplasties in clinical trials are performed under general anesthesia, often using propofol with or without muscle relaxants or volatile anesthetics. Small doses of short-acting preoperative or intraoperative opioids (100 μg of fentanyl with supplementation as needed) are used for analgesia.

2. Review of abdominoplasty clinical trials

2.1. Table of studies reviewed

Table 2 details 13 clinical trials performed since 2014 in acute postoperative pain after abdominoplasty. Studies were identified by searches of the NIH National Library of Medicine (PubMed), clinicaltrials.gov, and Google search. We included only randomized, placebo-controlled studies that were intended to evaluate the efficacy of investigational analgesic drugs for the purpose of U.S. regulatory approval. Studies designed for U.S. regulatory approval are well-suited to our analysis because they share the following characteristics:

- These studies typically use single-agent therapy, rather than multimodal therapy, as the experimental treatment
- These studies recruit from a homogenous patient population and use standardized surgical and anesthetic variables
- These studies domicile patients in in-patient units for the entire treatment period in which postoperative pain is measured for the study's primary efficacy endpoint

Of the 13 studies collected, 11 had published data available, whether in the form of a published article, poster, public results on clinicaltrials.gov, or a press release highlighting topline results. Of these, 2 incorporated additional surgical models besides abdominoplasty and public data were not separated by the model. These were removed from the analysis, leaving 9 abdominoplasty-only studies with public results.

Table 2 shows 13 abdominoplasty studies reviewed for our analysis.

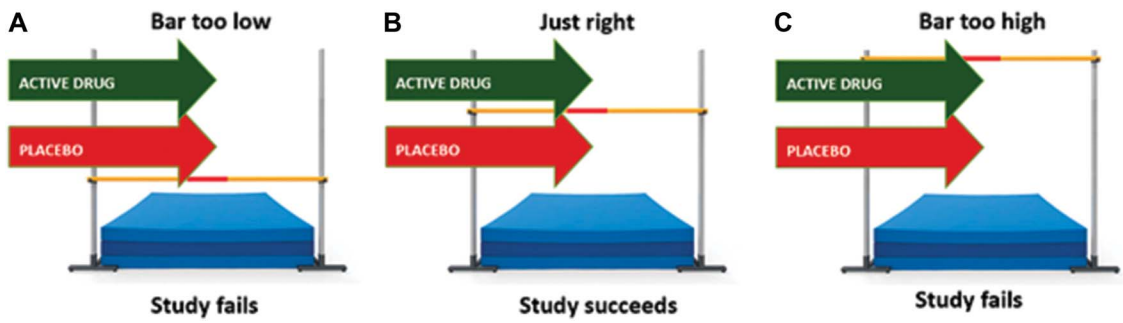

Figure 3. Seeking a level of postoperative pain where an effective drug provides relief, but placebo does not.

Table 2

Abdominoplasty studies.

Sponsor	Study title	Data source	Phase	Total study n	No. of study arms	Randomization ratio	# Of sites (per CTG)	Clinicaltrials.gov link	Study date/ duration (per CTG)	Study drug
Public data available										
Avenue Thera.	A phase 3, multicenter, randomized, double-blind, three-arm study to evaluate the efficacy and safety of tramadol infusion (AVE-901) versus placebo and morphine in the management of postoperative pain following abdominoplasty	Manuscript: Minkowitz et al. 2020[12]	3	360	3	3:3:2 (placebo/study drug/ morphine)	3	https://clinicaltrials.gov/ct2/show/NCT03774836	12/18-5/19	Tramadol
Baudax Bio	A phase 3, multicenter, randomized, double-blind, placebo-controlled, evaluation of the efficacy and safety of N1539 following abdominoplasty surgery	Manuscript: Singla et al. 2018[16]	3	219	2	1:1	4	https://clinicaltrials.gov/ct2/show/NCT02678286	1/16-10/16	Meloxicam
Bonti Thera.	A phase 2 study to evaluate safety and efficacy of EB-001 intramuscular (IM) injections in reducing musculoskeletal pain in subjects undergoing elective abdominoplasty surgery	Clinicaltrials.gov posted results: https://clinicaltrials.gov/ct2/show/results/NCT03429556?view=results	2	23	4	12:4:4:3 (placebo/3 doses of the study drug)	1	https://clinicaltrials.gov/ct2/show/NCT03429556	5/18-7/18	Botulinum toxin
Concentric Analgesics	A phase 2, randomized, double-blind, placebo-controlled efficacy, pharmacokinetics and safety study of CA-008 in subjects undergoing complete abdominoplasty	Clinicaltrials.gov posted results: https://www.clinicaltrials.gov/ct2/show/results/NCT03789318	2	54	5 (across 2 cohorts)	1:1 (cohort 1); 1:1:1 (cohort 2—placebo/2 doses of the study drug)	1	https://clinicaltrials.gov/ct2/show/NCT03789318	12/18-5/19	Vocacapsaicin
Heron Thera.	A phase 2, randomized, controlled evaluation of the efficacy and safety of HTX-011 or HTX-002 for post-operative analgesia following abdominoplasty surgery	Poster: Leiman et al. 2017[10]	2	277, 41 subjects detailed in publication	2 detailed in publication	1:1	8	https://clinicaltrials.gov/ct2/show/NCT02689258	2/16-3/17	Bupivacaine & meloxicam
Innocoll	A randomized, double-blind, placebo-controlled study to evaluate the	Press release[6]	3	366	2	1:1	4	https://clinicaltrials.gov/ct2/show/NCT04785625	4/21-10/21	Bupivacaine

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Table 2 (*continued*)

Sponsor	Study title	Data source	Phase	Total study n	No. of study arms	Randomization ratio	# Of sites (per CTG)	Clinicaltrials.gov link	Study date/ duration (per CTG)	Study drug
	efficacy and safety of a 300-mg dose of the INL-001 (bupivacaine hydrochloride) implant in patients undergoing abdominoplasty									
Trevena Inc.	A phase 2, randomized, double-blind, placebo- and active-controlled study of TRV130 for the treatment of acute postoperative pain following abdominoplasty	Manuscript: Singla et al. 2017[19]	2	200	3	2:2:1 (study drug/ morphine/placebo)	2	https://clinicaltrials.gov/ct2/show/NCT02335294	12/14-7/15	Oliceridine
Trevena Inc.	A phase 3, multicenter, randomized, double-blind, placebo and active-controlled study of oliceridine (TRV130) for the treatment of moderate to severe acute pain after abdominoplasty	Manuscript: Singla et al. 2019[21]	3	407	5	1:1:1:1:1 (placebo/3 doses study drug/ morphine)	5	https://clinicaltrials.gov/ct2/show/NCT02820324	5/16-12/16	Oliceridine
Vertex	A phase 2, randomized, double-blind, placebo-controlled, multi-dose study evaluating the efficacy and safety of VX-548 for acute pain after an abdominoplasty	Press release[23]	2	303	4	1:1:1:1 (placebo/2 doses study drug/hydrocodone-acetaminophen)	7	https://clinicaltrials.gov/ct2/show/NCT05034952	8/21-12/21	VX-548
No data available										
Vivozon	A multicenter, randomized, double-blind, parallel group, placebo- controlled trial to evaluate the efficacy and safety of VVZ-149 injections for the treatment of post-operative pain following abdominoplasty	None	3	307	2		5	https://clinicaltrials.gov/ct2/show/NCT03997838	5/19-8/19	Opiranserin
Teikoku Pharma	A double-blind, placebo-controlled evaluation of the dexmedetomidine transdermal system for postoperative analgesia following abdominoplasty	None	2	164	2	1:1	4	https://clinicaltrials.gov/ct2/show/NCT04242407	7/20-2/21	Dexmedetomidine

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Table 2 (*continued*)

Sponsor	Study title	Data source	Phase	Total study n	No. of study arms	Randomization ratio	# Of sites (per CTG)	Clinicaltrials.gov link	Study date/ duration (per CTG)	Study drug
Mixed-model studies										
AcelRx (abdominoplasty/ abdominal surgery)	A multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of the sublingual sufentanil tablet 30 mcg for the treatment of post-operative pain in patients after abdominal surgery	Manuscript: Minkowitz et al. 2017[13]	3	80 (abdominoplasty) and 161 (all models)			4 (not clear; all sites performed abdominoplasty)	https://clinicaltrials.gov/ct2/show/NCT02356588	2/15-6/15	Sufentanil
iX Biopharma (abdominoplasty/ bunionectomy)	A phase 2, multiple-dose study of the efficacy and safety of Wafermine™ (sublingual ketamine) in participants experiencing acute post-operative bunionectomy or abdominoplasty pain	Press release[7]	2	125 (all models)			1	https://clinicaltrials.gov/ct2/show/NCT03246971	8/17-7/18	Ketamine

Sponsor	Drug class	Method of administration	Intra- operative or postoperative dosing	Primary endpoint	Primary comparison	Primary endpoint *P*	Rescue regimen	Efficacy dropouts in placebo arm	Full or mini	Mean baseline pain (if postop dosing)
Public data available										
Avenue Thera.	Opioid/Mu-agonist	IV	Post	SPID24	Tramadol vs placebo	< 0.001	Ibuprofen 400 mg, q 4 h	4.40%	Mini	6.5
Baudax Bio	NSAID	IV	Post	SPID24	Meloxicam 30 mg vs placebo	0.0145	Oxycodone 5 mg orally q 2 h	Not listed	Mini	7.3
Bonti Thera.	Paralytic	Injection	Intra-	AUC 12-96	EB-001 vs placebo	Not listed	Not listed	Not listed	Full	N/A
Concentric Analgesics	Local analgesic/ TRPV1 agonist	Infiltration	Intra-	"NRS at a specific time (96 h)"	CA-008 vs placebo	0.2912	Not listed	Not listed	Full	N/A
Heron Thera.	Local anesthetic + NSAID	Infiltration	Intra-	SPI24 (AUC)	HTX-011 vs placebo	0.0919	"Opioid rescue" - details not specified	Not listed	Full	N/A
Innocoll	Local anesthetic	Implant	Intra-	SPI24 (AUC)	Xaracoll vs placebo	0.002	Regimen included morphine/other details not specified	Not listed	Mini	N/A
Trevena Inc.	Opioid/Mu-agonist	IV/PCA	Post	"Model-based, time-weighted average change in NPRS over 24 h (TWA NPRS 0-24)"	TRV130 regimens a and B vs placebo	0.0001 (A), 0.0005 (B)	Oral ibuprofen 400 mg q 6 h (1st line), oral oxycodone 5 mg q 2 h (2nd line)	5%	Mini	7.7

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Table 2 (*continued*)

Sponsor	Drug class	Method of administration	Intra- operative or postoperative dosing	Primary endpoint	Primary comparison	Primary endpoint *P*	Rescue regimen	Efficacy dropouts in placebo arm	Full or mini	Mean baseline pain (if postop dosing)
Trevena Inc.	Opioid/Mu-agonist	IV/PCA	Post	Proportion of treatment responders over 24 h	TRV130 0.1, 0.35 and 0.5 regimens vs placebo	0.029 (0.1), < 0.0001 (0.35). 0.0004 (0.5)	Etodolac 200 mg q 6 h,	1.20%	Mini	7.4
Vertex	NaV1.8 inhibitor	Oral	Post	SPID48	VX-548 vs placebo	0.0097 (high dose), 0.1266 (low dose)	Not listed	Not listed	Not listed	Not listed
No data available										
Vivozon	GlyT2 transporter blocker	Injection		AUC 0-12	VVZ-149 vs placebo		Not listed			
Teikoku Pharma	Sedative	Transdermal		SPI4-96	DTMS vs placebo		Opioid rescue, precise regimen not listed			
Mixed-model studies										
AcelRx (abdominoplasty/ abdominal surgery)	Opioid/Mu-agonist	Sublingual wafer	Post	SPID12	SST vs placebo	< 0.001	IV morphine, 1 mg q 1 h	N/A (mixed model study)	Not listed	
iX Biopharma (abdominoplasty/ bunionectomy)	Dissociative anesthetic	Sublingual wafer	Post	SPID12	Wafermine 75, 50 and 25 mg vs placebo	0.10 (75 mg)	Not listed	Not listed	Not listed	

AUC, area under the curve; NSAID, nonsteroidal anti-inflammatory drug. SPID, Summed Pain Intensity Difference.

Table 3

Abdominoplasty standardized effect sizes.

Sponsor	Study	Full or mini	Drug	Drug class	Route	Endpoint	SES Method*	24 HR. SES vs Placebo	48 HR. SES vs Placebo
Avenue	AVE-901-103	Mini	Tramadol 50 mg	Opioid	IV	SPID	Cohen D	0.68	0.62
		Mini	Morphine 4 mg	Opioid	IV	SPID	Cohen D	0.76	0.61
Baudax	REC-15-015	Mini	Meloxicam	NSAID	IV	SPID	Cohen D	0.38	0.38
Heron	HTX-011-C2015-203	Full	Bupivacaine + meloxicam	Local anesthetic + NSAID	Infiltration	SPI	*P*-value	0.54	0.76
Innocoll	INN-CB-024	Mini	Bupivacaine	Local anesthetic	Implant	SPI	*P*-value	0.33	
Trevena	CP130-2002	Mini	Oliceridine higher dose	Opioid	IV/PCA	SPID	Cohen D	0.89	
			Oliceridine lower dose	Opioid	IV/PCA	SPID	Cohen D	0.82	
			Morphine	Opioid	IV/PCA	SPID	Cohen D	0.82	
Trevena	CP130-3002	Mini	Oliceridine higher dose	Opioid	IV/PCA	% Responders	*P*-value	0.57	
			Oliceridine middle dose	Opioid	IV/PCA	% Responders	*P*-value	0.63	
			Oliceridine lower dose	Opioid	IV/PCA	% Responders	*P*-value	0.35	
			Morphine	Opioid	IV/PCA	% Responders	*P*-value	0.52	
Vertex	VX21-548-102	Un-known	VX-548 higher dose	Na_v 1.8 inhibitor	Oral	SPID	*P*-value		0.42
			VX-548 lower dose	Na_v 1.8 inhibitor	Oral	SPID	*P*-value		0.25
			Hydrocodone 5 mg/ acetaminophen 325 mg	Na_v 1.8 inhibitor	Oral	SPID	*P*-value		0.14

*In some instances, Cohen D was calculated from LS means provided in publications rather than arithmetic means.
NSAID, nonsteroidal anti-inflammatory drug; SES, standardized effect size; SPID, Summed Pain Intensity Difference.

3. Analysis

3.1. Study success rate

Seven of the 9 studies with available data were successful. The 2 studies that did not demonstrate superiority of study drug over placebo (Bonti Therapeutics' and Concentric Analgesics' Phase 2 studies) averaged 6 and 11 subjects per study arm, respectively (**Table 2**), and so may have been underpowered to demonstrate efficacy.

3.2. Enrollment rates

Enrollment rates (subjects enrolled per site per month) calculated from clinicaltrials.gov data can be unreliable because enrollment pauses for interim analyses or other reasons are included in CTG's listed enrollment durations (eg, a study that enrolled for 6 months with a 2-month pause is shown to have enrolled for 8 months, resulting in understated enrollment speed). To estimate normal enrollment rates for abdominoplasty, we consulted sponsors for multiple studies to find studies that did not include enrollment pauses (and received their permission to publish this information). The Avenue Therapeutics AVE-901-103 and Innocoll INN-CB-024 trials were confirmed to have had uninterrupted enrollment:

- AVE-901-103 enrolled **21.8** subjects per site per month across 3 centers (360 subjects in 5.5 months)
- INN-CB-024 enrolled **18.3** subjects per site per month across 4 centers (366 subjects in 5 months)

3.3. Efficacy assessments

The most common primary endpoints among all studies were as follows:

A. Summed Pain Intensity Difference, 6 studies
B. Area under the curve or Summed Pain Intensity, 4 studies

Summed Pain Intensity Difference, which calculates a difference from a baseline in pain intensity over time, was used for drugs administered postoperatively. When a study treatment is given postoperatively, investigators wait to randomize a patient until the patient reports a prespecified level of postoperative pain. Their pretreatment pain score is recorded as a baseline, and later assessments are used to assess a difference from this baseline score.

Area under the curve was used for drugs administered intraoperatively. In these studies, subjects do not report baseline pain, and virtually all subjects who undergo surgery are randomized. Area under the curve is a simple calculation based on pain intensity scores rather than a comparison of pain scores with a baseline.

3.4. Assay sensitivity

Standardized effect size (SES) is a reasonable shorthand metric for measuring a study model's experimental assay sensitivity. A larger SES is better, indicating that a model has a greater chance of separating a truly efficacious drug from placebo. Standardized effect size is typically calculated in one of 2 ways:

1. By direct Cohen D methodology: divide the difference in means between 2 groups (a measure of treatment effect) by their pooled standard deviation (a measure of variability)
2. Estimated from group sample sizes and *P*-values

In either case, SES is agnostic of the units used to measure one's original data. It can be considered a universal measure of an experiment's signal-to-noise ratio and, thus, allows comparisons between studies using different measurements or endpoints.

Jacob Cohen, creator of the Cohen D methodology, defined a small SES as 0.2, medium as 0.5, and large as 0.8,[4] and this standard is commonly used.[9] In experimental conditions associated with a higher SES (eg, sensitive study model or potent study drug), fewer subjects are needed to detect a treatment effect.

Table 3 shows standardized effect sizes for 15 comparisons of active treatments vs placebo across 7 abdominoplasty studies with sufficient public data.

Abdominoplasty generally showed strong SES' at 24 hours, averaging 0.61 across all comparisons (not weighted for study n).

Table 4

Standardized effect size: highest dose of study drug vs placebo for primary endpoint.

Study	Primary endpoint	Drug class	SES
Avenue	SPID24	Opioid	0.68
Baudax	SPID24	NSAID	0.32
Heron	SPI24	Local anesthetic + NSAID	0.54
Innocoll	SPI24	Local anesthetic	0.33
Trevena P2	Modified SPID24	Opioid	0.89
Trevena P3	% Responders, 24 h	Opioid	0.57
Vertex	SPID48	Nav 1.8 inhibitor	0.42

NSAID, nonsteroidal anti-inflammatory drug; SES, standardized effect size; SPID, Summed Pain Intensity Difference.

There does not seem to be a clear correlation between the class of study drug and effect size. Although opioids showed strong effect sizes in the Avenue and Trevena programs, in the Vertex program, hydrocodone with acetaminophen showed a weak effect size. Local or infiltration analgesics showed mixed results, whereas the sole NSAID-only compound (from Baudax) showed modest effect sizes. More data are needed to draw conclusions on the relative favorability of abdominoplasty for various drug classes.

Standardized effect size data for effect sizes based on the comparison of each study's highest dose of study drug vs placebo, for each study's prespecified primary endpoint, are presented in Table 4. These data represent SES′ for the "make or break" comparison that determines study success. The average SES (not weighted for study n) was 0.54 across studies:

Table 4 shows standardized effect sizes for the highest dose of study drug vs placebo for 7 studies' respective primary endpoints.

Three studies included morphine comparator arms. Since morphine is a potent analgesic known to work, effect sizes for morphine vs placebo (as opposed to experimental agents vs placebo) are of interest in determining a model's true assay sensitivity. The average SES was 0.7 for morphine vs placebo across studies:

Table 5 shows standardized effect sizes for morphine vs placebo in the 3 abdominoplasty studies that used a morphine comparator arm.

3.5. Effect sizes: bunionectomy vs abdominoplasty

Three sponsors (Avenue, Baudax, and Vertex) performed similar studies (involving a shared high dose of study drug, similar inclusion/exclusion criteria, etc.) in bunionectomy alongside their studies in abdominoplasty,[14,20,23] allowing a direct comparison of SES between these 2 enhanced recruitment models.

Table 5

Standardized effect size: morphine comparator arms vs placebo.

Study	Primary endpoint	SES
Avenue	SPID24	0.76
Trevena P2	Modified SPID24	0.82
Trevena P3	% Responders, 24 h	0.52

SES, standardized effect size; SPID, Summed Pain Intensity Difference.

Table 6

Standardized effect size vs bunionectomy (high-dose IP vs placebo).

Sponsor	Abdominoplasty	Bunionectomy
SPID24		
Avenue	0.68	0.46
Baudax	0.32	0.37
Vertex	N/A	N/A
SPID48		
Avenue	0.62	0.33
Baudax	0.38	0.41
Vertex	0.42	0.42

SPID, Summed Pain Intensity Difference.

Table 6 compares standardized effect sizes between similar abdominoplasty and bunionectomy studies, in comparing high-dose IP vs placebo.

Abdominoplasty SES at 24 and 48 hours were slightly inferior to those of bunionectomy in the Baudax studies and substantially superior to bunionectomy in the Avenue studies. Standardized effect sizes across both Vertex studies were identical. Historically, NSAIDs (such as Baudax's meloxicam) have tended to work well in bunionectomy studies, possibly because of the osteotomy and subsequent periosteal disruption in bunionectomy giving rise to inflammatory pain. The above data tentatively support the concept that NSAIDs may fare better in bunionectomy, and non-NSAID agents such as opioids (and perhaps infiltration analgesics) may fare better in abdominoplasty. But further data are needed to draw meaningful conclusions.

3.6. Baseline pain intensity

Average baseline pain scores at randomization (when patients first report adequate pain to be randomized, before study treatment) for postoperative dosing studies (Avenue, Baudax and Trevena) ranged from 6.5 to 7.7. Bunionectomy studies performed by the same 3 sponsors (all using "postoperative day 1" designs, where a nerve block is left in place until the day after surgery) showed similar average baseline pain scores, ranging from 6.7 to 6.8.[14,20,24]

3.7. Time to onset of pain relief

A comparison of available time with onset data (using the 2-stopwatch method) from the Avenue, Baudax, and Trevena phase 3 abdominoplasty and bunionectomy programs is presented below in **Table 7**. All numbers are median time to onset in minutes.

There seems to be no clear pattern in the available time to onset data. Abdominoplasty showed faster onset than bunionectomy for some drugs and slower onset for others. Time to onset may be more closely related to the properties of each study drug rather than the study model. Further analysis of time to onset data across acute pain models is called for.

3.8. Rescue medication

In acute pain studies, the rate of early terminations due to inadequate pain relief is associated with the rescue regimen allowed by the protocol. Liberal rescue (eg, strong opioids) can reduce efficacy dropouts but can also confound data and reduce the likelihood that an effective drug separates from placebo.

Table 7

Time to pain relief (minutes).

Sponsor	Abdominoplasty	Bunionectomy
Perceptible or confirmed perceptible		
Avenue		
Tramadol 50 mg	27	167
Placebo	69	NE
Baudax		
Meloxicam	46	31
Placebo	77	95
Trevena		
Oliceridine 1 mg	6	6
Oliceridine 0.35 mg	6	6
Oliceridine 0.5 mg	6	6
Morphine 1 mg	6	6
Placebo	12	18*
Meaningful		
Avenue		
Tramadol 50 mg	106	321
Placebo	145	NE
Baudax		
Meloxicam	180	130
Placebo	180	191
Trevena		
Oliceridine 1 mg	84	12
Oliceridine 0.35 mg	42	12
Oliceridine 0.5 mg	60	12
Morphine 1 mg	72	30
Placebo	294	NE

* Exact number not presented in the article; estimated from the graphical data.

Weaker rescue (eg, acetaminophen) can give rise to excessively high placebo-arm dropout rates in acute pain models such as bunionectomy.[18] An ideal rescue regimen is balanced for the study model to provide enough relief to prevent high placebo dropouts but not so much that data are heavily confounded. The optimal approach is to provide the lowest level of rescue that (A) still prevents excessive dropouts and (B) provides adequate patient care and is ethically and clinically reasonable.

Of the 6 studies for which information on rescue medication regimen was available, 2 used opioid rescue alone, 2 used NSAID rescue alone, and 1 used a multiple-line approach (NSAID as first-line, followed by opioid if needed). One additional study (Innocoll) used opioid rescue, but public data did not clarify whether it was used alone or as part of a multiline approach.

3 studies published dropout rates because of the lack of efficacy (Avenue Therapeutics and both Trevena studies). All 3 studies used mini-abdominoplasties. 2 used NSAID-only and 1 used first-line NSAID/second-line opioid rescue. All 3 showed placebo-arm dropout rates for lack of efficacy at or below 5%. This suggests that relatively weak rescue regimens are adequate for mini-abdominoplasty studies—a single NSAID (400 mg oral ibuprofen or comparable) is likely ideal.

3.9. Demographics

Pooled demographic data from 5 studies with published results, totaling 1231 patients, are presented below. Abdominoplasty in clinical research is overwhelmingly performed on female patients, which matches clinical practice: a study of over 25,000 abdominoplasties in clinical practice found that 97% of patients were female.[25] Programs with a regulatory or market requirement for exposures to male patients will require alternate or additional models.

Table 8

Demographics.

	n = 1231	
	Mean	**SD**
Age	40.14	9.4
BMI	26.95	3.23
Sex	**% Female**	**% Male**
	99.04	0.96
Race	**% Of total**	
Amer. Indian/Alaskan Native	0.5%	
Asian	2.4%	
Black	28.6%	
Native Hawaiian/Pacific islander	0.8%	
White	65.7%	
Others	1.2%	
Multiple	0.7%	
Ethnicity	**% Hispanic**	**% Non-Hispanic**
	45.57%	54.93%

BMI, body mass index.

The mean subject BMI is relatively low at 26.95, which reflects abdominoplasty data from clinical practice—2 studies reviewing relatively large samples of abdominoplasty patients found mean BMIs of 26 and 27.5, respectively.[8,22] Although the abdominoplasty procedure can be performed concurrently with liposuction, it is not a weight loss surgery per se but rather serves to cosmetically tighten the appearance of the abdomen by manipulation of the skin, ligaments, and muscle tissue.

Table 8 shows subject demographics for studies with available data.

Table 9

Adverse events.

Study	AE	% Placebo Patients
Avenue		
	Nausea	37
	Headache	14.8
	Vomiting	6.7
	Dizziness	6.7
Baudax		
	Nausea	37.6
	Headache	16.5
	Dizziness	9.2
	Vomiting	9.2
Heron		
	Pruritus	14.3
	Nausea	9.5
Trevena phase 2		
	Nausea	18
	Headache	13
	Hypoventilation	10
	Phlebitis	10
Trevena phase 3		
	Nausea	45.8
	Headache	28.9
	Vomiting	13.3
	Hypoxia	4.8

AE, adverse event.

3.10. Adverse events

Among studies with published articles or posters, the most common adverse events in the placebo arms across studies (and thus not secondary to the study drug or comparator) were as follows:

1. Nausea, which was reported in 5/5 studies and occurred at an average rate across studies of 31%.
2. Headache, which was reported in 4/5 studies and occurred at an average rate across studies of 18.3%

Table 9 shows adverse events in studies with available data.

4. Limitations

The major limitation of the current analysis is a lack of published data. Although abdominoplasty has matured into a common model in the clinical trial industry in recent years, the backlog of published studies in the model remains limited. Potential trends including abdominoplasty's relative strength for different drug classes (opioids vs NSAIDs, etc), the nuances of the pain trajectory for full vs mini-abdominoplasty past 24 hours, and other key questions cannot be meaningfully addressed until more ongoing and future studies publish results. Data from 2 large recent studies by Teikoku Pharma and Vivozon would have meaningfully expanded the scope of our analysis but have not been made public.

5. Conclusions

Abdominoplasty is a well-validated soft-tissue surgical model that provides high-quality experimental outputs, enabling the efficacy of investigational analgesics in soft-tissue pain to be understood successfully. Abdominoplasty studies are also quick to enroll and can, therefore, decrease clinical trial time and cost relative to other models. Because abdominoplasty's use in clinical pain trials is relatively new, there is not yet adequate public data to meaningfully analyze some nuances of the model. As the popularity of abdominoplasty in clinical trials continues to expand, researchers can expect a fuller understanding of its characteristics.

Conflict of interest statement

N. Singla is the Chief Scientific Officer 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 abdominoplasty, as well as studies in bunionectomy, molar extraction, joint arthroplasty, and other acute pain models. N. Singla and his Lotus colleagues conceived and developed the use of abdominoplasty as an acute postoperative pain model, including designing and performing the pilot studies used to characterize the model as well as the initial acute pain trials used to validate the model. T. Rogier is the Director, Scientific Communications for Lotus Clinical Research, as well as studies in bunionectomy, molar extraction, joint arthroplasty, and other acute pain models.

Supplemental video content

A video abstract associated with this article can be found at http://links.lww.com/PAIN/B683.

Article history:
Received 15 April 2022
Received in revised form 3 June 2022
Accepted 6 June 2022
Available online 17 August 2022

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